Medicinal Chemistry, 2023, *19*, 509-537

REVIEW ARTICLE

Prevention of Oxidative Stress and Diseases by Antioxidant Supplementation

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ARTICLE HISTORY

Received: April 27, 2022
Revised: September 02, 2022
Accepted: September 27, 2022

DOI:
10.2174/1573406419666221130162512

Abstract: Excessive and uncontrolled oxidative stress can damage biomacromolecules, such as lipids, proteins, carbohydrates, and DNA, by free radical and oxidant overproduction. In this review, we critically discuss the main properties of free radicals, their implications in oxidative stress, and specific pathological conditions. In clinical medicine, oxidative stress can play a role in several chronic noncommunicable diseases, such as diabetes mellitus, cardiovascular, inflammatory, neurodegenerative diseases, and tumours. Antioxidant supplements can theoretically prevent or stop the progression of diseases, but a careful literature analysis finds that more evidence is needed to dissect the ultimate beneficial effect of antioxidants versus reactive oxygen species in several diseases.

Keywords: Free radicals, oxidative stress, antioxidants, oxidative damage, diseases, reactive oxygen species.

1. INTRODUCTION

Maintaining human health and increasing the health span as well as the quality of life are a matter of concern in modern societies. Major factors to consider in this respect are the accelerated growth of the population, which is estimated to top over 9 billion by 2050, the increasing mean age of the population that has risen at a rate of about 3 months/year in the last two centuries [1], and the increased incidence of chronic noncommunicable diseases worldwide. Prevention of diseases has, therefore, become a key aspect of health care systems worldwide.

The role of free radicals in health and disease is part of this scenario, and research is trying to dissect pathogenic mechanisms as well as potentially beneficial strategies. Free radicals were discovered more than a century ago, with the idea that all oxidation reactions involving organic molecules are mediated by free radicals. Free radicals were detected in biological systems in the 1950s [2] and thought to play a role in human diseases [3]. The mechanisms regulating the production of free radicals and their involvement in homeostatic processes have also been used to propose the free radical theory of aging [4]. The discovery of the superoxide dismutase enzyme (SOD) [5] and other antioxidant enzymes showed that living organisms have protective systems and that the deleterious effects of free radicals can be controlled by specific antioxidant systems. Free radicals also have a beneficial biological action; reactive oxygen species (ROS) and reactive nitrogen species (RNS) can operate in concert with reactive halogen species to fight against infection produced by invading microorganisms as part of the cellular immune response [6-8]. The signaling functions of ROS and RNS are the most recent important biological discovery regarding free radicals [8-11].

In the 1980s, research has confirmed that the generation and elimination of free radicals in living organisms are normally well balanced, but the imbalance between these two processes can occur during several diseases. Sies *et al.* [12] proposed the first definition of oxidative stress as "imbalance between oxidants and antioxidants in favour of the oxidants, which can potentially cause damage". The implications of the processes linked to free radicals involve all biological and medical disciplines and involve replicative inactivation of DNA, mutation, atherosclerosis, arthritis, carcinogenesis, neurodegenerative diseases, and aging [13, 14]. More recently, antioxidant supplements have been considered a *panacea* for oxidative damage and have been transformed into attractive compounds, and natural foods rich in antioxidants have become super functional or nutraceutical foods.

This review focuses on the main principles related to the properties of free radicals, their implications in oxidative stress and related pathological conditions. The system of

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antioxidant defence and the benefits of food supplementation with antioxidants in maintaining health will be discussed.

2. FREE RADICALS

The ability to use oxygen implies that humans can metabolise fats, proteins, and carbohydrates to produce energy. Paradoxically, however, oxygen can contribute to aging and illness. Cells using oxygen generate free radicals, generally ROS and RNS, which result from the cellular redox process [14].

Free radicals can be defined as reactive molecular entities or fragments containing one or more unpaired electrons in an outer atomic or molecular orbital [15]. Free radicals attempt to mate with other molecules, atoms, or individual electrons to create a stable compound, either donating an electron and acting as reducing agents or accepting an electron and acting as oxidizing agents from other molecules [15, 16]. Both ROS and RNS can be classified into two groups of compounds, namely radicals and non-radicals. In particular, radicals include compounds, such as superoxide ($O_2^{\bullet -}$), oxygen radical ($O_2^{\bullet\bullet}$), hydroxyl ($OH^{\bullet}$), alkoxy radical ($RO^{\bullet}$), peroxyl radical ($ROO^{\bullet}$), nitric oxide (nitrogen monoxide) ($NO^{\bullet}$), and nitrogen dioxide ($NO_2^{\bullet}$) [17]. By contrast, non-radical species include hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), hypobromous acid (HOBr), hypoiodous acid (HOI), ozone (O_3), singlet oxygen ($^1O_2$), nitrous acid (HNO_2), nitrosyl cation (NO^+), nitroxyl anion (NO^-), dinitrogen trioxide (N_2O_3), dinitrogen tetraoxide (N_2O_4), nitronium (nitryl) cation (NO_2^+), organic peroxides (ROOH), aldehydes (HCOR), and peroxynitrite (ONOOH) [17, 18]. Reactive sulfur species (RSS) and thiol radical (RS) are formed by the reaction between ROS and thiols. RSS include radical species, such as glutathionyl radical, and non-radicals, such as sulfane species. RSS can trigger both oxidation and reduction reactions [19]. The reactive electrophile species (RES) have remarkable biological activity by stimulating gene expression and acting as molecular signal [15, 20]. Hypohalous acids are powerful oxidizing agents, determined by the halogen atom and not by the oxygen atom, with the decreasing oxidizing capacity in order HOCl > HOBr > HOI, called reactive halogen species (RHS) [21]. RHS react with proteins, lipids, and carbohydrates; high levels of RHS cause damage to cells and biomolecules. Non-radical species can easily lead to free-radical reactions in living organisms [22].

The imbalance between free radical production in the tissues and organs, *e.g.*, ROS, RNS, RES, RSS, RHS, and antioxidant defenses, leads to oxidative stress, cellular damage, and dysfunctions (Fig. **1**). This process paves the way for several pathological conditions [23].

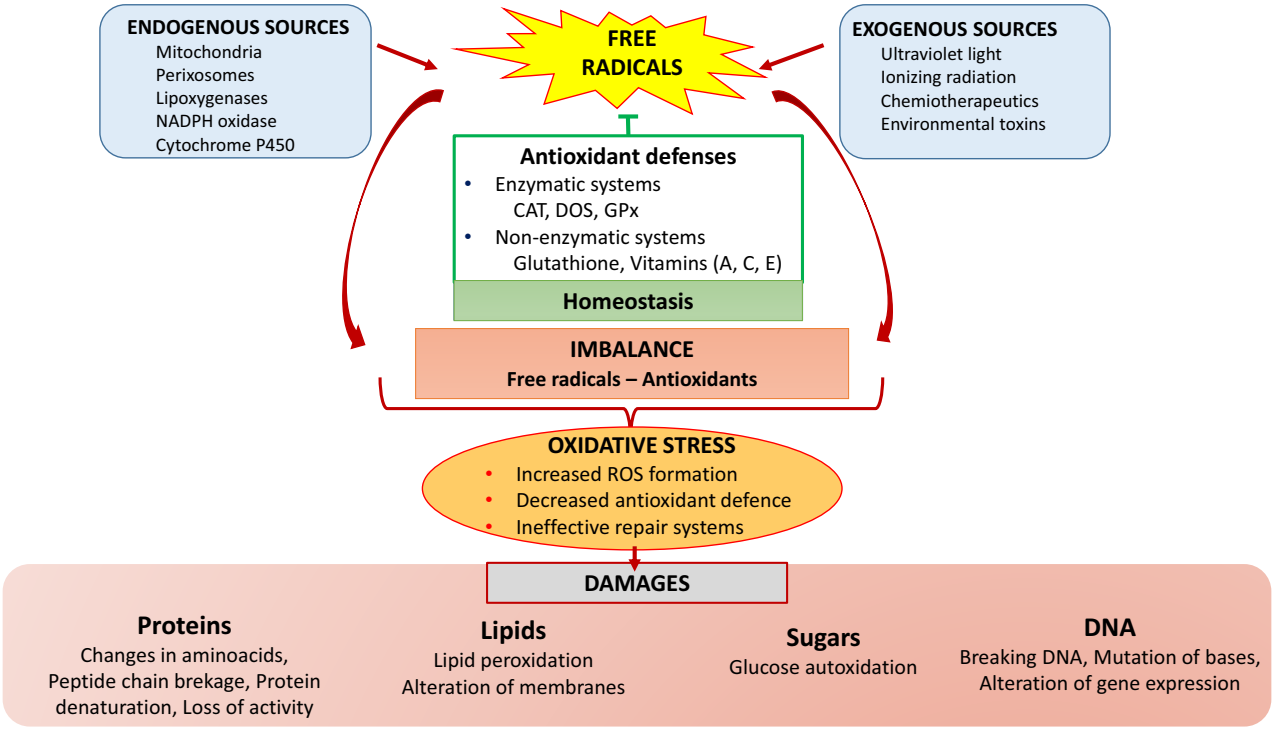

Fig. (1). Schematic representation of the role of free radicals/oxidants in determining oxidative stress. The main endogenous sources of free radicals/oxidants are mitochondria and peroxisomes and different cytosolic enzyme systems. Additionally, external agents can activate the production of free radicals/oxidants. The antioxidant defense system, enzymatic (CAT, SOD, GPx) and non-enzymatic (glutathione, Vitamins A, C, E,), counteracts and regulates the levels of free radicals/oxidants to maintain physiological homeostasis. The imbalance between oxidant and antioxidative defense in favor of the former in tissue and organs leads to oxidative stress, cellular damage to proteins, lipids, and DNA dysfunction. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).
Abbreviations: CAT: catalase; SOD: superoxide dismutase; GPx: glutathione peroxidase; Vitamins: A, β-carotene, C, ascorbic acid, E, α-tocopherol.

3. OXIDATIVE STRESS

This is a condition occurring when oxidative damage results from an imbalance between the action of ROS/RNS and the antioxidative protection systems [24-26]. The concept implies the recognition of the homeostatic balance between the physiological production of oxidants (oxidizing free-radicals and related species) and the existence of operative antioxidant defenses. The concept of imbalance recognizes the homeostatic rupture of the physiological effectiveness of the antioxidant defenses in maintaining both oxidative stress and cellular damage at the minimum level under physiological conditions [27, 28]. In addition, the disruption of the pro-oxidant/antioxidant balance in favor of oxidants leads to an interruption in redox signaling and in control and/or molecular damage [29]. The oxidant/antioxidant balance is maintained dynamically through the regulation of the levels of antioxidants in response to oxidative stress. However, the concept of oxidative stress is not limited to the detrimental effect of free radicals on biomolecules, but is based on the identification of the perturbation of the cellular redox state [30] as a rupture in redox signaling and control. The action of antioxidant systems is, therefore, more complex than simply blocking the reactive free radicals [31, 32]. Indeed, oxidative stress combines the basic chemical notion of oxidation-reduction, which includes electron transfer, free radicals, and oxygen metabolites, with the biological concept of stress (Fig. **2**).

Many years ago, Selye *et al*. [33] formulated the concept of eustress *vs.* distress. In normal adaptive processes (stress responses), the physiological oxidative stress called “oxidative eustress” and the excessive load defined as “oxidative distress” may lead to oxidative damage [32, 34]. The alteration in the basal redox tone is considered as initiating the stress response, with physiological alterations, defined as "oxidative eustress" and supra-physiological alterations, leading to oxidative distress [32]. Oxidative eustress represents the preponderant part of redox control and physiological redox signaling [32, 35], and corresponds to redox homeostasis [36]. Therefore, the concept of oxidative stress has been modified, incorporating the new knowledge on the role of signaling and redox control, considering that reactive species are coupled to each other and to cellular signaling networks [35, 37] (Fig. **2**). However, there may be an imbalance of redox homeostasis, usually in favor of oxidants; in this case, levels of ROS exceed the physiological levels (up to 100 nM) and become potentially dangerous [8]. This leads to functional disturbances caused by oxidative distress, which determines alterations in biomolecules and signalling pathways. Then oxidative stress was reconsidered as an imbalance between prooxidants and antioxidants in support of the former, which results in the disruption of redox signaling and molecular damage [32, 38], resulting in a wide range of diseases (Fig. **3**).

During acute oxidative stress, the adaptation mechanism relies on cells that respond to and cope with the increased basal level of ROS within a few minutes/hours of the stress [34, 39, 40]. Conversely, chronic oxidative stress is a sustained increase in ROS levels with corruption of antioxidant systems and ROS regulatory patterns, and potential progression to pathological conditions [11, 41]. Oxidative stress is characterized by the generation of high levels of free radicals/oxidants, disruption of redox signaling, the inability of antioxidants to scavenge free radicals, and ineffective repair systems.

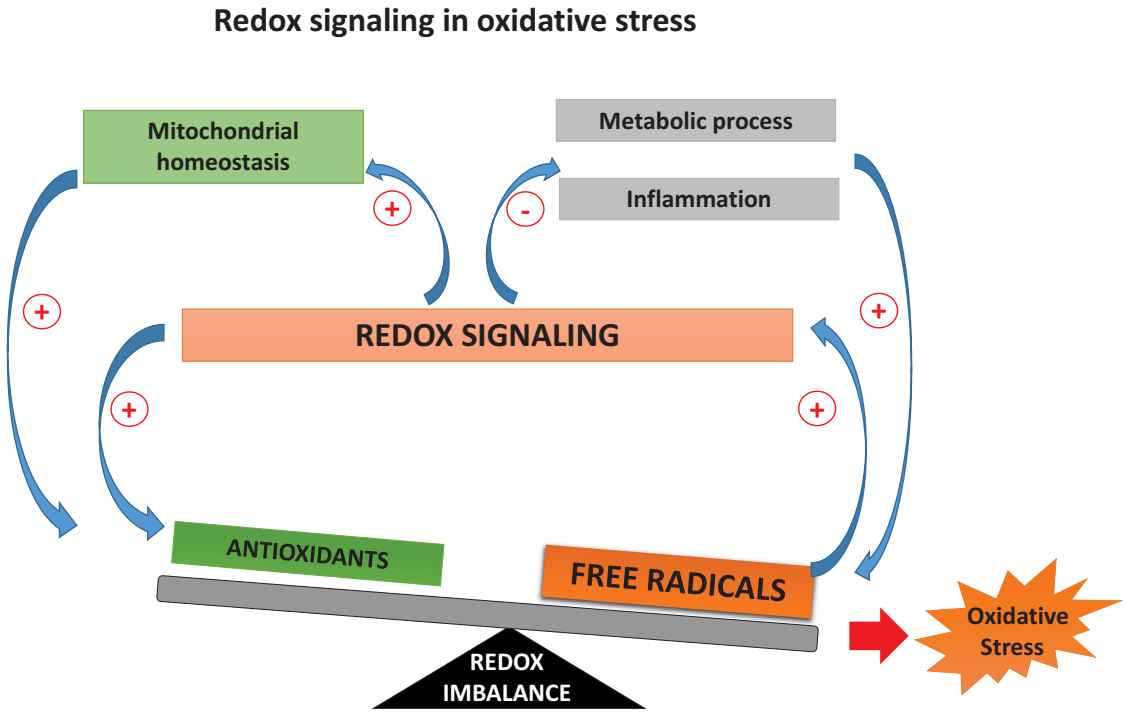

Fig. (2). Redox signaling in oxidative stress. A rise in ROS levels may constitute a stress signal that activates specific redox-sensitive signaling pathways linked to stress. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

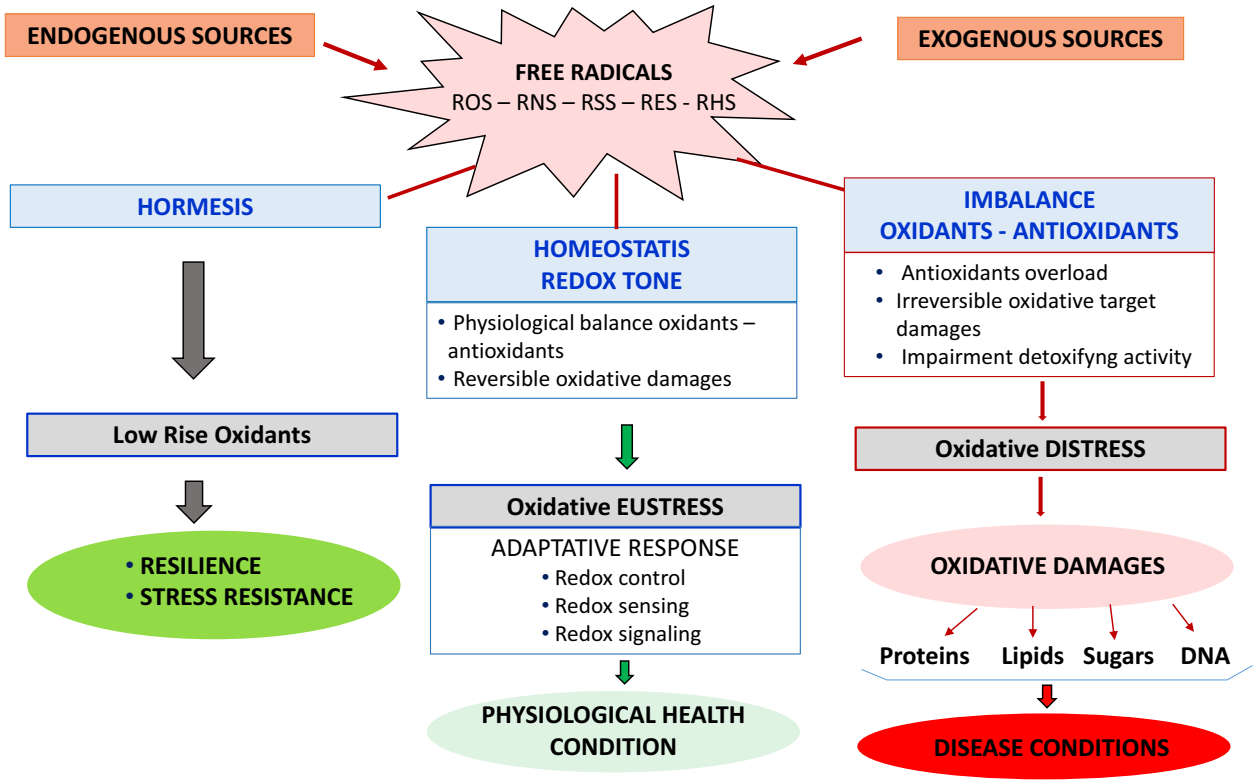

Fig. (3). Representation of free radicals/oxidant and redox signaling in determining oxidative stress. Endogenous and exogenous sources produce oxidants. A low level of oxidative stress is used in redox signaling and redox control (eustress), while a high load, called oxidative distress, leads to the disruption of redox signaling and oxidative damage to biomolecules, which is involved in multiple pathological processes. Adaptive responses regulate and contrast. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.1. Biochemistry of Oxidative Stress

Oxidative stress is associated with several damaged molecular species, including lipids, proteins, sugars, and nucleic acids (Fig. **1**) [25, 42, 43]. Free radicals are generated during normal metabolic processes or following the effect of different environmental factors. Various processes within cells lead to the production of free radicals by enzymatic and/or non-enzymatic reactions. They can be generated by electron leakage during the electron transport chain (ETC), by the activity of xanthine oxidase and aldehyde oxidase, in inflammatory cells as a result of NADPH oxidase activity, in macrophages in the form of nitric oxide ($NO^{\bullet}$), in platelets and leucocytes due to lipoxygenase activity, and in peroxisomes by the cytochrome P450 system during the metabolism of xenobiotics [23, 44, 45]. They are also generated during various stress conditions, inflammation, ischemia, reperfusion, and during exercise [46].

The intracellular sources of chemical reactive species are mainly mitochondria, endoplasmic reticulum, lysosomes, peroxisomes, cytosol, and plasma membrane [23, 47]. The major endogenous enzymatic sources of $O_2^{\bullet-}$ and H_2O_2 are transmembrane NADPH oxidases (NOXs) [48] and the mitochondrial ETC [49]. In the mitochondria, ETC complex I and II release $O_2^{\bullet-}/H_2O_2$ towards the mitochondrial matrix. The release from complex III takes place towards the lumen of the cristae and the intermembrane space; other oxidases produce H_2O_2 in the endoplasmic reticulum and peroxisomes. The mitochondrial ETC and the reactions catalysed by nitric oxide synthase are the main endogenous sources of oxidizing species [48, 50]. During energy transduction, a small number of electrons leak from the inner membrane to form the superoxide radical anions ($O_2^{\bullet-}$) that can lead to other ROS, such as H_2O_2, hydroxyl radicals ($OH^{\bullet}$) and hydroxyl ions (OH^{-}). RNS are produced when O_2•− reacts with nitric oxide (NO•) to generate peroxynitrite (ONOO−). Thus, other types of nitrogenated species are formed, such as nitrogen dioxide (NO2•) and nitrosoperoxycarbonate (ONOOCOO−). Reactive sulfur species, generated by the reaction between ROS and thiols, play an important role in redox signaling for peptides and protein reactions [19]. The reactive electrophile species can be produced through O_2-mediated peroxidation and subsequent fragmentation of poly-unsaturated fatty acids (PUFAs). RES can be produced enzymatically through lipoxygenase-mediated oxygenation; non-enzymatically produced RES include 2-propenal (acrolein), malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) [20, 51]. Both xenobiotic and endogenous electrophiles act as signalling molecules [52]. RES stimulate the expression of genes by reacting with nucleic acids, proteins and small molecules, and indirectly lowering pools of cellular reductants [20].

Hypohalous acids are strong oxidizing agents that react with proteins, lipids, and carbohydrates. The accumulation of

reactive halogen species causes damage to cells and biomolecules and has negative implications in the antioxidant defense [53, 54]. Halogenating stress is closely associated with oxidative, nitrosative, and carbonyl stress, since RHS reactions with various compounds and functional groups lead to the formation of reactive oxygen and nitrogen species and carbonyl compounds [55]. Sources of exogenous oxidants include cigarette smoke, environmental pollution, ionizing/solar radiation (UV, visible, infrared-A), and certain unhealthy diets [56, 57].

3.1.1. Biomolecule Damage

3.1.1.1. Lipid Oxidation

Polyunsaturated fatty acids (PUFAs) and the double layers of phospholipids in the cell membranes are the main sites of lipid oxidation [58, 59]. PUFAs, in particular, arachidonic acid and docosahexaenoic acid (DHA), are likely prone to oxidation with the consequent production of MDA and 4-HNE that are recognized as markers of lipid oxidative decay [60, 61]. Products may stick to the proteins and undermine their function [62]. Peroxidation of PUFAs determines the production of isoprostanes that are products pointing to oxidative stress [63]. The increase in lipid peroxidation affects the integrity of the cell membrane, damages the membrane proteins and receptors, thereby inactivating the enzymes and ion channels [61, 64]. Lipid peroxidation has been implicated in the pathogenesis of several diseases. Aldehyde and other by-products of lipid peroxidation are involved in physiological and pathological conditions of liver, kidney, and brain toxicity. Increased levels of products of lipid oxidation occur in diabetes, atherosclerosis, and liver disease. Oxidative modification of low-density lipoproteins (LDLs) is involved in the development of atherosclerosis and cardiovascular disease [65]. Oxidized cholesterol or fatty acids in plasma LDL can contribute to atherosclerosis [59, 66], Alzheimer's and Parkinson's diseases [67].

3.1.1.2. Protein Oxidation

Proteins are among the major components of cells and are the main targets for free radicals [68], which can cause the unfolding or alteration of the protein structure [69]. Reversible oxidative changes regulate protein activity, whereas irreversible changes in proteins can cause their inactivation with consequent lasting harmful effects. ROS oxidize both the backbone and the lateral chain of proteins and generate carbonyl functions and modification of amino acids**.** Protein modification is initiated by hydroxyl radicals, leading to the oxidation of amino acid side chains, protein cross-binding, and eventually, protein fragmentation. All amino acids are sensitive to oxidation. Cysteines and methionines are readily oxidizable; oxidation of lysine, proline, arginine, and threonine also yields carbonyl derivative markers [70]. Oxidation of plasma thiol causes oxidation protein damage, leading to the final products of advanced glycation [71]. Methionine sulfoxide, 2-oxohistidine and protein peroxides are considered biomarkers of oxidative stress of protein. Protein oxidation leads to backbone fragmentation, unfolding and misfolding, with consequent loss of activity [72]. Increased protein carbonylation levels have been observed in various pathological conditions, such as neurodegenerative and age-related diseases [69, 73].

3.1.1.3. DNA Oxidation

Oxidative damage to DNA is the result of DNA interaction with ROS or RNS. Mitochondrial DNA (mtDNA) is susceptible to oxidative damage due to the lack of protective proteins, such as histones, and limited repair systems [74, 75]. In addition, mtDNA is more vulnerable than nuclear DNA to the effect of ROS because it is close to the ROS generation site, and its mutation rate is about ten times higher than the nuclear one. The main results of RNA oxidation are the breaking of the nucleotide strand and impairment in ribosome function [76].

Free radicals react with DNA by adding bases or extracting hydrogen atoms from the sugar fraction. Free radicals damage nucleic acids, causing DNA protein crosslinks, filament breakage and structural alteration in purine and pyridine bases, resulting in DNA mutations [75]. The hydroxyl radical oxidizes the guanosine or thymine in 8-hydroxy-2-deoxyguanosine and thymine glycol, respectively. Among the bases of DNA, guanine is the most susceptible to oxidative damage. The main mutagenic lesion is 8-oxoguanine or 8-hydroxyquinine, which mates with adenine rather than cytosine, and thus generates transverse mutations after replication [77]. Accumulation of 8-oxoguanine is oncogenic and can cause mitochondrial dysfunction.

3.1.1.4. Carbohydrate Oxidation

Free radicals, such as $^{\bullet}OH$, react with carbohydrates abstracting a hydrogen atom from one of the carbon atoms, producing a carbon-centered radical. Oxidative damage to the sugars of the nucleic acids results in the breaking of the filament. Free carbohydrates produce oxidants, such as reactive carbonyls [78]. Non-enzymatic glycosylation generates glycoxidation products that accumulate in the tissues [79]; the end products of advanced glycoxidation (AGE) and receptor interaction (RAGE) cause glyco-oxidative stress. The first mechanism of damage induced by AGE is a consequence of intracellular accumulation induced by hyperglycemia and the consequent alteration of cytoplasmic and nuclear structures, including proteins involved in the regulation of gene transcription [80]. The binding of AGEs to a specific receptor (RAGE) on the cell surface promotes ROS production and induces transcription factors (NF-kB, MAP kinase), which, in turn, stimulate the production of proinflammatory cytokines and growth factors [81]. This is one mechanism leading to vascular damage [82]. In addition, oxidative and glycol-oxidative stress (carbonyl) plays an important role in the pathogenesis of diabetic nephropathies, as well as in other diabetic complications [83, 84].

3.2. Adaptive Stress Responses

Cells respond to oxidative stress with increased proliferation, cell division prevention, senescence, or cell death mechanisms, such as necrosis and apoptosis. The effects vary with the cell type and are influenced by factors, such as the presence of some receptors on the cell surface, by the mechanisms of signal transduction, and by levels of antioxi-

dant defense. Intracellular free Ca^{2+} and levels of iron catalytic increase in response to free radical reactions [51]. Several cell types respond to mild oxidative stress by proliferation, although this step can lead to tissue fibrosis [85].

Free radicals can play either a physiological or pathological role. For example, NOS is formed during vasodilatation (eNOS) or nerve impulses (nNOS). This step, in turn, produces low levels of NO, which has physiological action. On the contrary, high concentrations of NO (nmol) can damage proteins, lipids, and DNA either directly or after reaction with superoxide, which leads to the formation of the highly reactive nitroperoxide [51, 86]. Superoxide and/or hydrogen peroxide at low concentrations exert a physiological effect on cell proliferation and survival by regulating signal transduction [23]. In contrast, at high concentrations, the compounds stimulate signal transduction pathways of apoptosis or cellular necrosis. The real challenge is the definition of the limit between the negative and positive effects of free radicals, and how it is possible to influence and/or control free radicals.

Stress responses are adaptive mechanisms to overcome stress stimuli. Different stress factors or different stress intensities induce different responses. Mild oxidative stress increases cell proliferation; moderate oxidative stress modifies cell physiology to increase the level of protective systems that make the cell more resistant to subsequent attacks (hormesis), while hard stress triggers severe cellular injury, cellular senescence and/or cell death [87, 88]. Responses to mild and/or moderate stress can be obtained by different systems, including regulation of apoptosis induction [89], repair of damage, and synthesis of protective molecules [87, 90]. Apoptosis can be overcome by activating the anti-apoptotic genes and proteins, such as FLICE inhibiting proteins (FLIP), members of the B-cell lymphoma-2 family (BCL2), inhibitors of apoptosis proteins (IAP), and ROS scavenging molecules [87, 88].

Cells may adapt to stress by up-regulating defense and/or repair systems. When the body's defense protection fails, repair systems recognize damaged molecules and disrupt them by means of proteinases, lipases, or DNA repair systems at the level of modified DNA bases [91, 92]. The removal of damaged macromolecules can be achieved by the ubiquitin-proteasome (UPP) pathway and autophagy. UPP plays an important role in the degradation of soluble proteins, mainly in the cytosol [93]. High oxidative stress condition inactivates the proteasome and inhibits ubiquitination, resulting in the accumulation of oxidatively damaged proteins [93]. Autophagy degrades large cell loads that are first enclosed in double-membrane vesicles delivered to the lysosomes for degradation [94]. Chaperone-mediated autophagy targets and carries some proteins directly through lysosomal membranes through a specific receptor [95].

Cellular repair is mediated through several pathways, including gene expression models [96], DNA repair systems [92], and induction of molecular chaperones [97]. During stress, alterations in transcription are frequently mediated by microribonucleic acids (miRNAs); heat shock factors are considered transcriptional regulators of genes coding for stress proteins, such as molecular chaperones, heat shock proteins, and other stress proteins [98, 99].

The essential detoxification system for breaking down ROS and maintaining the cellular redox state and homeostasis relies on endogenous antioxidants. These include the catalase family of enzymes, the glutathione group, thioredoxin and superoxide dismutase, together with exogenous antioxidants, such as carotenoids, micronutrients and vitamins [100-102].

3.3. Redox Regulation

Redox regulation contributes to the regulation of cellular processes. In multicellular organisms, protection against ROS, nitric oxide, heavy metals, RSS, RES and RHS is primarily mediated by the redox-sensitive signaling pathway. Recent data on ROS [35], RNS [103], RSS [104], RES [105] and RHS [106] indicate the evolution and complexity of multiple free radical interactions in redox control and balance processes [107]. ROS and RNS act as signalling molecules by reversible redox alterations in enzymes that control cellular processes, such as S-nitrosation of caspase-3, which controls apoptosis or kappa β nuclear factor activation (NF-kB) [108, 109]. Other pathways include mitogen-activated protein kinases and tyrosine kinases, and transcription factors [110, 111]. Particularly, transcription factors, such as activator protein-1 (AP-1), $NF\text{-}_KB$, and/or NF-E2-related factor (NRF2), participate in redox-modulated cell signaling [112].

The Keap1-Nrf2 [Kelch-like ECH-associated protein 1-nuclear factor (erythroid-derived 2)-like 2] molecular regulatory mechanism plays a central role in protecting cells against oxidative and xenobiotic stresses [113, 114]. Nrf2 operates as the main transcription factor that controls the basal and inducible expression of an array of antioxidant and detoxification enzymes [115]. It regulates the transcription of more than 200 eukaryotic genes involved in cellular protection against oxidative stress, detoxification of electrophiles, and proteasomal activity [116]. When oxidative stress occurs, cellular activity leads to the activation or silencing of genes that encode defensive enzymes, transcription factors and structural proteins [117]. The analysis of microarray gene expression on a genomic scale [118] enables the evaluation of ROS-responsive genes expressed during oxidative stress.

Both O_2^- and H_2O_2 are important signaling molecules. H_2O_2 peroxide has emerged as the main metabolite operative in sensing, signaling and redox regulation and as a key metabolite in oxidative stress [8, 119, 120]. H_2O_2 is recognized as the major ROS in the redox regulation of biological activities [9, 121]. H_2O_2 modulates the activity of transcription factors in mammalian cells (AP-1, NRF2, CREB, HSF1, HIF-1, TP53, NF-κB, NOTCH, SP1 and SCREB-1) [119]. Physiological concentrations of H_2O_2 (1–100 nM) are considered as the conditions corresponding to physiological oxidative stress (eustress) [32]. As a messenger molecule, H_2O_2 diffuses through cells and tissues to initiate immediate cellular effects, such as cell shape changes, initiation of proliferation and differentiation and recruitment of immune cells; its action may occur by direct oxidation of the target or indirectly by involving peroxiredoxins, a class of peroxidases that reduce hydrogen peroxide and lipid hydroperoxides [122]. Higher concentrations of H_2O_2 in blood plasma lead to

adaptive stress responses through master switches, such as nuclear factor erythroid 2-related factor-2/Kelch-like ECH-associated protein1 (Nrf2/ Keap1) or NF-κB. Supraphysiological concentrations of H_2O_2 (>100 nM) correspond to pathophysiological conditions (distress), leading to biomolecular damage and cellular dysfunctions [32].

3.4. Biomarkers of Oxidative Stress

Identification of oxidative stress biomarkers plays a pivotal role in clinical diagnostics. Biomarker can be defined as "any substance, structure or process that may suffer or predict the incidence of outcomes or diseases and be measured in the body or its products" [123]. Blood and urine are usually used to detect oxidative stress and, in particular conditions, also cerebrospinal fluid and other tissues [124, 125]. Potential markers for clinical and diagnostic purposes exist [124], and classification of oxidative stress biomarkers has been recently proposed [126]. Redox biomarkers can point to lipid peroxidation [127] and oxidation of DNA [128], and are detectable in obesity [129], diabetes [130], cardiovascular diseases [131] or inflammation [132].

The state of oxidative stress can be assessed in different ways: by analyzing free radicals, damaged/oxidized biomolecules, or antioxidants. Direct measurements of reactive species/free radicals, such as $O_2^{\bullet -}$, H_2O_2, and $NO^{\bullet}$, are hard to quantify because they are highly reactive and have a short half-life. Samples must be prepared and analyzed quickly, and this is not always possible in clinical practice.

The different measurement methods include electronic spin resonance (ESR) or electron paramagnetic resonance (EPR) [133], fluorescence magnetic resonance and mass spectrometry techniques [134], magnetic resonance imaging (MRI) [135], or positron emission tomography [136] and immunospin trapping [137]. Flow cytometry is the widely used method, and many fluorescent probes have been developed for the detection of reactive species with different specificity and sensitivity [138]. EPR is a suitable method for measuring ROS, RNS, and their secondary products [139, 140]. EPR spectroscopy permits the direct detection of free radicals at concentrations of up to 1 μM and can detect ROS directly *in vivo* [139]. The concurrent employment of different techniques, *e.g*., EPR, high-performance liquid chromatography (HPLC), fluorescence, and liquid chromatography tandem mass spectrometry (LC-MS/MS), may be the best way to quantify ROS and RNS in biological systems, because these techniques provide useful information to identify the species formed by detecting the specific adducts and final products [141-143].

In addition, the thiobarbituric acid (TBARs) method is widely used to measure lipid peroxides by measurement of MDA concentration [144]. For the measurement of MDA and 4-HNE, immunohistochemical and ELISA methods could also be used [145]. Isoprostanes are regarded as the most reliable markers of oxidative stress in humans [63]. These compounds are specific and relatively stable products of lipid oxidation and provide information regarding the oxidative status of an individual; they are found in body fluids, such as blood and urine at detectable levels, and so can be measured without the need for invasive procedures [63]. For the measurement of F2-isoprostanes, gas/liquid chromatography combined with mass spectroscopy techniques (HPLC/ GC-MS) is recommended [63], while commercial immunoassays are less suitable [146]. Oxidation of thiol groups takes into consideration the oxidative damage of proteins, together with the carbonylation that leads to advanced glycation end products. The measurement of additional carbonyl groups in proteins formed because of their oxidation induced by ROS was measured quantitatively with 2,4-dinitrophenylhydrazine [147]. Given the wide range of pathways involving ROS, some authors measure the redox state of thiols in ROS targets [148]. ROS oxidise specific protein residues of cysteine into sulfenic acid in a reversible manner; this molecule acts as an oxidative stress/nitrosative stress sensor within enzymes and transcriptional regulatory factors and may enable priming of the paths of the versatile ROS action [149]. Markers of damage to nucleic acids are represented by derivatives of modified guanidine, of which 8-hydroxyguanine is the most commonly used [150]. Kits for measuring enzymatic antioxidant activity, such as that of superoxide dismutase, catalase, or glutathione peroxidase, are available on the market. One method simultaneously evaluates glutathione levels, hydrogen peroxide and superoxide in a single cell, together with alterations in cell viability, thus allowing both the oxidant-antioxidant balance and cell death to be defined, following the administration of a specific stimulus [151]. In some cases, levels of low-molecular-weight antioxidant substances, such as ascorbic acid [152], tocopherol [153], uric acid [154], carotenoids and anthocyanins, are measured and used as markers of oxidative stress [155]. The measurement of antioxidant capacity comprises different assays known as total antioxidant capacity, total antioxidant state, biological antioxidant potential, oxygen radical absorbance capacity, or ferric reducing antioxidant potential. Many studies have applied these capacity tests but none of them are universal and they have been the subject of some controversy in the literature [156]. They only consider the quenching potential of the sample itself with respect to an artificial radical source used for the specific assay. Most of the antioxidant activity in plasma originates from uric acid; thus, a high concentration of uric acid may lead to an incorrect interpretation of test results [157].

The redox state can be measured through the variations in the response of the defense systems to oxidative stress by evaluating the protein residues of the cysteine, the pool of antioxidants, the enzymes that generate ROS and the transcription factors that regulate them [158-160]. However, the techniques and methods used have shown limitations; therefore, a redox state index has been proposed, *i.e*., a global index of oxidative stress, based on a coordinated evaluation of pro-oxidant and antioxidant biomarkers [161-163].

4. IMPLICATIONS OF OXIDATIVE STRESS IN DISEASES

The imbalance between free radicals/oxidants and antioxidant defenses leads to oxidative stress, cellular damage, and tissue injury (Fig. **4**). Excessive oxidative stress, acting either as a cause or consequence, is likely correlated with over 200 clinical disorders. The mechanisms involve an imbalance between antioxidant and pro-oxidant factors. In the following paragraphs, we describe the potential implications of oxidative stress in a series of chronic diseases, such as

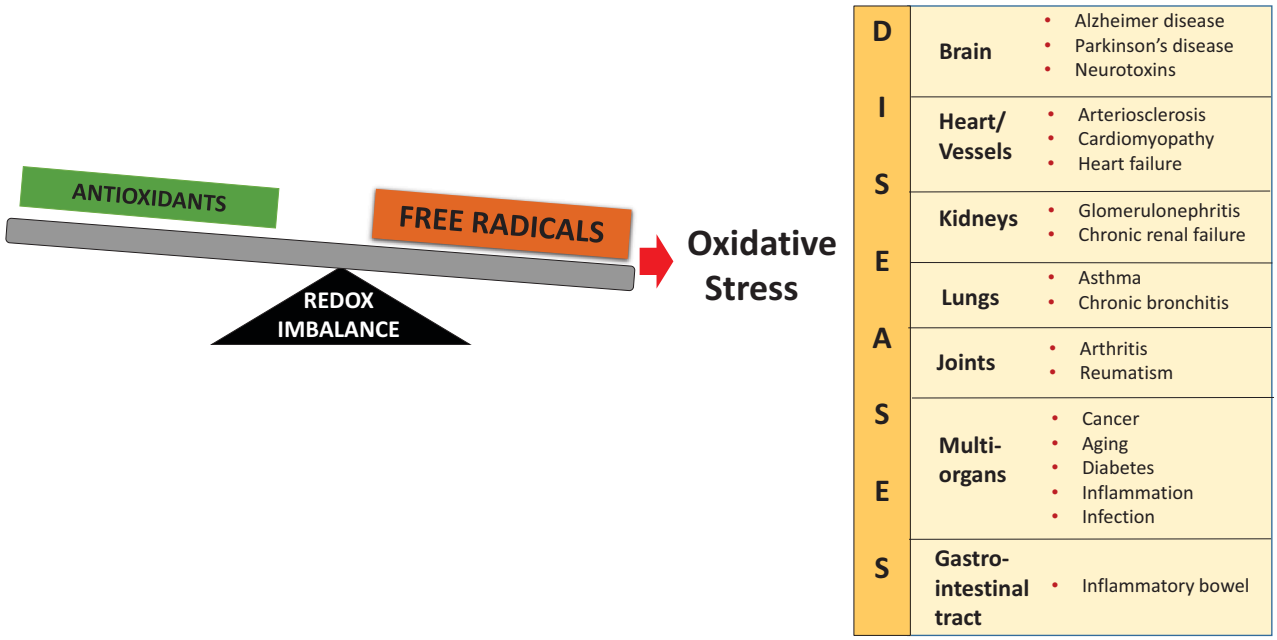

Fig. (4). Schematic representation of oxidative stress damage promoting diseases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

diabetes, cardiovascular diseases, neurodegenerative diseases, and other inflammatory and immune disorders.

4.1. Diabetes Mellitus

The term diabetes mellitus encompasses three main etiological entities. Type 2 diabetes (T2DM) accounts for over 90% of cases in Europe, the United States, and Canada (ranging from insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance), while type 1 diabetes (T1DM) accounts for 5-10% of cases (consisting of pancreatic beta-cell destruction, a condition leading to absolute insulin deficiency). The third form of diabetes is due to other causes [164]. The global prevalence of T1DM is 5.9 per 10,000 people, while the incidence has increased over the last 50 years, currently estimated to be 15 per 100,000 people per year [165].

Genetic defects can play a role, but monogenic causes of T2DM are only a small number of cases. Indeed, most cases due to genetic risk originate from the interaction of complex polygenic risk factors. The gut microbiota appears to play a pathogenic role in contributing to the development of T1DM mainly through modulation of the immune system [166] and to T2DM because of the critical role played in the maintenance of metabolic homeostasis [167-170].

According to the current diagnostic criteria [171], it is necessary to differentiate between diabetes mellitus and prediabetes mellitus, which consists of impaired fasting glycaemia (IFG) and impaired glucose tolerance (IGT) [172]. In particular, the diagnosis of diabetes mellitus requires the assessment of fasting plasma glucose (FPG) with levels ≥126 mg/dL or haemoglobin A1c (HbA1c) ≥6.5% and, if still in doubt, oral glucose tolerance test (OGTT) needs to be conducted with a 2 h plasma glucose ≥200 mg/dL or the presence of symptoms plus a random plasma glucose (RPG) ≥200 mg/dL. The diagnosis of pre-diabetes mellitus by IGT requires an FPG <126 mg/dL and a 2 h plasma glucose ≥140 to 199 mg/dL. The diagnosis by IFG is based on FPG of 100-125 mg/dL and a 2 h plasma glucose <140 mg/dL.

Diabetes mellitus is associated with oxidative stress [173, 174]. The increased production of free radicals caused by hyperglycaemia occurs through increased glycolysis, activation of the sorbitol pathway, autoxidation of glucose, and protein glycation [175]. Insulin preserves glucose homeostasis by regulating the metabolism of sugars, proteins, and lipids. Insulin resistance has a significant influence on liver, skeletal muscle, and adipose tissue activity [176]. Oxidative stress is associated with reduced glucose uptake in muscle and fat cells and reduces insulin secretion in pancreatic beta cells [177, 178]. Hyperglycemia increases the production of ROS in cells, confirmed by high levels of MDA. Oxidative stress induced by hyperglycemia inhibits insulin secretion in pancreatic beta cells through the activation of a protein decoupling-2 (UCP-2), which reduces the ATP/ADP ratio by the release of protons into the cell [84]. Mitochondrial oxidative stress is associated with insulin resistance, T2DM and its complications [179, 180]. A positive association exists between the urinary concentration of an oxidative stress marker, the 8-epi-prostaglandin F2α (8-epi-PGF2α), insulin resistance [181] and reduced tolerance to glucose [182].

With oxidative stress, the overproduction of free radicals induces several signaling cascades leading to the transcription of stress-related genes. This latter step promotes the onset of diabetic complications [183]. Epigenetic factors regulate the translation of genes that generate ROS or proinflammatory genes in the context of hyperglycemia [184], also related to the concept of hyperglycemic memory, according to which the complications caused by hyperglycemic stress persist even after the normalization of glucose levels [185]. The micro-RNA (miRNA) involved in the post-

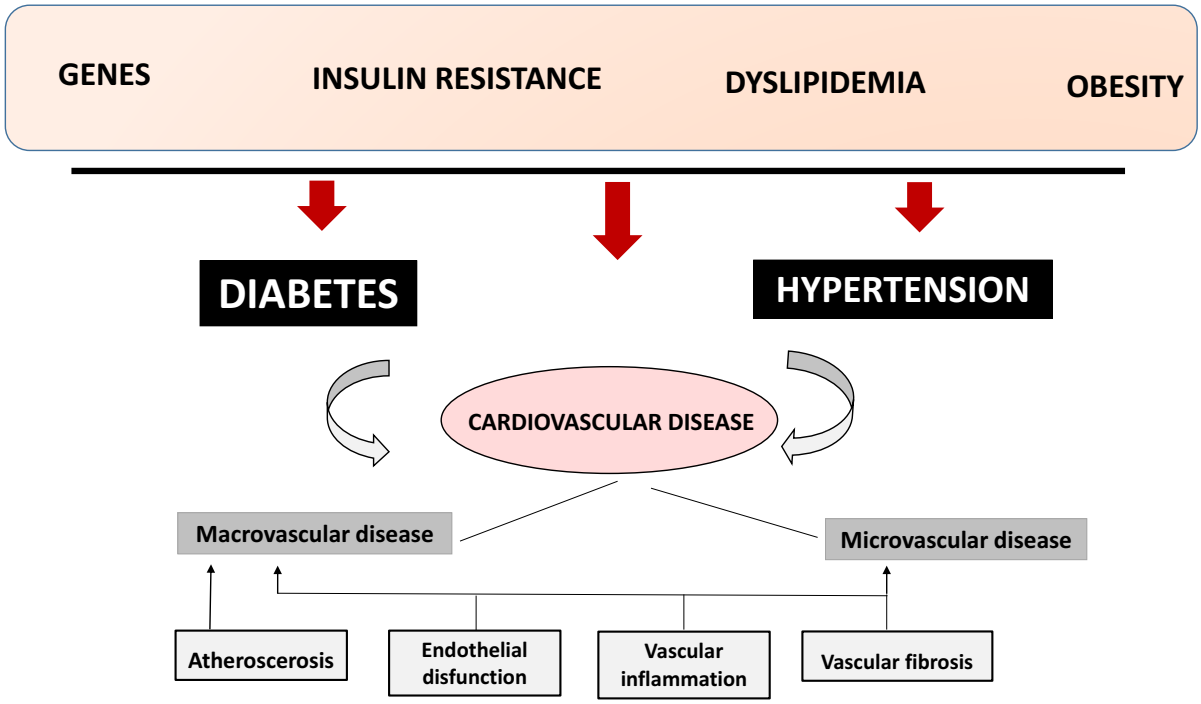

Fig. (5). The role of oxidative stress in diabetes, hypertension, and cardiovascular diseases. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

transcriptional regulation of gene expression can serve as potential biomarker of T2DM [186].

Diabetes is considered the major risk factor for cardiovascular diseases (CVD), and involves both macro- and microvascular diseases. The ongoing endothelial dysfunction in T2DM is also associated with blood hypertension [187, 188] (Fig. **5**). Hyperglycaemia and insulin resistance play a crucial role in initiating vascular complications through oxidative stress, activation of the AGE-RAGE axis and inflammation [189]. Macrovascular disease or CVD is an inflammatory process that leads to myocardial infarction, stroke, and lesions of the peripheral vessel.

Diabetic complications involve different mechanisms [84, 190], such as an increase in the flow of glucose and other sugars *via* the polyol pathway, an increase in the formation of end products of AGE *via* the hexosamine pathway, the expression of their receptor RAGE [191], and activation of the protein kinase C (PKC) pathway through diacylglycerol (DAG). These mechanisms increase the production of glycative, glycoxidative and carbonyl free radicals [84, 192, 193]. Hyperglycemia can lead to the reaction of peroxidation in lipids and proteins and an increase in genotoxicity and apoptosis, thus having a significant impact on the mechanisms of DNA repair [194]. Oxidative damage to mitochondrial DNA leads to the death of axon cells, provoking neuropathies [195]. AGEs inhibit axonal regeneration [196]. Increased DNA damage and stimulation of the PKC pathway, and NF-κB and TGF-β increase extracellular matrix deposition [197] involved in neuropathy. High AGEs may result in diabetic retinopathy [198]; vision is impaired by the progressive accumulation of AGE in the crystalline and retina, which causes the death of retinal cells [198].

Diabetes mellitus (type 1 and 2) leads to macro- and micro-vascular complications [199], while in T2DM, oxidant stress promotes prothrombotic reactions, leading to cardiovascular complications [200]. In addition to hypertension [201], diabetes can cause distinct pathological alterations in the myocardium, referred to as diabetic cardiomyopathy, regardless of its effect on blood pressure and coronary atherosclerosis [202].

4.2. Cardiovascular Disease

According to the World Health Organisation (WHO), CVD is the leading cause of death worldwide. CVD is a complex of heterogenous pathophysiologic conditions directly or indirectly associated with increased oxidative stress [203]. Atherosclerosis is the leading cause of CVD, with high rates of mortality and morbidity worldwide due to coronary, carotid artery disease, renal artery stenosis, and peripheral artery disease [204]. The biomarker of oxidative degeneration in obesity and related metabolic syndrome is a low-density protein (ox-LDL) that, within the vascular endothelium, leads to the expression of the chemotactic protein-1 of monocytes, which promotes vascular endothelial dysfunction and increases thrombogenicity and thus represents the central step in the development of atherosclerosis. Ox-LDL is atherogenic and causes the formation of atherosclerosis plaques. In addition, ox-LDL is cytotoxic and may cause direct damage and apoptosis to endothelial cells [205].

The dysmetabolism that occurs in obesity and related disorders, such as prediabetic, diabetes, and metabolic (dysfunctional)-associated fatty liver diseases (MAFLD), includes increased concentrations of circulating free fatty acids, which activate the PKC directly and indirectly by induc-

ing *de novo* synthesis of DAG in endothelial cells [206]. PKC contributes to the onset of cardiac fibrosis through the upregulation of TGF-β expression and connective tissue growth factor [207]. Moreover, PKC increases vascular permeability by increasing the expression of vascular endothelial growth factor (VEGF) [208].

In the vascular endothelium, different enzymes are involved in the production of free radicals and reactive species, including NADPH oxidase, mitochondrial enzymes, xanthine oxidase, myeloperoxidases, lipoxygenases, and endothelial nitric oxide synthase (eNOS) [209]. Those enzymes are stimulated by different risk factors, such as hyperglycemia, diabetes, hypertension, and smoking, resulting in the overproduction of ROS.

Diabetes also affects the heart muscle, causing heart failure, both systolic and diastolic. The mechanisms underlying heart disease are complex and may include impaired calcium homeostasis, lipid accumulation, increased fatty acid oxidation, abnormal autophagy, increased fibrosis and rigidity, increased NADPH oxidase activity, mitochondrial dysfunction and DNA repair malfunction [210, 211].

4.3. Carcinogenesis

Free radicals play an essential role in carcinogenesis. Oxidative stress may cause unregulated cell growth and carcinogenesis [212]. Oxidative stress is involved in three different stages of cancer development, namely beginning, progression and promotion [213]. In the initial phase, ROS cause a mutation that continues to accumulate if the DNA is not repaired [214]. Cancer cells are more prone than normal cells to mitochondrial dysfunction due to their higher metabolic rate [215]. Tumour cells exhibit high levels of oxidative stress due to the activation of oncogenes and loss of tumour suppressors [216]. By altering growth signals and gene expression, free radicals cause the continuous proliferation of cancerous cells [56]. Cancer cells alter metabolic processes and stimulate increased ROS production [217]. ROS can also alter the expression of oncogenes or tumour suppressor genes by epigenetic modifications, such as methylation or acetylation [218]. The tumours show several characteristics, including sustained proliferation, resistance to apoptosis, angiogenesis, invasion and metastasis, and inflammation that promotes the tumour [219]. Oxidative stress activates cell signalling pathways and increases blood supply to cancer cells and promotes their metastasis [220]. The high level of ROS plays a significant role in the expansion of cancer cells by altering the genes associated with apoptosis, cell proliferation, and transcription factors [43]. ROS subregulate pro-apoptotic proteins by interfering with the signalling pathway of phosphoinositide 3-kinase PI3K/Akt and ERK cells and over-regulate anti-apoptotic genes [221, 222]. During the progression of cancer, ROS disturb cellular processes and upregulate the production of metalloproteinases, preventing the process of angiogenesis by means of antiproteases and provoking the metastasis of tumor cells [214, 217, 223]. High levels of oxidative stress markers and a significant decrease in total antioxidant capacity have been observed in patients with breast, lung, prostate and colorectal cancer [224-226].

4.4. Inflammatory Diseases

Oxidative stress and inflammation are closely interrelated since oxidative stress can cause inflammation which, in turn, can induce oxidative stress [227, 228]. Both oxidative stress and inflammation cause injury to cells. Inflammation is usually considered as a protective complex reaction in response to exogenous and endogenous stimuli. Generation of O2•−, HOCl, and H_2O_2 by phagocytes is important for defense against various bacterial and fungal strains [229]. There are two stages of inflammation, acute and chronic inflammation. Acute inflammation is an early stage of inflammation (innate immunity), mediated by the activation of the immune system; it persists only for a short time and is usually beneficial to the host. If the inflammation lasts for a longer period, chronic inflammation occurs, which may predispose the host to various chronic diseases [230].

At the site of the stimulus, there is the infiltration of inflammatory cells, such as neutrophils, monocytes, and lymphocytes, which release numerous enzymes (neutral protease, elastase, collagenase, acid hydrolase, phosphatase, and lipase), reactive species (O2•−, OH•, H_2O_2, HOCl, ONOO, and NO), and chemical mediators (eicosanoids, complement components, cytokines, chemokines, and nitric oxide), which induce tissue damage and oxidative stress [230]. ROS/RNS trigger intracellular signalling cascade that stimulates proinflammatory gene expression [231]. The expression of numerous genes involved in inflammation is controlled by NF-κB, such as cycloxygenase-2 (COX-2), vascular endothelial growth factor (VEGF), pro-inflammatory cytokines (IL-1, IL-2, IL-6 and TNFα), chemokines (IL-8, MIP-1α and MCP-1), adhesion molecules, growth factors, immunoreceptors, and other factors involved in the proliferation and invasion process [232]. A prolonged and/or uncontrolled inflammatory process can lead to tissue damage and cause many diseases [230].

4.4.1. Rheumatoid Arthritis

Rheumatoid arthritis is a chronic multisystemic disease characterised by synovial inflammation, swollen joints, morning stiffness, destruction of articular tissue, joint deformity, loss of appetite and weakness [233-235]. Oxidative stress must play a role in the pathogenesis of rheumatoid arthritis since both ROS and RNS can damage the cartilage. Oxygen metabolism and increased ROS production have an important role in the pathogenesis of rheumatoid arthritis [236, 237]. Macrophages and T cells trigger synovitis [238], activating ROS production by tumor necrosis factor-α (TNF-α) and interleukin (IL-1) [239]. ROS can provoke the death of chondrocytes and promote joint damage [240]. Synovial fluid exhibits a high level of lipid peroxidation, and serum MDA is positively associated with proinflammatory cytokines [241]. Tissue damage caused by inflammation triggers the production of $NO^{\bullet}$ by the articular chondrocytes and synovial fibroblasts [237]. High levels of $NO^{\bullet}$, MDA, protein carbonyls, oxidised hyaluronic acid and oxidised LDL have been reported in patients with rheumatoid arthritis [242-244].

4.4.2. Inflammatory Bowel Disease

Intestinal inflammation associated with oxidative stress plays an important role in various gastrointestinal diseases, such as inflammatory bowel diseases [245, 246], attributed to the excessive formation of ROS [247]. Inflammatory bowel diseases, namely Crohn's disease and ulcerative colitis, are characterised by chronic inflammation and swelling associated with oxidative stress in the gastrointestinal tract [246]. Food particles, pathogens, or microbiota imbalance may irritate the gastrointestinal tract causing increased production of ROS, the decay of endogenous antioxidant defense [248], and oxidative stress, which destroys the intestinal epithelial barrier and permeability and exacerbates inflammation [246, 249]. The release of cytotoxic reactive oxygen metabolites by over-stimulating phagocytes has been observed in the inflamed intestinal mucosa [250] as well as other sources of ROS, including enzymes, such as cyclooxygenase, xanthine oxidase, and 5-lipoxygenase [251].

4.4.3. Diseases of the Immune System

Inflammation and activation of the immune system play an important role in the pathogenesis of kidney disease. Acute renal damage (AKI) is commonly linked to bacterial infections, sepsis or ischemia-reperfusion damage (I/R) that can lead to chronic renal disease [252]. Chronic kidney disease (CKD) is often associated with diabetes, hypertension, obesity, and autoimmunity. AKI can lead to CKD, and the two conditions are inextricably interconnected [253]; if not controlled, both can lead to end-stage renal disease. Several factors are involved in kidney disease, including the complement system, toll-like receptors (TLRs), dendritic cells, macrophages, natural killer cells (Nks), and inflammatory cytokines. The mechanisms involved in the progression of CKD involve a complex interaction between hemodynamic, immunological, metabolic and inflammatory events [254]. Changed complement regulation is implicated in the development of chronic kidney disease [255]. Activation of TLRs triggers a number of intracellular pathways, such as the N-terminal c-Jun kinases (JNK), the mitogen-activated protein kinase (MAPK) and NF-kB, which culminate with the secretion of proinflammatory cytokines and chemokines [256]. TLRs are directly related to the severity of kidney disease and inflammatory markers [257, 258], and thus to CKD. Both AKI and CKD, including autoimmune glomerulonephritis, are linked to an increase in the number of macrophages in the kidney [259]. Macrophages act as important mediators of inflammation and immune modulation, and are prevalent in the kidneys of patients with chronic renal disease [260]. Activated macrophages release inflammatory cytokines, promote oxidative stress, and lead to the development of renal fibrosis [261]. Once this process is activated, it becomes progressive, leading to end-stage renal disease. Injury and inflammation are mediated by the release of inflammatory cytokines derived from macrophages, such as interleukin (IL-1, IL-6, IL-23), and the generation of ROS/RNS implicated in impaired renal function [262]. Many cytokines increase the activation of NF-κB, the transcription factor that further promotes the proinflammatory phenotype [263]. In fact, the expression and/or activation of NF-kB increase in the kidneys of patients with glomerulonephritis [264], diabetic nephropathy [265], and acute kidney injury [266].

4.5. Disorders in the Respiratory System

The correlation between chronic inflammation and oxidative stress is implicated in disorders of the respiratory system, such as asthma and allergic rhinitis [267-269]. The increased presence of superoxide radical anions, hydroxyl radicals, and peroxides may promote several alterations in nasal and airway mucosa [269]. The involvement of oxidative stress in allergic rhinitis is believed to be identical to that expressed in asthma [270]. Asthma is the most common disorder of the respiratory system [271]. High levels of oxidative stress markers, such as hydrogen peroxide, 8-isoprostane, nitric oxide, and carbon monoxide, have been reported in the exhaled air of asthmatic patients [272]. In allergic rhinitis, many inflammatory cells, such as mast cells, CD4-positive T cells, B cells, macrophages, and eosinophils, penetrate the nasal mucosa exposed to the allergen [269]. Respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), are common conditions responsible for many deaths throughout the world [271, 273]. Oxidants, such as atmospheric pollutants and cigarette smoke, contribute to increasing oxidative stress, directly damaging the alveoli and connective tissues of the lungs, thus exacerbating the development of COPD [274]. Overproduction of ROS can activate inflammatory cells, which in turn generate more ROS in the lungs, triggering a vicious cycle of chronic inflammation and oxidative stress, as observed in COPD [274].

4.6. Neurodegenerative Diseases

In neurodegenerative disorders, various pathological mechanisms are due to oxidative stress, including alterations in antioxidant systems, cytotoxicity, mitochondrial dysfunction, deregulation of redox balance and alterations in redox trace metals, neuroinflammation, dysfunction in protein metabolism and proteasome, and formation of advanced glycation end products [275]. The central nervous system is a very active organ; it requires about 20% of the total energy consumption of the body [276], thus containing a high amount of mitochondria, particularly active, resulting in a high amount of ROS [277]. The demand for energy is remarkably high in neurons to maintain axonal transport and neuronal conduction, as well as in oligodendrocytes to maintain myelination; therefore, mitochondrial dysfunction has been associated with axonal degeneration and impairment of viability of oligodendrocytes [277, 278]. The central nervous system is particularly susceptible to oxidative damage due to the presence of high lipid content, high consumption of oxygen, and low levels of antioxidant enzymes, such as SOD, mainly localized in neurons, and glutathione (GSH) in astrocytes [279]. Brain regions, such as the hippocampus, substantia nigra, and striatum are particularly susceptible to attack by free radicals [280, 281]. Lipid peroxidation by ROS leads to the progressive loss of membrane fluidity, decreases membrane potential, and increases permeability to ions, such as Ca^{2+}. The exhaustion of membrane phospholipids, deriving from lipid peroxidation, has been considered the main cause of neurodegenerative diseases [282, 283]. The interaction

between oxidative stress and neuroinflammation leads to amyloid-β (Aβ) generation [284]. The β-amyloids reinforce the ability to start lipid peroxidation. Lipid peroxidation can induce neuronal death through multiple mechanisms, such as impairment of ion pump functioning (both Na^{+}/K^{+}- ATPase and Ca^{+2}-ATPase) and glucose and glutamate transporters [285]. Inflammation and immune system alterations have been linked to neurodegenerative disorders [286]. The proinflammatory cytokines and other inflammatory mediators, such as prostaglandins and complement factors, favour the recruitment of peripheral immune cells, promoting neuroinflammation. Alzheimer's and Parkinson's diseases are considered the most common neurodegenerative disorders.

4.6.1. Alzheimer's Disease

Alzheimer's disease is the most frequent cause of dementia in the elderly [26, 287] and is caused by the interaction between genetic profile and environmental factors. Oxidative stress is one of the most important factors in the pathogenesis of Alzheimer's disease. Mild cognitive impairment, which has been proposed as an intermediate state between normal aging and dementia, indicates that oxidative stress damage in Alzheimer's disease may occur before the onset of the disease and contribute to the development of Alzheimer's disease [288]. Microglia can hyperactivate and produce high amounts of ROS/RNS, leading to neuroinflammation and cell death [289].

Neurobiological mechanisms involved in the pathogenesis of Alzheimer's disease are complex (Fig. **6**). According to the common hypothesis, amyloid-β aggregation is the main factor underlying Alzheimer's disease, and is associated with oxidative stress [290]. Alzheimer's disease is characterized by selective neuronal death and two pathological signs, that is, senile plaques formed by extracellular deposits of amyloid-β peptides (Aβ) and neurofibrillar tangles (NFTs) composed of intracellular aggregations of hyperphosphorylated tau protein [291]. The Aβ peptides are generated after the enzymatic cleavage of the amyloid precursor protein by three enzymes, ɣ-secretase, β-secretase and α-secretase [292]. β-amyloid plaques cause cytotoxicity and are the central actors involved in the pathogenesis of Alzheimer's disease [293]. The oligomers Aβ induce oxidative stress through the peroxidation of proteins and lipids, making them unstable and dysfunctional, thereby leading to the progression of Alzheimer's disease [294].

NFTs consist of arrays of coupled helical filament structures, which mainly contain auto-aggregated hyperphosphorylated tau, a multifunctional protein involved in the assembly and stabilization of microtubules [295]. Hyperphosphorylation of tau proteins causes the helical and straight filaments to form neurofibrillary tangles. Oxidative stress plays a role in the hyperphosphorylation and polymerization of tau by the oxidation of fatty acids [296]. The role played by Aβ-oligomers in inducing hyper-phosphorylation of the tau protein through activation of glycogen synthase kinase-3 beta (GSK-3β) has been identified as a link between Aβ-plaques and tau pathologies in the progression of Alzheimer's disease [297]. Abnormal hyperphosphorylation of tau destabilizes microtubules by breaking the axonal transport process and depriving neurons of trophic factors necessary for their survival, thus causing neurodegeneration and

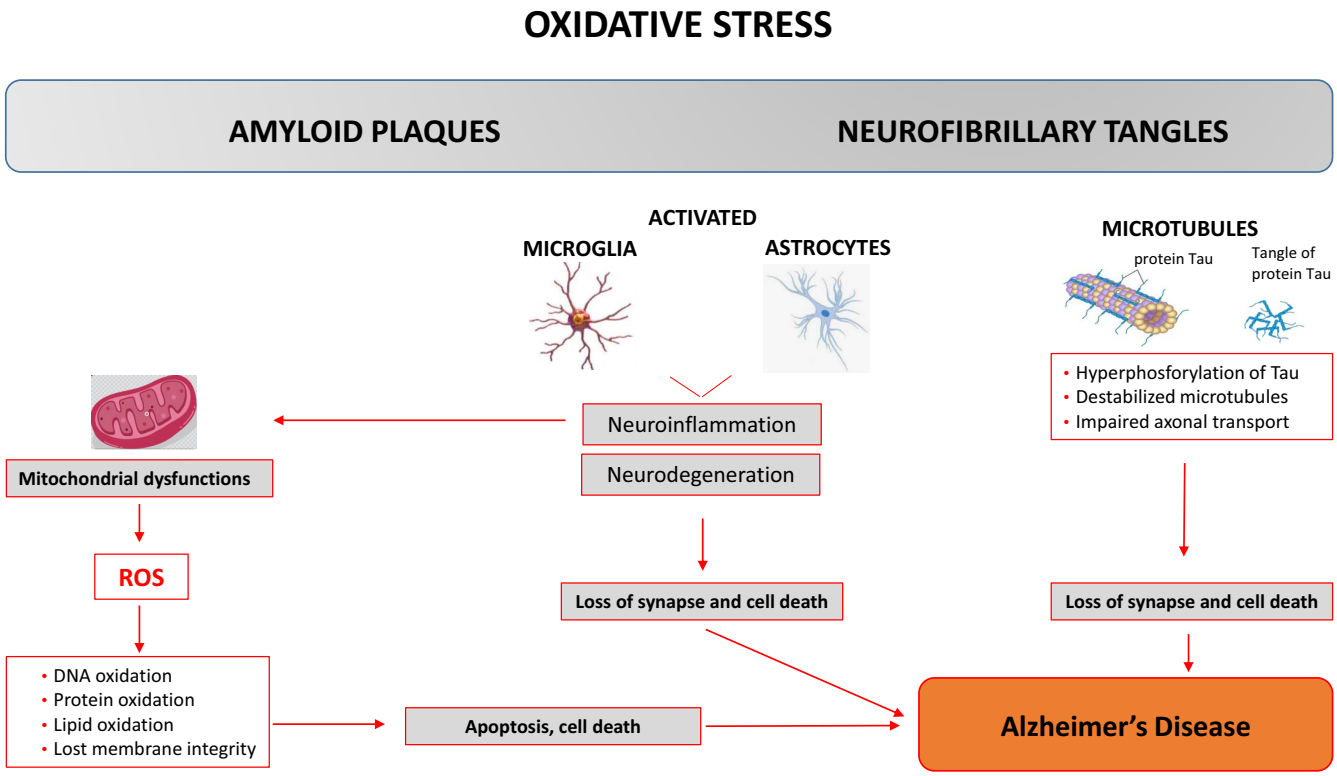

Fig. (6). Neurobiological mechanisms involved in the onset and development of Alzheimer's disease. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

neuronal death [298]. The hyperphosphorylation of the tau protein causes its dissociation from microtubules, promoting the union of the hyperphosphorylated tau wires. Many tau phosphorylated wires join together to generate NFTs that can block synaptic junctions, thus causing the interruption of axonal transport and the death of neuronal cells.

Vascular dysfunctions and mitochondrial and metabolic dysfunctions contribute to Alzheimer's disease [284, 288]. Mitochondrial dysfunction plays a crucial role in the pathogenesis of Alzheimer's disease. Aggregation of amyloid β proteins and increased influx of calcium ions cause a rapid increase in ROS/RNS that trigger oxidation processes of DNA, proteins and lipids, and the loss of membrane integrity and cell death, which are distinctive features of neuronal degradation and Alzheimer's disease development [299]. The convergence of Aβ and tau pathologies in mitochondria dysfunction has been demonstrated in the brain of animals [300]; it leads to synaptic loss and neuronal death [301].

Many studies indicate the relationship between the oxidative imbalance induced by Aβ and the high levels of lipid peroxidation by-products (4-hydroxylamine, malondialdehyde), protein oxidation (carbonyl) and DNA/RNA oxidation (8-hydroxydeoxyguanosine, 8-hydroxyguanosine) [288, 299, 302]. Lipid oxidation products, such as 4-hydroxyenal (HHE), already increase in the first phase of the disease [303], and may increase ɣ-secretase activity and thus β-amyloid accumulation [304, 305]. High levels of β-amyloid were observed in the cortex and hippocampus of Alzheimer's disease patients, and associated with high levels of oxidative markers resulting from lipid, protein, and DNA oxidation [290, 306].

Much evidence has shown that the presence of extensive oxidative stress is a characteristic of Alzheimer's disease in addition to the established pathology of senile plaques and NFT [302]. High levels of reactivity and hippocampal cytotoxicity have been detected for HNE, which is able to accumulate in significant amounts in Alzheimer's disease [307, 308]. Protein carbonylation, also because of the degradation induced by oxidative stress, has been observed in the frontal cortex and in the parietal and hippocampus regions of the brain in Alzheimer's disease [309, 310]. Recognized markers of oxidative stress, including acrolein, MDA, F2- isoprostanes and HNE, protein carbonyls and 3-nitrotyrosine, have been observed in the brain and in cerebrospinal fluid of patients with Alzheimer's disease or mild cognitive impairment [285, 311]. Among the products of lipid peroxidation, 4-HNE and acrolein are highly reactive, and both induce apoptosis and disrupt the ionic homeostasis of neuronal cells [312]. In addition to free radical damage, changes in the activities or expression of antioxidant enzymes, such as SOD and catalase, have been observed in both the central nervous system and peripheral tissues of patients with Alzheimer's disease [313].

Neuroinflammation is a fundamental hallmark of Alzheimer's disease that involves both cellular and molecular players in the loss of synapses and cellular death, brain atrophy, and cognitive decline [286, 314]. Cytokines, chemokines, ROS, and complement proteins are proinflammatory intermediates that are released by both microglia and astrocytes [315]. Amyloid Aβ attracts and activates both microglia and astrocytes, leading to neuronal death [316]. The accumulation of Aβ plaques induces the activation of the complement system that can cause neuronal damage and death. The complement C3a peptide stimulates the recruitment of peripheral immune cells in the brain [317]. Aβ deposits can activate NLRP3 inflammasome and induce the production of interleukin (IL)-1β and IL-18, which contribute to the pathogenesis of Alzheimer's disease and cause cognitive deterioration [318, 319]. Cellular components of the immune system, such as granulocytes, monocytes, natural killer cells and T cells, may participate in the pathogenesis of neuroinflammation and the development of Alzheimer's disease [320].

4.6.2. Parkinson's Disease

Oxidative stress and inflammation play a fundamental role in the pathogenesis of Parkinson's disease [321, 322]. The underlying mechanisms are not well defined. Parkinson's disease, which affects learning, memory and motor control, is characterized by a gradual loss of dopaminergic neurons, especially in the midbrain area called the substantia nigra, and agglutination as well as α-synuclein build-up [75]. The redox imbalance causes oxidative damage to these neurons, alteration of the synthesis and metabolic activities of dopamine, and the formation of quinine that leads to a further increase in oxidative stress [281]. Dopaminergic neurons are exposed to ROS and RNS throughout their life through the actual metabolism of dopamine. Dopamine is a relatively unstable molecule in nature and undergoes an auto-oxidation process in the strial tract, thereby producing ROS [323]; auto-oxidation itself may increase with age [324]. Markers of lipid peroxidation, such as MDA and 4-HNE, have been found in the substantia nigra of Parkinson's disease patients [325]; also, high levels of 8-hydroxysideguanosine associated with mitochondrial DNA alterations in unaffected dopaminergic neurons [326], protein carbonyls resulting from protein oxidative damage [327], and nitration and nitrosylation of proteins resulting from the action of RNS [328], have also been found to be present in the brains of patients with Parkinson's disease. The pathological sign of the disease is the accumulation of fibrous protein deposits in neuronal cytoplasm (Lewy bodies) and nerve fibres (Lewy neurites) in the brain [329].

Inflammation is an important factor in the initiation and development of Parkinson's disease [321]. Microglial reactivity is an early and characteristic feature of Parkinson's disease [330]. Glial cells can cause neurotoxicity and trigger a series of inflammatory reactions [331]. Patients with Parkinson's disease often exhibit innate immune system activation and increased inflammatory markers, mainly IL-1β, IL-6, and TNF-α [230].

5. ANTIOXIDANTS AND THEIR SUPPLEMENTATION

5.1. Characteristics of Antioxidants

In biological systems, organisms develop a series of mechanisms against oxidative stress induced by free radicals. Such mechanisms include preventive defenses, repair mechanisms, and antioxidant defenses [332, 333]. Antioxi-

dants act as radical scavenger, hydrogen donor, electron donor, peroxide decomposer, singlet oxygen quencher, enzyme inhibitor, synergist and metal-chelating agents [334]. Antioxidants prevent tissue damage induced by free radicals by preventing the formation of radicals, scavenging them, or by promoting their decomposition. Antioxidant systems include enzymes, such as SOD, which convert superoxide to hydrogen peroxide, catalase that converts hydrogen peroxide to water, glutathione peroxidase, and peroxiredoxins that neutralize hydrogen peroxide through the disulfide bond formation, as well as various nonenzymatic compounds, such as selenium, ascorbic acid (vitamin C), α-tocopherol (vitamin E), GSH, carotenoids, and flavonoids [335, 336]. Repairing antioxidants (*de novo*) of biomolecules are enzymes present in mitochondria and cytosol, which repair DNA damage, such as polymerase, nuclease, and glycosidase, as well as decompose and remove oxidized proteins (peptidases and proteases) [92]. It is also interesting to consider the question of homeostasis in the redox states of tissues, considering the action of antioxidants in exploiting the mechanisms of adaptation, where the signal generated by a free radical determines the synthesis and transport of a suitable antioxidant to the specific site [337]. To counteract the stress and oxidative damage, endogenous antioxidant defense mechanisms act together with exogenous antioxidants, such as dietary polyphenols and vitamins [338] (Fig. **7**). In particular, exogenous antioxidants include vitamin C, which scavenges hydroxyl and superoxide radical anion, vitamin E, which is involved in lipid peroxidation of cell membranes, and polyphenols (phenolic acids, flavonoids and stilbene), selenium, zinc, and drugs, such as acetylcysteine [29].

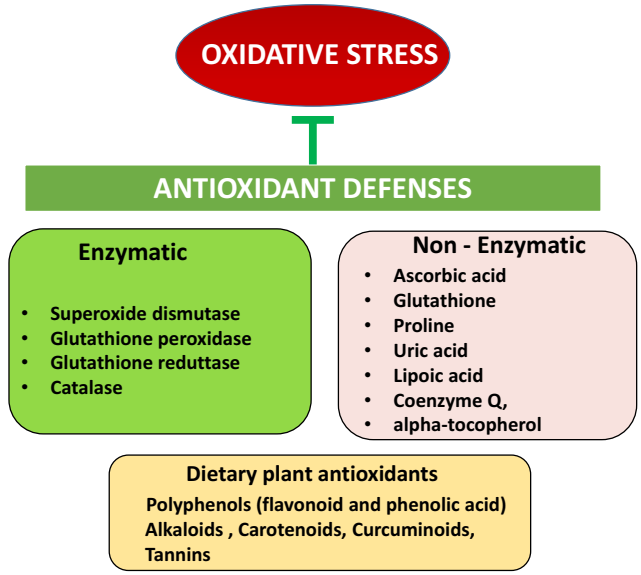

Fig. (7). Schematic representation of antioxidant defenses to oxidative stress. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Antioxidants act synergistically or by trapping single electrons as free radicals or by reducing ROS enzymatically. Food-derived antioxidants (vitamins A, C, E, minerals, and phenolic compounds) are defined as secondary defense system in the human body [17, 339]. Carotenoids are the neutraliser of singlet oxygen in biological systems and have been reported to be beneficial in the prevention of free radical-associated diseases, including atherosclerosis, cataracts, age-related muscular degeneration, and cancer [340, 341]. Carotenoids, in the condition of lipid oxidation, act as scavenger radicals and singlet quenchers of oxygen. Their antioxidant activity involves scavenging singlet oxygen, peroxylic radicals, sulfonyl and NO_2 radicals, and protection from hydroxyl attack and superoxide radicals [272]. Tocopherols represent the most important family of antioxidants that protect membrane lipids. α-tocopherol involves antioxidant properties, inhibiting lipid peroxidation induced by peroxynitrite and inflammatory reactions [342]. γ-tocopherol, δ-tocopherol, and ɣ-tocotrienol show both antioxidant and anti-inflammatory activities. They can scavenge RNS, retard the formation of eicosanoids catalyzed by COX-2 and 5-lipoxygenase, and extinguish proinflammatory signaling of NF-kB and JAK/STAT [343]. Flavonoids, such as flavones, flavonols, flavanols, flavanones, isoflavones, anthocyanins, and non-flavonoids, such as phenolic acids, stilbenic derivatives, and lignans, have a remarkable ability to reduce the effects of free radicals. They are present mainly in fruits and vegetables, medicinal plants, and plant-based food. The antioxidant activity of polyphenols is linked to the number and position of -OH groups on the aromatic ring, and therefore, to the replacement of hydroxyl groups in the aromatic ring [344].

5.2. Nutritional Prevention

Extensive observational studies suggest that a higher intake of different nutrients and functional foods significantly reduces the risk of cardiometabolic risk [204, 345, 346], and several studies have reported various health benefits arising from antioxidant supplementation in processes, such as stress, aging, diabetes, CVD, and metabolic disorders [347, 348]. Much progress has been made in preventive medicine in recent decades. Different preclinical studies have revealed the effects of polyphenol-rich nutrients for mitigating oxidative stress and inflammatory diseases [349-351].

Nutrition plays a crucial role in the prevention of chronic diseases, as most of this can be related to diet; there is an inverse relationship between the dietary intake of antioxidant-rich food and medicinal plants and the incidence of human diseases. The functional properties of food involve the preservation of a state of well-being or health and/or the prevention and reduction of the risk of a pathologic process or disease [352], while a nutraceutical is a food supplement that has scientifically proven health benefits both for the treatment and prevention of disease. Many epidemiological studies indicate that a diet or a specific component of the diet is associated with a lower risk of a given disease. Synthetic and natural antioxidants are used routinely in foods and medicine. However, in view of increasing risk factors associated with various deadly diseases in human beings, there has been a global trend towards the use of natural antioxidants rather than synthetic ones [353, 354] and toward the use of natural substances present in medicinal herbs and dietary plants as therapeutic antioxidants. Dietary antioxidant supplements and functional foods containing antioxidants,

such as α-tocopherol, vitamin C, or plant-derived phytochemicals, such as lycopene, lutein, isoflavones, green tea extract, and grape seed extracts, are now more widely available on the market [355]. Antioxidant nutrients play a specific therapeutic and preventive role in many diseases, such as rheumatoid arthritis, cardiovascular disorders, ulcerogenesis, and acquired immunodeficiency diseases [356, 357]. Other studies have suggested that nutritional antioxidants from diets or supplements can improve asthma control and lung function in asthmatic patients [358]. Antioxidant applications have also been shown to restore redox balance, thereby mitigating intestinal damage and maintaining the health of the gastro-intestinal tract [245]. It is important to emphasize that even though antioxidants might help to mitigate the progression of respiratory diseases, antioxidant supplements can act as pro-oxidants or inducers of oxidative stress if consumed in amounts significantly exceeding the recommended dietary intake [14].

5.3. Antioxidant Supplements

Plant foods contain many secondary metabolites; polyphenols are the most abundant and nutritionally important phytochemicals. They are natural substances useful for the prevention of many diseases (Fig. **7**). Antioxidant supplements are derived directly from plant materials, fresh fruit and vegetables, cereals, legumes, and nuts [354]. In addition, most spices and herbs are rich sources of antioxidants, such as flavones, isoflavones, flavonoids, anthocyanin, coumarin lignans, catechins, and isocatechins [359-361]; while these make up a very small percentage of the food eaten during a meal, they can make an important contribution to the intake of antioxidants. A wide variety of vegetables, such as potatoes, spinach, tomatoes, and legumes, show high antioxidant potential [362]. Strong antioxidant activity has been observed in berries, cherries, citrus fruits, plums, and olives; phenolic compounds constitute up to 30% of the dry weight of green and black tea [363]. Flavonoids, the main active nutraceutical ingredients of plants present in fruits and vegetables, are regularly consumed by humans [364, 365]. The main sources of these are apples, onions, mulberries, bilberries, and beverages, such as tea, beer, and wine. Consumption of bilberries is associated with a decrease in inflammation and serum levels of IL-6, IL-12, and reactive high sensitivity protein [366]. Clinical studies have shown the ability of extra virgin olive oil rich in polyphenols to reduce IL-6 and C-reactive protein expression in patients with stable coronary artery disease [367]. Hydroxytyrosol and resveratrol inhibit the activation of NF-kB and the expression of VCAM-1 in the endothelial cells of the vein stimulated by LPS [368]. Flavanols and flavonols exert CVD protection by suppressing LDL oxidation or by improving the LDL/HDL ratio that determines the protective activity of the endothelium [369].

Flavonoids have been shown to inhibit enzymes, such as cyclooxygenase and xanthine oxidase, involved in the production of free radicals, and to have free-radical scavenging and iron chelator properties [370]; flavonoids can produce complexes with metals [371] and inhibit the initiation of lipid oxidation by metals. Overall, as a consequence of their antioxidant capacity, flavonoids have been found to have a wide spectrum of pharmacological properties, including anti-allergic, anti-inflammatory, antidiabetic, hepato- and gastroprotective, antiviral, neuroprotective effect, and antineoplastic activities [372-374]. Flavonoids reduce insulin resistance and protect from diabetes, improving insulin secretion by reducing apoptosis of pancreatic β-cells [375]. The high consumption of flavonoids may reduce the incidence of Parkinson's disease and delay the onset of Alzheimer's disease [376, 377]. The epigallocatechin gallate exerts neuroprotective activity thanks to its antioxidant activities (SOD, GSHPX) and the cellular content. Anthocyanins improve oxidative stress and reduce the deposition of Aβ [378]; they can modulate neuronal and glial signal pathways [379]. Polyphenols can regulate NF-kB-induced iNOS expression in glial cells [380]. Polyphenolic compounds have shown the ability to inhibit the proliferation of different types of cancer, such as prostate, bladder, lung, gastrointestinal tract, breast, and ovary cancer [381, 382]. Polyphenols can stop cancer metastasis by inhibiting the activity of NF-kB [381, 383]. Several compounds, such as quercetin, resveratrol, carvacrol, green tea polyphenols [384], epigallocatechin-3-gallate [385], and curcumin [386], have shown efficacy as anticancer compounds.

Several controlled clinical trials have indicated that antioxidants do not have a beneficial effect on controlling diseases [387-389]. Many dietary polyphenols have been proven valid in experiments on cells but found ineffective when administered to animals or humans. Thus, many studies have reported the anti-cancer effect of polyphenols on several tumour cell lines in controlled conditions [390]. However, few polyphenols can be considered as antitumour agents in clinical settings [391]. Furthermore, the optimal intake of antioxidant nutrients is still an open question, and there is little information on antioxidant bioavailability *in vivo* in humans [392, 393]. In fact, it is difficult to quantify the benefits offered by dietary polyphenols due to their absorption and metabolic fate, *i.e.*, their bioavailability, by measuring their concentration in plasma and urine [394, 395]. Systemic bioavailability depends on the concentration of the compound that can be transmitted to specific organ sites and whether the antioxidant can perform the expected function. Additionally, the lack of specificity of antioxidants and their possible interactions could explain their inefficiency in the treatment of diseases related to oxidative stress. Most of the antioxidants exogenously administered are not selective and are not distributed uniformly across various parts of the cells or tissues [396, 397]. Further research on targeted antioxidants is needed before this supplementation can be recommended as adjuvant therapy in the prevention and treatment of diseases.

The clinical aspects of the effectiveness of antioxidants and individual nutrient supplements on the prevention and treatment of oxidative stress-related diseases have been extensively explored and gained considerable interest over the last decade.

Observational and epidemiological studies suggest that a diet rich in fruits, vegetables, fiber, and antioxidants (such as the Mediterranean diet) is associated with a lower risk of cardio-metabolic diseases. However, despite the biological and pharmacological properties of these nutrients, polyphenols, vitamins, and supplements could account for a plausi-

ble beneficial effect as shown by multiple preclinical studies (cellular and animal studies); their efficacy and exact mode of action in humans remain unclear [398].

In this regard, recent dietary interventions, antioxidant supplements and natural polyphenol compounds have shown effective antioxidant and anti-inflammatory effects and reduction of cardio-metabolic risk [399-403]. However, it is not totally clear whether these results are related to the type and/or dose of antioxidant agents present in diet/supplements.

CONCLUSION

Free radicals generated in the body cause damage to the main cellular biomacromolecules (lipids, proteins, carbohydrates, and DNA). Oxidative stress results from the imbalance between free radical production and antioxidant defense mechanisms. Oxidative stress plays a role in modern epidemics, such as diabetes, cardiovascular diseases, inflammatory, carcinogenesis and neurodegenerative diseases. In this context, antioxidant supplements are commonly recommended to prevent or stop the progression of such diseases. However, data are lacking in this field since studies do not ultimately suggest that antioxidants have a beneficial effect on controlling such diseases. Indeed, many issues related to antioxidant supplementation remain unresolved, suggesting the need for further research on targeted antioxidants before such supplementation can be recommended as adjuvant therapy in the prevention and treatment of diseases.

AUTHORS' CONTRIBUTIONS

G.M. contributed to conceptualization, writing and critical review of the draft; P.P. performed critical revision of the manuscript; V.C., M.M. and M.K. performed literature review, writing of some paragraphs, and editing; A.G.D. contributed to conceptualization, figures conception, supervision, and funding acquisition. All authors have read and agreed to the published version of the manuscript.

LIST OF ABBREVIATIONS

AKI	=	Acute renal damage
AGE	=	Advanced glycoxidation
CVD	=	Cardiovascular disease
CKD	=	Chronic kidney disease
COPD	=	Chronic obstructive pulmonary disease
DHA	=	Docosahexaenoic acid
DNA	=	Deoxyribonucleic acid
ETC	=	Electron transfer chain
ERK	=	Extra-cellular signal-regulated kinase
EPA	=	Eicosapentaenoic acid
EPR	=	Electron paramagnetic resonance
FPG	=	Fasting plasma glucose
GSH	=	Glutathione
HNE	=	4-hydroxynonenal
HIF-1	=	Hypoxia-inducible factor-1
IL	=	Interleukin
IFG	=	Impaired fasting glycaemia
IGT	=	Impaired glucose tolerance
Keap1	=	Kelch-like ECH-associated protein 1
LDL	=	Low-density lipoprotein
MDA	=	Malondialdehyde
NFTs	=	Neurofibrillar tangles
Nrf2	=	Nuclear factor erythroid 2-related factor-2
NADPH	=	Nicotinamide adenine dinucleotide phosphate
NF-κB	=	Nuclear factor-κb
PKC	=	Protein kinase c
PUFAs	=	Polyunsaturated fatty acids
RAGE	=	Receptor interaction
RNS	=	Reactive nitrogen species
ROS	=	Reactive oxygen species
SOD	=	Superoxide dismutase
PUFAs	=	Polyunsaturated fatty acids
RHS	=	Reactive halogen species
RSS	=	Reactive sulfur species
T1DM	=	Type 1 diabetes mellitus
T2DM	=	Type 2 diabetes mellitus
TLRs	=	Toll-like receptors
TNF-α	=	Tumor necrosis factor-α
UPP	=	Ubiquitin-proteasome

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This study was supported by the Innovation and Competitiveness Cooperation Programme Interreg V/A Greece-Italy (EL-IT) 2014-2020 co-financed by the European Regional Development Fund (ERDF) – INNO.TRITION (Mis. Code: 5003778).

CONFLICT OF INTEREST

Dr. Piero is the Editorial Advisory Board member of the journal MC.

ACKNOWLEDGEMENTS

Declared none.

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