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Review article

The role of antioxidants in the chemistry of oxidative stress: A review

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ABSTRACT

This Review Article is focused on the action of the reactive oxygenated species in inducing oxidative injury of the lipid membrane components, as well as on the ability of antioxidants (of different structures and sources, and following different mechanisms of action) in fighting against oxidative stress.

Oxidative stress is defined as an excessive production of reactive oxygenated species that cannot be counteracted by the action of antioxidants, but also as a perturbation of cell redox balance. Reactive oxygenated/nitrogenated species are represented by superoxide anion radical, hydroxyl, alkoxyl and lipid peroxyl radicals, nitric oxide and peroxynitrite.

Oxidative stress determines structure modifications and function modulation in nucleic acids, lipids and proteins. Oxidative degradation of lipids yields malondialdehyde and 4-hydroxynonenal, but also isoprostanes, from unsaturated fatty acids. Protein damage may occur with thiol oxidation, carbonylation, side-chain oxidation, fragmentation, unfolding and misfolding, resulting activity loss. 8-hydroxydeoxyguanosine is an index of DNA damage.

The involvement of the reactive oxygenated/nitrogenated species in disease occurrence is described. The unbalance between the oxidant species and the antioxidant defense system may trigger specific factors responsible for oxidative damage in the cell: over-expression of oncogene genes, generation of mutagen compounds, promotion of atherogenic activity, senile plaque occurrence or inflammation. This leads to cancer, neurodegeneration, cardiovascular diseases, diabetes, kidney diseases.

The concept of antioxidant is defined, along with a discussion of the existent classification criteria: enzymatic and non-enzymatic, preventative or repair-systems, endogenous and exogenous, primary and secondary, hydrosoluble and liposoluble, natural or synthetic. Primary antioxidants are mainly chain breakers, able to scavenge radical species by hydrogen donation. Secondary antioxidants are singlet oxygen quenchers, peroxide decomposers, metal chelators, oxidative enzyme inhibitors or UV radiation absorbers.

The specific mechanism of action of the most important representatives of each antioxidant class (endogenous and exogenous) in preventing or inhibiting particular factors leading to oxidative injury in the cell, is then reviewed. Mutual influences, including synergistic effects are presented and discussed. Prooxidative influences likely to occur, as for instance in the presence of transition metal ions, are also reminded.

1. The oxidative stress

1.1. The concept of oxidative stress

Oxidative stress was defined as the lack of balance between the occurrence of reactive oxygen/nitrogen species (ROS/RNS) and the organism's capacity to counteract their action by the antioxidative protection systems [1].

Oxidative stress emerges from an enhanced ROS/RNS generation or from a decay of the antioxidant protective ability, being characterized by the reduced capacity of endogenous systems to fight against the oxidative attack directed towards target biomolecules. Its severeness is associated with several pathologies like cardiovascular, cancer and aging [2,3].

Free radical-induced damage in oxidative stress has been confirmed as a contributor to the pathogenesis and pathophysiology of many chronic health problems such as neurodegenerative

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conditions (Parkinson, Alzheimer, Huntington's disease and amyotrophic lateral sclerosis) emphysema, cardiovascular and inflammatory diseases, cataracts and cancer [2–5]. It has been assessed that oxidative stress is correlated with over 100 diseases, either as source or outcome [6,7]. An irreversible progression of oxidative decay caused by reactive oxygen species also exerts its negative influence on the status of the biology of aging, consisting in the impairment of physiological functions, promoting disease incidence, and reducing life span [4].

Oxidative stress was first characterized by Sies [8] as "a disturbance in the prooxidant to antioxidant balance in favor of the oxidant species, leading to potential damage". Oxidative stress has been understood as an excessive amount of ROS, that is the outcome of an imbalance between the generation and depletion of ROS. Hence, oxidative stress is the repercussion of an enhanced free radical occurrence, but also of a reduced activity of the protective antioxidant defense system [9].

Oxygenated reactive species are mainly held responsible for the damaging oxidative reactions. N-containing radical species were also distinguished, called reactive nitrogen species, RNS, derived from the nitric oxide radical. Moreover, ROS or RNS are viewed not just as species able to engender the damage of biomolecules. It was asserted that enzyme systems synthesize reactive species not only for chemical defense or detoxification, but also for cell signaling and biosynthetic reactions [2].

1.2. The reactive oxygen and nitrogen species: occurrence, characterization, activity

Free radicals represent reactive chemical species possessing an unpaired electron in the external orbit [9,10], and they are, at the same time, capable of independent existence [11].

Reactive oxygen species (ROS) are represented by both free radical and non-free radical oxygenated molecules such as hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet -}$), singlet oxygen (1/2 O_2), and the hydroxyl radical (·OH). Reactive nitrogen, iron, copper, and sulfur species are also encountered [6,10]. Oxidative stress and impairment of the redox balance can be assigned to these radical species. The endogenous and exogenous free radical incidence cannot be hampered, owing to both metabolic processes currently occurring, and the action of environmental oxidants [12]. Free radicals are generated in aerobic processes such as cellular respiration, exposure to microbial infections involving phagocyte activation, during intensive physical activity or the action of pollutants/toxins such as cigarette smoke, alcohol, ionizing and UV radiations, pesticides, and ozone. Reactive oxygenated species in low amounts represent signaling molecules, that are involved in the regulation of cell proliferation, apoptosis and gene expression by triggering transcription factors. Their generation by phagocytes is essential in the defense mechanism against various strains of bacteria or fungi [9].

In the aerobic process that employ oxygen to oxidize carbon and hydrogen-containing biomolecules to produce chemical energy and heat, molecular oxygen is stepwise reduced to a series of intermediate species: hydroperoxyl radical, superoxide radical anion, hydrogen peroxide, hydroxyl anion and hydroxyl radical. The progressive molecular oxygen reduction occurs as follows [11]:

$$O_2 + e^- + H^+ \rightarrow HO_2\cdot$$

$$HO_2\cdot \rightarrow H^+ + O_2^{\bullet -}$$

$$O_2^{\bullet -} + 2H^+ + e^- \rightarrow H_2O_2$$

$$H_2O_2 + e^- \rightarrow HO^- + HO\cdot$$

$$HO\cdot + H^+ + e^- \rightarrow H_2O$$

It has been assessed that *superoxide radical anion* is actually generated when one electron enters the Π^* 2p orbitals of oxygen [11]. Superoxide results from one electron reduction of oxygen by various oxidases, such as dihydro nicotinamide adenine dinucleotide phosphate oxidase, xanthine oxidase, cyclooxygenase. Superoxide radical anions may also be formed in the mitochondrial electron transport chain, in the course of oxidative phosphorylation that yields ATP [13,14]. In aqueous solution, superoxide radical anion proved a weak oxidising agent towards ascorbic acid and thiols. It also turned out as a strong reducing agent, versus some iron complexes like cytochrome C and ferric-EDTA. The protonated form, the hydroperoxyl radical is both a stronger oxidant and reductant than superoxide anion, but hydroperoxyl is much less stable than superoxide anion, at pH 7.40: at this physiological pH value, the hydroperoxyl radical $HO_2\cdot$, with a pKa value of 4.80, dissociates, resulting the superoxide anion radical [11].

Superoxide anion was distinguished itself as an active nucleophile, able to attack positively charged centers, and as an oxidizing agent that can react with hydrogen donors (e.g. ascorbate and tocopherol). Superoxide anion radical can dismutate, yielding molecular oxygen and hydrogen peroxide [15].

$$2\ O_2^{\bullet -} + 2H^+ \rightarrow O_2 + H_2O_2$$

Superoxide radical anion can be transformed by enzymes belonging to the superoxide dismutase family, which deplete superoxide anion radicals occurring from the action of extracellular factors (including ionizing radiation and oxidative impairments), or from oxygen metabolism, in the electron transport chain [16,17].

Hydrogen peroxide can be generated by any system yielding superoxide, as the radical anion readily disproportionates. The presence of oxidases (urate oxidase, glucose oxidase, D-aminoacid oxidase) can result in direct hydrogen peroxide synthesis by two-electron transfer to molecular oxygen. H_2O_2 is able to produce highly reactive radicals as a result of its interaction with metal ions [11]. Direct action of H_2O_2 involves the attack on haem proteins structure with release of iron, enzyme inactivation and oxidation of DNA, lipids, -SH groups, and keto-acids [15].

H_2O_2 can be depleted by catalase, the ferriheme-containing enzyme engaged in converting hydrogen peroxide (but not other peroxides) to water [16,18].

OH· radical is a highly aggressive radical species, responsible for the oxidative damage of most biomolecules, this type of reaction occurring at a quasi diffusion-controlled rate. These highly damaging hydroxyl radicals resulted from Fenton-type reactions, may also emerge from the radiolysis of water [11]. OH· has been reported as the most powerful oxidizing radical that can interact at the site of its generation with most organic and inorganic molecules - DNA, proteins, lipids, amino acids, sugars, and metals. These reactions are characterized by high rate giving the reactivity and short life-span of hydroxyl radicals, and involve hydrogen abstraction, addition, and electron transfer [15,19].

Molecular oxygen is not a free radical, yet it is considered an oxygenated species endowed with high reactivity, as spin restriction of oxygen is removed, which enhances its oxidative power [11].

Ozone proved highly oxidizing towards lung proteins, lipids and DNA.

Nitric oxide and nitrogen dioxide present unpaired electrons, and therefore can be regarded as free radicals, whereas nitrous oxide does not [11]. Endogenous nitric oxide, biosynthesized from L-arginine, oxygen and NADPH, by enzymes belonging to nitric oxide synthase class or by reduction of inorganic nitrate, is one of the rare gaseous signalling molecules involved in vasodilation and

neurotransmission. It is also released by phagocytes (monocytes, macrophages, and neutrophils) as result of the immune system reaction. Its reacts with superoxide radical anion, giving a highly reactive, damaging nitrogen species, namely peroxynitrite, a powerful oxidant versus many biological molecules. Peroxynitrite can be decomposed to yield hydroxyl radicals, independently on the presence of transition metals [11,20–22].

$$ONOO^- + H^+ \rightarrow OH\cdot + \cdot NO_2$$

The protonated form of peroxynitrite (ONOOH) is a strong oxidizing agent that determines depletion of sulfhydryl groups and oxidative damage on most biomolecules, acting similarly to hydroxyl radical. It is also responsible for DNA damage causing breaks, protein oxidation, and nitration of aromatic amino acid moieties in protein structure (e.g. 3- nitrosotyrosine) [15].

Essential biochemical reactions involving nitric oxide are also S-nitrosation of thiols and nitrosylation of transition metal ions. Hemoglobin structure may be altered by NO direct attachment to heme in the nitrosylation reaction, or by S-nitrosation of the thiol moieties, yielding S-nitrosothiols [23].

Hypochlorous acid emerges due to the myeloperoxidase presence in macrophages and neutrophils, and is endowed with high oxidative abilities. Myeloperoxidase is responsible for catalytical generation of hypochlorous acid from hydrogen peroxide in the presence of chloride anion. HClO induces oxidative chlorination on biomolecules such as lipids, proteoglycans, amino acids, and also of other membrane or intracellular compounds [24].

The increase, in pathological status, of active oxygen species occurrence has been tightly correlated to cytotoxicity. These processes may result in modified antioxidant enzyme activity, inactivation or leakage from cells. Superoxide and hydrogen peroxide were reported as not very reactive by themselves, and hydroperoxides proved nearly stable under normal physiological conditions. Superoxide and hydrogen peroxide reactivity are enhanced by the presence of haem proteins and low molecular weight transition metal chelates, as this may result in more reactive species like hydroxyl radical or ferryl haem protein radical. The latter can engender the formation of alkoxyl and peroxyl radicals. The antioxidant potential manifestation at the proper site may prevent the oxidative damage of enzymes, ion channels, structural proteins and membrane lipids, which, otherwise, could result in the impairment of a series of cell functions, having pathological consequences and eventually cell death [25,26].

1.3. The chemistry of oxidative stress: reactive oxygen species and biomolecule impairment

Reactive oxygen species modulate the function of all classes of biomolecules, targeting almost all substrates in the cell. Lipids are the most susceptible to undergo oxidation: polyunsaturated fatty acids, especially arachidonic acid and docosahexaenoic acid, which lead to malondialdehyde and 4-hydroxynonenal, recognized markers of lipid oxidative decay. Reactive oxygen species are able to oxidise both the backbone and the side chain of proteins, which subsequently interact with amino acid side chains to generate carbonyl functions. ROS damage nucleic acids, in that they may cause DNA-protein crosslinking, strand breaking, and alteration in purine and pyridine bases structure, having as outcome DNA mutations [16].

The most significant endogenous sources of oxidizing species responsible for aging were identified in mitochondria, mainly in the electron transport chain and nitric oxide synthase-catalysed reactions. Nonmitochondrial free radical sources are Fenton reaction, microsomal cytochrome P450 enzyme complex, peroxisomal beta-oxidation, and activated phagocytic cells [7,9,27].

Taking over these considerations, it is important to remind that the novel concept of oxidative stress is not restricted to free radical damage of the biomolecules, but relies on identifying perturbation of cellular redox status [2]. Based on recent studies on redox signaling pathways, on antioxidant mechanism and oxidative stress markers, Dean Jones re-defines oxidative stress as “a disruption in redox signaling and control”, hence the action of the antioxidant systems is viewed as more complicated than merely blocking reactive free radicals [28,29].

In this perspective, the ROS occurrence steps were described focusing on how this process of generation takes place in the electron transport chain in the mitochondrial inner membrane [1,30]. In the electron transport chain, the electrons are transferred from NADH and $FADH_2$ to molecular oxygen by four membrane bound complexes (I–IV), eventually yielding water [30]. In this process, electrons leak from the inner membrane and are able to reduce molecular oxygen to superoxide radical anions ($O_2^{\cdot -}$). The latter can lead to other ROS, such as hydrogen peroxide (H_2O_2), hydroxyl radicals ($OH\cdot$) and hydroxyl ions (OH^-). The reactive nitrogen species emerge when $O_2^{\cdot -}$ reacts with nitric oxide (NO) to generate peroxynitrite ($ONOO^-$). Furthermore, these are able to form other types of nitrogenated species, like nitrogen dioxide (NO_2) and nitrosoperoxycarbonate ($ONOOCOO^-$). Brain astrocytes and microglia produce ROS and RNS when triggered, and also in reactions catalyzed by transition metal cations, such as copper and iron ions. The alterations in DNA, RNA, lipids and protein structure initiated by ROS/RNS, can then result in more reactive molecules' occurrence [31].

Under these circumstances, DNA oxidation is prejudicial, in view of its negative impact on transcription and replication of significant genes [32]. The most currently referred to marker taking account on DNA oxidation is 8-hydroxydeoxyguanosine [33] that emerges from the oxidation of the nucleoside guanosine by $OH\cdot$. The oxidation of RNA nucleobases occurs similarly, the most relevant index being the homologue of 8-hydroxydeoxyguanosine, 8-hydroxyguanosine [34]. It was asserted that RNA can more easily undergo oxidation, being located in a closer proximity to the ROS occurrence sites in the cell. The main outcome of the RNA oxidation is represented by the breakage of the nucleotide strand, and also by ribosomal dysfunction [35].

The oxidation of lipids has a damaging potential towards cell membranes. The unsaturated fatty acids proved primarily sensitive towards oxidation and readily undergo peroxidation by $OH\cdot$ attack. Peroxidation of polyunsaturated fatty acids leads to isoprostanes [36] and their levels are considered to accurately reflect the oxidative stress [37]. The oxidative attack on lipids also results in reactive aldehydes, such as malondialdehyde and 4-hydroxynonenal. The latter can get attached to proteins and may therefore impair their function [31].

Oxidation of proteins can occur with side-chain oxidation, backbone fragmentation, unfolding and misfolding, resulting in activity loss [38]. Oxidation of plasma thiol groups results in protein oxidative damage, along with carbonylation, leading to advanced glycation end products [39].

All amino acids are sensitive towards oxidation: cysteines and methionines are readily oxidizable; however, many of these oxidations are reversible due to the activity of disulfide reductases. A series of in vivo irreversible alterations may occur, such as formation of S-carboxymethylcysteine and S-(2-Succinyl)cysteine [40,41]. This implies formation of fumarate and dicarbonyl groups, covalently bound to cysteine residues. Oxidation of lysine, proline, arginine and threonine also gives rise to carbonyl derivatives – markers taking account on oxidative species-mediated protein oxidation [42]. It was assessed that carboxymethyl lysine is the outcome of lysine residues

oxidation and that oxidation of cysteine residues results in cysteine/cystine and homocysteine/homocystine [39].

The aromatic amino acids are also susceptible to be oxidized by different oxygenated species: OH radical-initiated oxidation of tyrosine results in dityrosine, reaction with reactive nitrogenated species forms 3-nitrotyrosine, while reaction with HClO gives 3-chlorotyrosine [39].

An interesting aspect to stress is that the damage of the mitochondrial membranes and protein structure can, at its turn, enhance reactive oxygenated species generation, leading to DNA impairment and cell death by apoptosis [43]. Apoptosis signal-regulating kinase 1 was considered an important marker taking into account apoptosis initiation by oxidative stress. Its activity is primarily controlled by thioredoxin-1, the redox sensitive oxidoreductase that binds the reduced form of apoptosis signal-regulating kinase 1 [44]. When thioredoxin-1 is oxidized, the binding to apoptosis signal-regulating kinase 1 is hindered, resulting in activation of the subsequent c-Jun N-terminal kinase apoptosis pathway [45]. The activity of apoptosis signal-regulating kinase 1 is also tuned by other redox proteins including glutaredoxin, heat-shock proteins, and glutathione–S-transferase. Another regulator of oxidative-mediated apoptosis is p53, which after its translocation in the nucleus is capable to trigger proapoptotic genes [46].

The major generators of reactive oxygenated species and the antioxidant defense manifestation as described for neurons and glia, are represented in Fig. 1 [16].

1.4. Oxidative stress and pathology

1.4.1. Oxidative stress and cancer

It was already established that oxidative stress, as unbalance between oxidant and antioxidants favouring the oxidants, implies the damage of all the essential biocompounds like proteins, DNA and membrane lipids, and can result in cell death [47]. It was assessed that cancer cells are characterized by higher amounts of reactive oxygen species than healthy cells, and is was proved that reactive oxygenated species are responsible for the maintaining of cancer phenotype [48].

Reactive oxygen species have also been identified as stimulators of oncogenes such as Jun and Fos genes [49]. Previously published studies have associated the development of cirrhosis with oxidative stress caused by radicals [50], while overexpression of Jun has been tightly linked to lung cancer [51,52].

In liver, it was assessed that endoplasmic reticulum and peroxisomes have a greater ability to generate ROS than mitochondria [53], and that inflammation occurs when nitrosothiols present free thiol groups, which become reversible due to glutathione-S-transferase activity [54]. A series of intermediates endowed with elevated reactivity and formed by nitrogen oxides (e.g. nitro-cool acid) can cause liver cell necrosis, inhibition of mitochondrial function and depletion of pyridine nucleotides, resulting in DNA breakdown. Nitric oxide and peroxynitrite can interact, resulting in hydrogen peroxide which initiates inhibition of mitochondrial respiration, of Na^+/K^+ pump T function and of kinases phosphorylation [55]. Enhancement of reactive nitrogenated species production results in nitrosylation reactions, altering and imparing the protein function [56]. Polyunsaturated fatty acids and radicals derived from hydrogen peroxide are intermediate species in the process of accumulation of lipid peroxides in cell membranes [57]. Peroxides may also result from aldehyde oxidation, leading to inflammation and organ fibrosis [58].

Several biochemical parameters (lipid peroxidase, glutathione, superoxide dismutase, and catalase in liver homogenates) and plasma lipid profile (total lipids, total cholesterol, total triglycerides, HDL and LDL) were assessed to establish the effect of radiation on tissues, and to determine the radioprotective role and antioxidant power of the anticancer drug quinoline sulfonamide against tissue injury and oxidative stress brought about by gamma radiation [48]. To test adverse effects which could result from the chemical treatment, liver enzymes and kidney function parameters (creatinine and urea) were assessed in plasma, along with haematological indexes. The results pointed that the damaging effects due to exposure to γ-radiation and cancer incidence on most of the assessed parameters could be moderately controlled by administration of quinoline sulfonamide prior to irradiation. No important adverse effects were noticed on the tested mice, due to the drug administration [48].

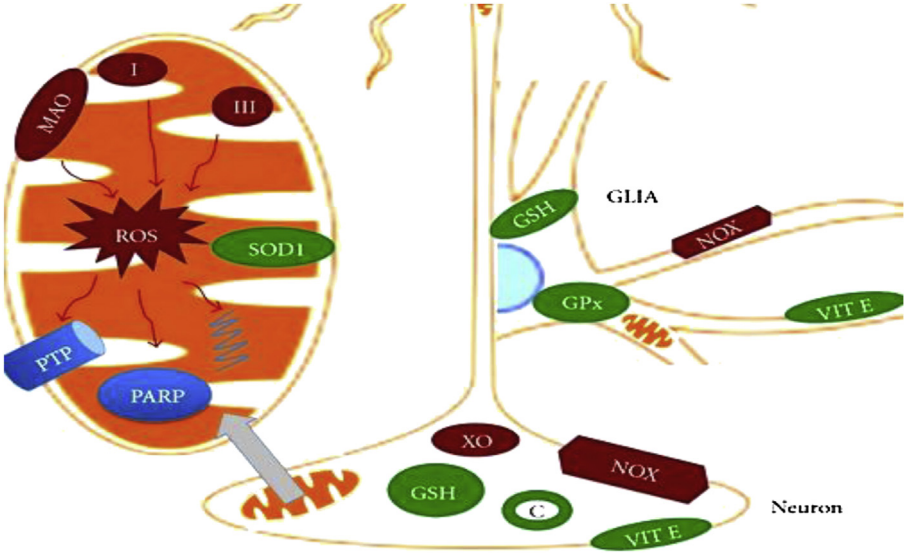

Fig. 1. Illustration of the major producers of ROS and of the antioxidant defense in neurons and glia, as represented in Ref. [16]. ROS producers are represented by monoamine oxidase (MAO), complex I and complex III in the mitochondria. Reactive oxygen species formed in mitochondria target the permeability transition pore (PTP), the polyADP ribose polymerase (PARP), and the mitochondrial DNA. NADPH oxidase (NOX) and xanthine oxidase (XO) are the major generators of ROS in the cytosol. The antioxidant defense system comprises: superoxide dismutase (SOD) in the mitochondria, glutathione (GSH), catalase (C), and glutathione peroxidase (GPx) [16].

It has been found that chlorinated free radicals formed from CCl_4, such as trichloromethyl ($\cdot CCl_3$) and trichloromethyl peroxyl ($\cdot OOCCl_3$), impair the hepatocyte, inducing morphological changes in the endoplasmic reticulum, Golgi apparatus, plasma membrane, and mitochondria of the targeted cells. Thus, carbon tetrachloride proved an aggressive hepatotoxin and cirrhosis-inducer, by generating the mentioned chlorinated free radicals. It was stipulated that reactive species emerged as a result of the metabolic changes occurring via the cytochrome P-450 enzyme complex [59]. Researches focused on the effect of CCl_4 on liver have also settled that an early production of TNFα after liver impairment could determine an elevated ICAM-1 expression and a diminished PECAM-1 expression, which were correlated to the migration of inflammatory cells into the parenchyma [60].

A study focused on the assessment of biochemical parameters in carbon tetrachloride-induced cirrhosis in rats, showed a pronounced increase of transaminase levels and lipid peroxidation (for which thiobarbituric acid reactive substances were assessed) in liver and lung tissue, and also elevated antioxidant enzymes superoxide dismutase and catalase activity, as well as the expression of TNF-α and IL-1β in the lung of animals. The reproduced model of liver cirrhosis is also associated with an impairment in the pulmonary system, with alterations in gas exchange and pulmonary vessels size [61] confirming that the respiratory tract also becomes affected by endogenous and exogenous oxidative processes [62,63]. The main source of tissue damage associated with lung chronic inflammation has been identified in the reactive species generated by phagocytes. Increased levels of markers of lung injury and proinflammatory cytokines (IL-1β, IL-6, and TNF- α) have also been associated to this pathology [64].

In lung cancers, p53, often mutated and defective in inducing apoptosis, is linked to reactive oxygenated species generation. When mutated, p53 can accumulate in the cytoplasm and may act as an oncogenic transcription factor [49,65]. Furthermore, alterations of protein and lipid structure are associated with increased risk of mutagenesis, caused by genotoxic by-products of lipid peroxidation able to interact with DNA, determining oxidative modification of DNA polymerase or inhibition of the DNA repair system [66].

Studies dedicated to skin cancer prevention and occurrence show that exposure to UV radiation may induce alterations in the genetic material. Most of this damage may efficiently be addressed to, by the intervention of repair systems such as nucleus proteins. However, under circumstances of extensive damage, DNA impairments may constitute themselves in irreversible mutations and can result in skin cancer occurrence. It was found that UV radiation induces a variety of photoproducts of DNA alteration, including cyclobutanetype pyrimidine dimers, pyrimidine-pyrimidone photoproducts, thymine glycols, cytosine damage, purine damage, DNA strand breaks, and DNA-protein crosslinks [67]. The unrepaired damage may affect regulatory tumor suppressor genes and lead to carcinogenesis. Moreover, the putative involvement of miRNAs in the etiology of skin carcinogenesis has been studied, and a general miRNA response to UV has been noticed, alongside wavelength-specific miRNA responses to UVA and UVB. It has been concluded that miRNA regulation is involved in skin cancer occurrence [68].

The elevated levels of oxidative stress markers in breast cancer have been assigned to both disease process and tissue injury [69–71]. Tissue injury promotes reactive oxygen species occurrence as a result of phagocyte activation or as consequence of transition metal ions release from the affected cells which proved able to further worsen the injury [72]. Previous studies stated that anticancer drugs can trigger oxidative stress and supported the interest in monitoring oxidative stress markers associated to this pathology [73]. It has been discovered that during cancer chemotherapy electrophilic aldehydes resulted from lipid peroxidation can delay cancer cell cycle development and determine cell cycle check-point disruption, or impede drug-intiated apoptosis. Moreover, it has been stipulated that this is likely to interfere with the capacity of anticancer drugs to exert their optimal cytotoxicity on cancer cells [73].

Important diminutions in total antioxidant capacity (32.7%–37.5%), uric acid (28.1%–49.2%), malonyl dialdehyde (20.7%–25.2%) and nitric oxide (50.4%–61.9%) contents were noticed in cancer breast patients, with reference to the control group. Seric Cu^{2+} levels were diminished in metastatic cancer group, in comparison to both control and nonmetastatic cancer groups. The Fe^{2+} serum content was lowered in the case of patients belonging to nonmetastatic cancer group, compared to healthy subjects and patients with metastatic cancer. Uric acid was determined by the uricase/peroxidase bienzymatic method. Values were lower for subjects belonging to metastatic group, compared with nonmetastatic cancer patients [71].

For the total antioxidant capacity assay, the hydrogen peroxide remaining after reaction with sample antioxidants was determined colorimetrically by an enzymic reaction with 3, 5-dichloro-2-hydroxy benzenesulphonate [74]. Trace copper and iron assessment was performed by flame atomic absorption spectrometry. Malonyl dialdehyde was assessed by determining thiobarbituric reactive substances [75].

1.4.2. Oxidative stress and cardiovascular diseases

Oxidation was confirmed to play a role in the pathogenesis of atherosclerosis [76]. The oxidation of low-density lipoproteins proved able to initiate LDL uptake by macrophages and foam cell formation [77]. Also, oxidation processes may result in oxidized lipids with proinflammatory effect [78]. Moreover, lipids other than LDL and lipoproteins present in the blood vessel wall lead to inflammation and atherosclerosis [79]. Increased levels of isoprostanes in the aortic tissue, alongside with the severeness of atherosclerotic injuries in the proximal aortas of apoE-deficient mice, were corroborated with vitamin E deficiency resulting from disruption of the alpha-tocopherol transfer protein gene [80].

Epidemiologic studies indicate an increased antioxidant vitamins intake such as vitamin E, vitamin C, and beta carotene may result in a lowered risk of atherosclerotic vascular disease [81]. Although expression of apoE is not able to lower plasma cholesterol levels, it can delay isoprostanes occurrence in urine, plasma LDL, and aortic tissue. Hepatic apoE expression also results in a regression of preexisting advanced atherosclerotic injuries, with disappearance of macrophage-derived foam cells. Hence, it has been proved that the antiatherogenic effects of apoE are correlable with its antioxidant properties in vivo [76].

Heterooligomeric class of vascular NADPH oxidases were identified as able to constantly initiate ROS generation [82,83]; although a specific role has not been assigned to each enzyme, it has been established that both NOX expression and activity are upregulated in the vasculature of hypertensive subjects, and are linked to the development of macro and microvascular diseases [84].

As enzymes belonging to the NOX class are enhancers of oxidative stress, they turned out to play a major role in the pathology of diabetes-induced vasculopathies [85,86]. Studies performed on Ginko Biloba extract EGB761 proved a beneficial effect on the diastolic function in cardiomyocytes through the regulation of myocardial sarcoplasmic reticulum calcium transport regulatory. Upregulating SERCA2a function (whose deficiency is associated with advanced heart failure and is considered the source of progressive systolic and diastolic dysfunction) is achieved through the increase of the number of Ser16 sites available in the course of PLN phosphorylation. Treatment with Ginko Biloba extract contained

the intracellular occurrence of advanced glycation end-products, retards cellular senescence, and promotes the re-uptake of Ca^{2+} stores in the sarcoplasmic reticulum [83].

Experimental and clinical studies have asserted oxidative stress and reactive oxygen species involvement in the pathogenesis of atrial fibrillation [87], as well as in electrical heart remodelling [88]. Mainly NADPH oxidase activity can be enhanced by activators of atrial fibrillation such as angiotensin II and atrial stretch [88]. N-acetylcysteine, polyunsaturated fatty acids and antioxidant vitamins proved able to contain heart oxidative stress and reduce cardiac arrhythmias [89–91].

1.4.3. Oxidative stress and neurodegenerative diseases

Depletion of membrane phospholipids, as main result of lipoperoxidation, has distinguished itself as major cause of neurodegenerative diseases, such as Alzheimer [92,93]. β-amyloids emphasized the capacity to initiate lipid peroxidation. Lipid peroxides occurrence and decreased antioxidant enzyme activities proved tightly correlated to senile plaques formation, and neurofibrillary tangles in Alzheimer disease brains. Recognized markers of oxidative stress such as acrolein, malondialdehyde, F2-isoprostanes and 4-hydroxy-2,3-nonenal have been noticed in Alzheimer brains and cerebrospinal fluids compared with control subjects. Hydroxynonenal was endowed with the most elevated reactivity, hippocampal cytotoxicity, and proved able to accumulate in significant amounts in AD condition [94,95]. Protein carbonylation, also as a result of the oxidative-stress induced decay, was noted in the frontal, parietal cortices and hippocampus of Alzheimer disease brain, but did not affect the cerebellum [96,97].

The damage of the functions of membrane proteins such as the neuronal glucose transporter GLUT 3, glutamate transporters, Na^+/K^+ ATPases, along with the activation of kinases, dysregulation of ionic transfers and calcium homeostasis (implying increased calcium amounts), can promote a series of events in the cell, resulting in enhanced ROS production and cellular death, that eventually engender an apoptotic mechanism leading to neurodegeneration [92].

Studies on primary rat cortical cell culture showed that β-amyloids induce deficiencies in both complex I (NADH dehydrogenases) and complex IV (cytochrome c oxidases), as proved by studies on primary rat cortical cell culture. Complex I is considered the main ROS promoter in regular physiological status, and it has been stated that mainly alterations in its functionality may result in enhanced ROS generation and lead to energy depletion, as outcome of disrupted oxidative phosphorylation. Mitochondrial injuries caused by β-amyloid overproduction in Alzheimer condition trigger reactive oxygenated species generation, that results in cell damage and finally death [98,99]. Neuronal ATP depletion results in neurotransmission malfunction and alters axonal transport. It affects the ATP-dependent ion channels, thus altering the cytosolic ion balance [98].

Parkinson's disease is the second oxidative stress-induced neurodegenerative disease that implies a gradual loss of dopaminergic neurons in the substantia nigra and α-synuclein agglutination [16]. In Parkinson disease, the concentration of polyunsaturated free fatty acids in the substantia nigra is lowered, with parallel enhancement of lipid peroxidation markers (such as malondialdehyde and 4-hydroxynonenal) [100]. Protein carbonyls, as a result of protein oxidative damage [101], are also present in Parkinson disease brain. Nitration and nitrosylation of proteins resulted from the action of reactive nitrogen species in Parkinson disease brain, has also been confirmed [102]. Elevated levels of 8-hydroxydeoxyguanosine [103], associated with an enhancement of commonly occurring deletions in the mitochondrial DNA of the non-affected dopaminergic neurons in substantia nigra, have been noticed as well [104].

Oxidative stress participates also in the essential biology of Down syndrome, namely the unbalance in the metabolism of free radicals plays a significant role in the Down neuropathology including the progression towards Alzheimer [105]. It has been confirmed that genes overexpressed on chromosome 21 are linked to oxidative stress and neuronal apoptosis: chromosome 21 comprises several genes involved in oxidative stress and leading to neurodegeneration such as Cu/Zn superoxide dismutase, amyloid precursor protein, Ets-2 transcription factors, Down Syndrome Critical Region 1 stress-inducible factor, beta-site amyloid precursor protein cleaving enzyme and S100 [106–108]. In a study dedicated to antioxidant supplementation influence in Down syndrome it was proved that antioxidant administration does not lead to amelioration in the cognitive function, nor can it stabilize the decline, in comparison with the placebo group. During the treatment period, average plasma α-tocopherol concentrations increased approximately 2-fold, with reference to placebo group. No important adverse effects assigned to the treatment were noticed, so it was concluded that antioxidant supplementation is safe, although lacking in effectiveness in the case of individuals with Down and Alzheimer-type dementia [109].

1.4.4. Oxidative stress and diabetes

In conditions of enhanced oxidative stress, cell damage may affect the pancreatic β cell function, which, given the impaired expression of antioxidant enzymes, is outstandingly sensitive to reactive oxygen and nitrogen species [110,111].

The reactive oxygenated species are able to interact with the substrates involved in the insulin intracellular signaling [112]. The high energetic loading on the cells, mainly resulting from the elevated sugar (glucose) amounts, enhances the flow of reduced coenzymes (NADH and $FADH_2$) in the mitochondrial electron transport chain. As the voltage gradient across the mitochondrial membrane attains a critical threshold blocking complex III, it enables coenzyme Q reduction by electrons. $CoQH_2$ can subsequently reduce molecular oxygen, finally generating superoxide radical anion [113]. This is the commonly followed pathway in type 2 diabetes mellitus complications involving increased flow in the polyols and hexosamines pathways [110].

It has been suggested that under deficient glycemic control, that can arise inspite of the use of pharmaceuticals, oxidative stress may be promoted via NADPH oxidase activity enhancement, with subsequent superoxide radical anion production. Studies assessing enzymatic and non-enzymatic markers of oxidative stress in diabetes mellitus condition showed that total superoxide dismutase activity and the lipid peroxidation were higher in diabetics when compared to healthy controls. Moreover, the total superoxide dismutase activity differed for the hypertensive diabetics in comparison with the prediabetics and normotensive controls. Lipid peroxidation was considerably increased in both groups of diabetics (hypertensive and normotensive) as compared with prediabetic groups and hypertensive and normotensive controls [110].

1.4.5. Oxidative stress and inflammatory diseases

The correlation between chronic inflammation and oxidative stress is already confirmed: the imbalance between the oxidative species' activity, promotor of oxidative insults, and the antioxidant defense, is involved in asthma and allergic rhinitis [114–116]. The enhanced occurrence of hydroxyl radicals, superoxide radical anions and peroxides, may initiate a series of alterations in nasal and airway mucosas: lipid peroxidation, marked airway reactivity, nasal mucosal sensitivity and secretions, as well as generation of chemoattractant molecules and high vascular permeability [114].

Basically, it has been noticed that reactive species and antioxidants influence the immune system. Oxidative stress causes disruption in cell signaling and impairs arachidonic acid metabolism, enhances airway and systemic inflammation [117]. It was stated that oxidative stress increases inflammation associated with TH1 or TH2 cytokine generation, and might determine alterations of TH2 phenotype [118], that may initiate allergic conditions [119–121].

Epidemiologic studies have assessed the association between genes regulating immune system and asthma risk [122]. Oxidative stress triggers the expression of genes that regulate the inflammatory events, hence epigenetic investigations were directed towards assessing this processes, during progression of asthma and allergy [123]. Moreover, a meta-analysis of case–control studies, corroborated deletions in GSTM1 and GSTT1 with a pronounced risk of asthma [124].

It has ben suggested that exposure to polycyclic aromatic hydrocarbons, involving methylation of the ACSL3 gene, is linked to asthma risk in children [125]. Systemic microRNA profiles assayed in peripheral blood samples of subjects with moderate asthma were affected by exposure to controlled diesel exhaust: high microRNAs levels were corroborated with systemic markers of oxidative stress boost, that could be attenuated by antioxidant supplementation [126].

In allergic rhinitis condition, plenty of inflammatory cells, such as mast cells, CD4-positive T cells, B cells, macrophages, and eosinophils, pentrate the nasal mucous membrane upon exposure to the allergen [114].

The involvement of oxidative stress in allergic rhinitis is believed to be identical to that manifested in asthma [127]. The marker of lipid peroxidation as average thiobarbituric reactive substances level evaluated in allergic rhinitis patients was higher, with respect to healthy controls. The susceptibility to undergo enhanced lipid peroxidation (as result of the oxidative damage) and the mean superoxide dismutase enzyme activity were significantly increased in the erythrocytes of patients with allergic rhinitis. Erythrocytes' marked susceptibility to oxidative impairment has been explained by the elevated levels of polyunsaturated fatty acids in the membranes of these cells, along with the increased amounts of oxygen and hemoglobin in the cell, leading to redox processes generating oxygenated radical species [114,128]. The increase in ceruloplasmin levels noted in allergic rhinitis was considered a reaction to the inflammation of airways, as well a component of the increased antioxidant response occurring after cell injury [114].

Oxygen metabolism and increased ROS production causing tissue damage, and associated with inflammation, have an important role in the pathogenesis of rheumatoid arthritis [129]. Reactive oxygen species occurring during cellular oxidative phosphorylation or generated by activated phagocytic cells and exceeding the antioxidant defense system's capacity, proved able to enhance the synovial inflammatory–proliferative response. It has been described that repetitive cycles of hypoxia and reoxygenation are linked to changes in synovial perfusion and may trigger hypoxia-inducible factor-1-α and nuclear factor-k-B, two key transcription factors that are regulated by changes in cellular oxygenation and cytokine stimulation. This results in the expression of a series of genes responsible for synovitis persistence [130].

Newly, the prevalent hypothesis that ROS promote inflammation was challenged when polymorphisms in neutrophil cytosolic factor 1, known for decreasing oxidative boost, turned out to worsen the pathological condition, as shown in animal studies. It has been suggested that some oxygenated radical species might also be able to control disease severeness and to reduce joint inflammation and connective tissue damage [129].

1.4.6. Oxidative stress and urolitiasis

Serum malonyl dialdehyde, nitrite, α-tocopherol, plasma ascorbate and erythrocyte superoxide dismutase levels were correlated with the pathogenesis of urolithiasis. Increased superoxide dismutase levels are part of the antioxidant response counter-balancing peroxidative stress. It has been emphasized that oxalate can promote lipid peroxidation by a not entirely elucidated mechanism involving impairment of the structural integrity of the membranes [49,131]. α-tocopherol was confirmed, as well as superoxide dismutase, to act as protector of the membrane against peroxidation [49,132].

2. Antioxidants

2.1. Definitions and classifications – discussion of the criteria up to now

The concept of biological antioxidant refers to any compound that, when present at a lower concentration compared to that of an oxidizable substrate, is able to either delay or prevent the oxidation of the substrate [19,67]. Antioxidant functions imply lowering oxidative stress, DNA mutations, malignant transformations, as well as other parameters of cell damage. Epidemiological studies proved antioxidants' ability to contain the effects of reactive oxygen species activity, and diminish the incidence of cancer and other degenerative diseases. Nevertheless, mainly at sustained free radical action, the defense system's capacity against ROS can be overwhelmed, leading to disease occurrence [67].

The first identified types of antioxidant defense systems developed against oxidative damage, are those that prevent reactive oxygen species occurrence and those that block, capture, radicals that are formed [133]. These systems present in aqueous and membrane cell compartments can be enzymatic and nonenzymatic. Another important antioxidant system of the cell is represented by repair processes, that remove the damaged biomolecules, before their aggregation enables alteration of cell metabolism [133]. The repair systems' intervention consists in repairing oxidatively damaged nucleic acids by specific enzymes [9], removing oxidized proteins by proteolytic systems, and repairing oxidized lipids by phospholipases, peroxidases or acyl transferases [130]. It has been assumed that the decay of the repair systems leads more to aging and age-related diseases than moderate changes in the antioxidant defense's potential against ROS occurrence [134–136].

It has been stated that, under physiological conditions, the balance between prooxidant and antioxidant compounds moderately favors prooxidants, thus engendering a slight oxidative stress, requiring the intervention of endogenous antioxidant systems of the organism [18]. Under these circumstances, this question of oxidative stress becomes more acute with age, when endogenous antioxidants (Fig. 2) and repair systems cannot counteract it effectively. Thus, various interventions limiting or inhibiting these aggressive factors are directed towards decreasing disease incidence. Nevertheless, the use of synthetic antioxidants for instance in cancer prevention and treatment, is still subject to controversy [19,67,133].

Redox homeostasis of the cell is ensured by its complex endogenous antioxidant defense system, which includes endogenous antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and non-enzymatic compounds like glutathione, proteins (ferritin, transferrin, ceruloplasmin, and even albumin) and low molecular weight scavengers, like uric acid, coenzymeQ, and lipoic acid [9].

It has been confirmed that exogenous antioxidants (Fig. 2) present in fruits and vegetables always counterpart the activity of the above-mentioned endogenous antioxidative defense.

Antioxidants like vitamin C and E, carotenoids, and phenolics (stilbenes, phenolic acids such as benzoic and hydroxybenzoic acids, cinnamic and hydroxycinnamic acid derivatives and flavonoids-flavonols, flavans, flavanones, flavanols, flavones and anthocyanidins as the aglycones of anthocyanins, presenting a flavylium or 2-phenylchromenylium ion skeleton), are presently considered to be the main exogenous antioxidants. Clinical studies proved that a diet rich in fruits, vegetables, whole grains, legumes, and omega-3 fatty acids could work as preventative agents regarding disease occurrence [137].

Another source of exogenous antioxidants is constituted by dietary supplements, as providers of nutrients such as vitamins, minerals, fibres, fatty acids or amino acids, which are either lacking or not found in necessary amounts in the diet. Food supplements may comprise a series of antioxidants, such as vitamin A (retinoids, carotenes), vitamins C and E (tocopherols), lycopene, lutein, ubiquinone, glutathione, polyphenols (flavonoids and nonflavonoids), resveratrol and N-acetylcysteine [9].

Providing cells with exogenous antioxidants may retard the uptake of endogenous antioxidants, for the total "cell antioxidant potential" to remain unaltered [9]. Thus, the antioxidant supplements may improve the organism's capacity to contain the oxidative stress, that cannot be amended by the intervention of endogenous antioxidant defenses. Nevertheless, the issue of the synthetic antioxidants has been subjected to controversies: for instance, there are claims that Recommended Daily Allowances of vitamin C and E are not sufficient to counteract oxidative stress. Moreover, it was stipulated that the ingestion of high amounts of antioxidant supplements may result in prooxidant effects, or in the so-called "antioxidative stress" [138]. Cutler suggested that most organisms are capable of keeping their set points of oxidative stress, irrespective of antioxidant supplementation. He also attributes to these supplements a minimal effect on longevity and postulates that most humans maintain their established level of oxidative stress even if they consume additional antioxidant supplements. The use of antioxidant supplementation proves its effectiveness if the initial oxidative stress level is above normal or above the individual's set point of regulation [139,140]. Thus, the antioxidant supplements may reduce the increased levels of oxidative stress that cannot be inactivated by the endogenous sources [9].

Various attempts meant to investigate and characterize the antioxidant activity, proved that their modality of action, as well as protection targets may vary depending on their use. In chemical industry, the term "antioxidant" most oftenly refers to a compound that delays autoxidation of chemicals such as rubber and plastics [141]. In this case, autoxidation is caused essentially by radical chain reactions between oxygenated species and substrates, antioxidants (sterically hindered phenols and amines) being chain-breaking radical scavengers. In food science, antioxidants comply with a larger purpose, this category including compounds that fight against fat rancidity, as well as *dietary antioxidants*, defined previously as chemical compounds that "significantly decrease the deleterious effects of reactive oxygen and nitrogen species, on normal physiological functions in humans" [142]. Thus, the concept of dietary antioxidant is not restrictive and it complies with all mechanisms of action, which implies "sacrificially" scavenging reactive oxygenated or nitrogenated species to interrupt the radical chain reactions, or preventing the reactive oxidants from developing. Dietary antioxidants may act as radical chain reaction inhibitors, metal chelators, oxidative enzyme inhibitors and antioxidant enzyme cofactors [141].

Synthetic antioxidants used in food preservation against rancidity and having no natural correspondents, include phenolics, such as gallic acid esters or synergistic butylated hydroxyanisole and butylated hydroxytoluene [143]; the phenolic compound less sterically hindered (BHA) can react with peroxyl radical yielding a highly unstable radical species, aryloxy, which can subsequently react with BHT, leading to BHA regeneration and the formation of a stable radical, unable to continue the radical chain process [144].

Comparative studies have emphasized that, while autoxidation of lifeless matter occurs by radical chain reactions, oxidation in biological media is essentially hosted by redox enzymes. Nevertheless, radical lipid autoxidation as nonenzymatic process may also develop in biological media. In view of the previously discussed aspects, biological antioxidants (both endogenous and exogenous) were classified in two main groups: enzymatic antioxidants (e.g., superoxide dismutase, catalase, glutathione peroxidase) and nonenzymatic antioxidants such as oxidative enzyme (e.g. cyclooxygenase or lipooxygenase) inhibitors, antioxidant enzyme cofactors (Se, coenzyme Q_{10}), ROS/RNS scavengers (vitamin C, vitamin E), and transition metal chelators (e.g. EDTA) [141].

Attempts were made to classify antioxidant systems from the reactivity standpoint: the so called "first line of defense" has been identified as the enzymatic antioxidant system, including superoxide dismutase which depletes superoxide radical anion $O_2^{\cdot-}$, catalase that decomposes H_2O_2, and also the glutathione peroxidase/glutathione reductase system. The "second line of defense" is represented mainly by reduced thiols and low molecular-weight antioxidants. The latter include a broad range of molecules that are either components found in dietary products, both hydro- and liposoluble (tocopherols, ascorbate, retinols, polyphenols, etc.) or metabolic compounds (urate, ascorbate, and reduced glutathione). These compounds impart basically the antioxidant capacity to biological media. The respective biomolecules can reach particular locations in cells affected by the oxidative attack [15,19,145–147].

Moreover, another classification of antioxidants (referring to both endogenous and exogenous, natural or synthetic) is the one that takes account on their solubility, such as water soluble (flavonoids, ascorbic acid, uric acid, glutathione) and lipid soluble (carotenoids, tocopherols, ascorbyl palmitate/stearate) antioxidants [143].

2.2. Mechanism of action of antioxidants

Antioxidants can act at different steps of the oxidative radical process and this can be described by taking into account the lipid peroxidation in cell membranes or foodstuffs, which implies the successive steps of initiation, propagation and chain termination [148].

$$In - In \rightarrow In\cdot + In\cdot \quad \text{initiation}$$

$$In\cdot + L - H \xrightarrow{k_{iLH}} In - H + L\cdot$$

$$L\cdot + O_2 \xrightarrow{k_{perox}} L - OO\cdot \quad \text{propagation}$$

$$L - OO\cdot + L - H \xrightarrow{k_p} L - OOH + L\cdot$$

$$2\,L - OO\cdot \xrightarrow{k_t} [L - OO - OO - L] \quad \text{termination}$$

$$[L - OO - OO - L] \rightarrow \text{Non radical species} + O_2$$

Detailed descriptions of the steps which are part of the radical sequence, especially focused on initiation and propagation, revealed that lipid oxidation in cell membranes can be *promoted* by exogenous physical and chemical factors, such as air pollution,

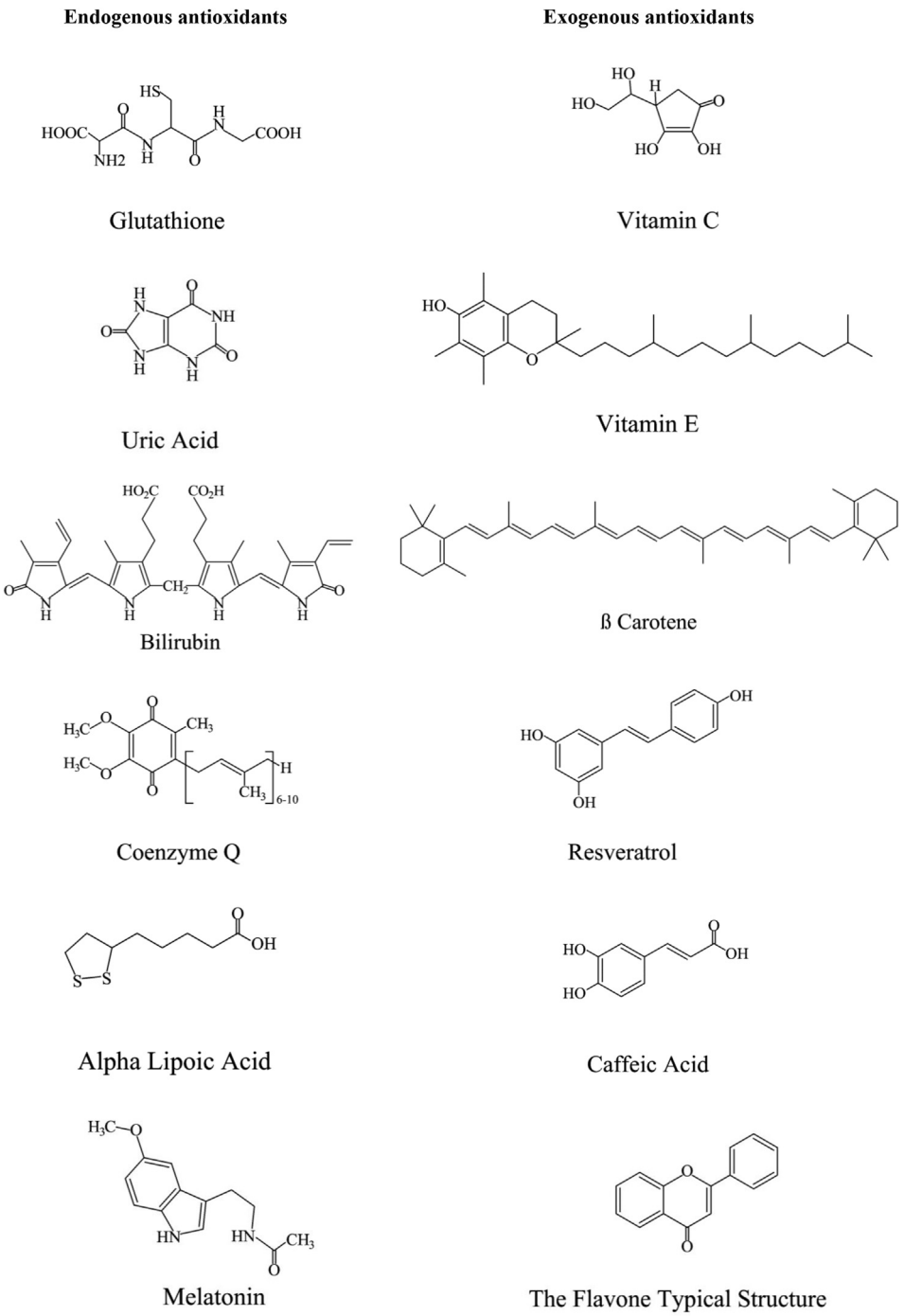

Fig. 2. Schematic representation of the structures of major endogenous and exogenous antioxidants.

smoking, UV-light, ionization radiation, endogenous enzyme systems (NADPH oxidase, xanthine oxidase, uncoupled nitric oxide synthase and cytochrome P450), as well as the electron transport chain in mitochondria [148].

It was described that the *propagation* step of peroxidation begins by oxygen addition to carbon-centered radicals, occurring at, or near the diffusion-controlled rate. The propagation, in most oxidations following a radical mechanism, occurs at a usually slow rate, and is represented by the transfer of a hydrogen atom to the chain carrying peroxyl radical. Peroxyl free radicals can additionate to carbon–carbon double bonds. Conjugated dienes may be especially subject to peroxyl addition. Intramolecular radical substitution on peroxide and radical cyclization reactions may occur, yielding cyclic peroxides, whereas polyunsaturated lipids participate in peroxidation reactions [148].

Antioxidants can react by depleting molecular oxygen or decreasing its local concentration, removing prooxidative metal ions, trapping aggressive reactive oxygen species such as superoxide anion radical or hydrogen peroxide, scavenging chain-initiating radicals like hydroxyl OH·, alkoxyl RO· or peroxyl ROO·, breaking the chain of a radical sequence or quenching singlet oxygen ($^1O_2$) [149].

Antioxidants inhibiting lipid peroxidation by removing oxygen, those acting by quenching O_2, decreasing its concentration, or by

removing pro-oxidative transition metal ions, are called preventative antioxidants. Those able to catalytically deplete reactive oxygen species are also preventative, and since they are represented by enzymes (e.g. catalase, superoxide dismutase and glutathione peroxidase) are not consumed in the reaction. On the other hand, chain-breaking antioxidants, singlet oxygen quenchers and metal chelators are expended, while fulfilling their protective role. In many cases, the same antioxidant can follow more possible mechanisms of action: propyl gallate, a partially water-soluble phenolic food antioxidant, is a chain-breaking antioxidant, a radical scavenger and his ability to bind iron has been reported as well [11,149].

It was established that chain breaking antioxidants, able to scavenge radical species are called primary antioxidants. Secondary antioxidants are singlet oxygen quenchers, peroxide decomposers that yield non-radical species, metal chelators, oxidative enzyme (e.g. lipooxygenase) inhibitors or UV radiation absorbers [143,144].

Secondary antioxidants may exhibit synergetic effects in combination with primary antioxidants, following several possible mechanisms [144]:

- stabilizing primary antioxidants by creating an acidic environment
- regenerating primary antioxidants by hydrogen donation
- chelating pro-oxidative transition metal cations
- quenching molecular oxygen

Moreover, it has been noted that antioxidant enzymes can catalyse the synthesis or the regeneration of non-enzymatic antioxidants [149].

2.3. The specific behavior of antioxidants in particular aspects of oxidative stress

2.3.1. Endogenous antioxidants

2.3.1.1. Superoxide dismutases. Superoxide dismutases are part of the enzyme defense system against oxidative decay, by turning superoxide radical anion to H_2O_2. Three types of superoxide dismutases can be encountered in mammalian tissues: *copper–zinc containing* superoxide dismutase (SOD1) present in the cytosol, *manganese containing* superoxide dismutase (SOD2) found in the mitochondrial matrix and *extracellular* superoxide dismutase (SOD3). All three are highly expressed, mainly in the renal tubules of healthy kidneys [39,150]. A recent study proved that SOD1 is a major antioxidant enzyme in controlling oxidative stress in conditions of renal injury [151].

2.3.1.2. Catalase. Catalase represents the enzyme involved in the reductive depletion of H_2O_2 to water. It is expressed in the majority of the cells, organs, and tissues and at elevated concentrations, in the liver and erythrocytes [39].

Other enzymatic antioxidants, including *peroxiredoxin*, *thioredoxin reductase*, *and glutathione peroxidase*, mainly intracellular, are responsible for H_2O_2 and also organic peroxides inactivation, yielding water/alcohols and oxygen [39].

2.3.1.3. Glutathione peroxidase. Glutathione peroxidase, a selenium-containing enzyme, catalyses both the reduction of H_2O_2, and organic hydroperoxides to water or corresponding alcohols. Reduced glutathione functions as effective electron donor in the process, as free thiol groups are oxidized to disulfide bonds, as follows [18]:

$$H_2O_2 + 2\ GSH \rightarrow GS\text{-}SG + 2H_2O$$

2.3.1.4. Thiols. Thiols proved essential antioxidant buffers, by intereacting with nearly all physiological oxidants. Their capacity to keep the homeostatic intracellular and tissue redox status is based on the thiol/disulfide redox couple such as in the case of glutathione, thioredoxins (possessing a dithiol-disulfide active site), and other cysteine-containing proteins [39]. Glutathione, recognized antioxidant and cytoprotectant, can scavenge hydrogen peroxide, hydroxyl anion and chlorinated oxidants [39]. It can be found in levels of 5–10 mM in most tissues [152].

The cysteine-rich class represented by *metallothioneins* are able to bind heavy metals owing to the presence of the –SH groups. *Cysteine residues* can capture aggressive oxygenated radical species like the superoxide and hydroxyl radicals [153]. Nevertheless, during this process, cysteine is oxidized to cystine, with subsequent release of the metal ions which were previously bound to cysteine. Metallothioneins control zinc ion signaling and are involved in the regulation of the tumor suppressor protein p53: co-expression of metallothioneins and p53 and their complex formation in tumor cells, may be involved in regulation of apoptosis in breast cancer epithelial cells [154,155].

2.3.1.5. Uric acid. Uric acid proved its ability to scavenge reactive radicals resulting from deleterious process, such as autoxidation of hemoglobin, or peroxide generation by macrophages [156,157]. Uric acid is an effective scavenger of singlet oxygen, peroxyl and hydroxyl radicals and protects erythrocyte membrane from lipid peroxidation. Previous studies emphasized that, the capacity of plasma urate to fight against lipid peroxidation is confirmed only in the presence ascorbic acid [158]. Studies directed towards its role in experimental allergic encephalomyelitis, reported the capacity of uric acid to block both peroxynitrite mediated nitrosylation of neuronal proteins and the increase in the blood brain barrier, with less leukocytes infiltration [159]. The intervention of both ascorbic acid and thiols is needed for thorough peroxynitrite scavenging [160]. It was assessed that the hydrophobic environment of lipidic media may detrimentally influence the antioxidant action of uric acid [161] and that oxidized lipids are able to turn uric acid into an oxidant [162]. Copper ions and lipid hydroperoxides are able to enhance the oxidative potential of uric acid versus low density lipoproteins, following a not thoroughly elucidated mechanism [162].

2.3.1.6. Bilirubin. Bilirubin exhibits an effective cytoprotective activity [151,163,164]. It has been firstly asserted that the nanomolar tissue concentrations of bilirubin, are much too low to counteract the activity of reactive oxygen species encountered at millimolar concentrations in most cells [152].

It has been confirmed that while the water-soluble glutathione essentially protects water soluble proteins, the lipophilic bilirubin prevents peroxidation of membrane lipids. Inspite of bilirubin tissue amounts that are thousands of times smaller than that of glutathione, the tetrapyrrolic antioxidant can act efficiently, because of the biosynthetic cycle allowing its regeneration from biliverdin, involving biliverdin reductase. After its oxidation to biliverdin, it can be swiftly reduced by biliverdin reductase, back to bilirubin. Depletion of biliverdin reductase caused by RNA interference significantly impairs the cytoprotective effects of exogenous bilirubin, and may result in an increase of oxygenated radical species production and cell death [165].

Along with biliverdin, bilirubin proved an active scavenger towards peroxyl radicals and also confirmed its ability to lower the mutagen influence of oxidative species, polycyclic aromatic hydrocarbons and heterocyclic amines [166,167].

2.3.1.7. Melatonin. This amphiphilic antioxidant has been reported as able to scavenge both oxygenated and nitrogenated species such

as hydroxyl radical, superoxide anion radical or nitric oxide [168,169], and to exhibit excellent protective activity against mitochondrial oxidative stress [170]. The free radical scavenging capacity of melatonin may expand to its secondary, tertiary and quaternary metabolites. Melatonin metabolites AFMK (N(1)-acetyl-N(2)-formyl-5-methoxykynuramine) and AMK (N1-acetyl-5-methoxykynuramine), with known reductive and antiradicalic activity, also downregulate pro-oxidant and proinflammatory enzymes such as inducible nitric oxide synthase and cyclooxygenase-2 [171]. AMK preserves the ability of its precursor to trigger mitochondrial complex I, enhancing ATP production by limiting electron outflow, and impedes the opening of the mitochondrial permeability transition pore [172,173]. Previous studies characterized melatonin as twice more effective than vitamin E, that had been classed as the most powerful lipophilic antioxidant [174].

2.3.1.8. Metal-binding proteins. Several inflammation proteic markers such as *transferrin*, *ferritin*, *lactoferrin*, *ceruloplasmin*, and even *albumin* have been confirmed as non-enzymatic antioxidants that act by sequestrating transition metal ions responsible for the generation of the most of the reactive oxygenated radical species [39]. The ferroxidase-type activity of the mentioned proteins (consisting in catalysing ferrous ion oxidation) results in inhibiting iron-dependent lipid peroxidation, or OH· generation from hydrogen peroxide and superoxide ions. Ceruloplasmin readily removes ferrous ion and reduces molecular oxygen to water, by a four-electron transfer occurring at the active site. Because of its capacity to also bind copper ions, the latter are sequestered in the plasma and their deleterious effects are reduced [114].

2.3.1.9. Reduced coenzyme Q. Reduced coenzyme Q, the essential electron-carrier in the electron transport chain, has proved, alongside vitamin C and vitamin E, its protective role towards cellular membranes and plasma lipoproteins, against radical damage [175,176]. In addition to its capacity to trap lipid peroxyl radicals [177], $CoQH_2$ was demonstrated to be an efficient regenerator of alpha-tocopherol from the alpha-tocopheroxyl radical [178]. $CoQH_2$ traps both the superoxide radical ($O_2^{-}\cdot$) and the perferryl radical (Fe^{3+}-$O_2^{-}\cdot$) [176] as follows:

$$CoQH_2 + O_2{}^{-\bullet} \rightarrow CoQ^{-\bullet} + H_2O_2$$

$$CoQH_2 + Fe^{3+} - O_2{}^{-\bullet} \rightarrow CoQ^{-\bullet} + Fe^{3+} + H_2O_2$$

Hydrogen peroxide is subsequently depleted by catalase, peroxidase, or glutathione peroxidase [176].

Reduced coenzyme Q also quenches carbon-centered lipid radicals or lipid peroxyl radicals [179].

Another stipulated mechanism on which the antioxidant activity of $CoQH_2$ relies, has been described in earlier investigations, reporting the interaction of superoxide dismutase with hydroquinones [180], and it has been finally proved that the former, in conjunction with DT-diaphorase, inhibits autooxidation of hydroquinones [181]. CoQ10 is able to contain ROS generation and DNA damage promoted by UVA, in human keratinocytes [67].

2.3.1.10. Alpha lipoic acid. Alpha lipoic acid is able to scavenge reactive oxygenated and nitrogenated species, as confirmed by biochemical assays involving long incubation times, but there are not significant evidences supporting its radical scavenging capacity within the cell [182]. Nevertheless, the scavenging activity of lipoic acid versus hypochlorous acid has been assigned to the strained conformation of the dithiolane ring, which is lost after reduction to dihydrolipoic acid, the reduced form being regarded as endowed with better bioactivity and antioxidant capacity [183].

Nontheless, the previously given considerations have been challenged by other aspects such as: the enhanced reactivity of the −SH groups, the low dihydrolipoic acid concentration in the cell, the facility of methylation of one or both −SH groups, the rapid side-chain oxidation to give lower molecular mass metabolites and the rapid outflow from the cell. It was suggested that intracellular dihydrolipoic acid establishes disulfide bonds mainly with cysteine moieties of cytosolic and mitochondrial proteins [184].

2.3.1.11. Endogenous organic selenium. It has been stated that selenium is not a direct reactive oxygen/nitrogen species scavenger itself, and that the assessed in vitro antioxidant capacity of selenium compounds is not relevant for the selenium functions in biological media. It functions primarily as cofactor of glutathione peroxidase, so contributes to reducing hydrogen peroxide and peroxides [141]. It is also present in the structure of selenoprotein P and thioredoxin reductase, the flavoenzymes that, with NADPH contribution, can keep thioredoxin in reduced state. Besides its role as *endogenous antioxidant enzyme cofactor*, it can be added that in organic exogenous sources [185–188], selenium is stored in seleno-aminoacids, as it will be shown in the next Subsection.

2.3.2. Exogenous antioxidants

It has been suggested that a diet rich in antioxidants can bring health benefits and a lot of interest is directed towards assessing the antioxidant capacity of natural products [2].

2.3.2.1. Ascorbic acid. Ascorbic acid, one of the most ubiquitous hydrosoluble antioxidants, is endowed with enhanced activity, being readily oxidized to dehydroascorbic acid. The latter suffers irreversible hydrolysis to 2,3-diketo-L-gulonic acid with subsequent decarboxylation, resulting in carbon dioxide and components of the pentose phosphate cycle, or oxalic acid and threonic acid. The L-enantiomer of ascorbic acid (vitamin C) is involved in maintaining vascular and connective tissue's integrity, in iron absorbtion and collagen biosynthesis, neuroprotection, but also in hematopoiesis and leukocyte functioning [189–196]. Vitamin C accomplishes essential roles in the brain, including being cofactor of dopamine beta-hydroxylase, and thus takes part in catecholamine biosynthesis. It also protects membrane phospholipids from peroxidative damage, and was demonstrated to be an efficient free radical scavenger in the brain [191,195,196]. A higher than 10-fold gradient between the concentration of ascorbic acid in brain and serum has been reported, indicating an active transport mechanism of ascorbic acid in the brain [192,197,198].

Vitamin C scavenges hydroxyl, alkoxyl and superoxide radical anion in biological media, but also reactive nitrogenated species, by forming semidehydroascorbic acid and therefore, prevents the oxidative decay of essential biomolecules [39,199,200]. Although ascorbic acid is not a direct scavenger of lypophilic radicals, it has a synergistic effect in combination with tocopherol, in lipid peroxide radicals removal. At the lipid-aqueous interphase, ascorbic acid reacts with membrane-bound oxidized tocopheroxyl radical reducing it, and regenerating active tocopherol, able to accomplish its antioxidant roles [200–202].

$$LOO\cdot + TOH \rightarrow LOOH + TO\cdot$$

$$AscH^{-} + TO\cdot \rightarrow Asc^{\bullet -} + TOH$$

where TO• represents the tocopheroxyl radical occurring from the reaction of tocopherol (TOH) with the peroxyl radical (LOO•), $AscH^{-}$ is the ascorbate monoanion, $Asc^{\bullet -}$ is the ascorbate anion radical [200].

Ascorbic acid efficiency as primary antioxidant in plasma, has

been reported as the greatest, followed by bilirubin, uric acid, coenzyme Q, and vitamin E [175].

A problem with ascorbic acid is its prooxidant activity, exhibited in the presence of transition metal cations: ascorbate ion, can reduce trivalent iron to its divalent form, being itself oxidized to dehydroascorbate [200,203,204].

$$2\ Fe^{2+} + \text{Ascorbate} \rightarrow 2\ Fe^{3+} + \text{Dehydroascorbate}$$

The metal ion can be consequently reduced, reoxidated and again reduced, in a redox cycle generating reactive oxygen species [200,203,204]. In the presence of molecular oxygen, superoxide radical anion is formed, which dismutes to hydrogen peroxide and molecular oxygen [200].

$$Fe^{2+} + O_2 \rightarrow Fe^{3+} + O_2^{\bullet -}$$

$$2\ O_2^{\bullet -} + 2\ H^+ \rightarrow O_2 + H_2O_2$$

The occurring Fenton-type reactions result in reactive oxygen species generation, namely the highly oxidizing hydroxyl radical and hydroxyl anion.

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\cdot + OH^-$$

2.3.2.2. Vitamin E. Vitamin E (alpha-tocopherol) fights against lipid peroxidation of cell membranes and can stop the radical chain by forming a low-reactivity derivative unable to attack lipid substrates [199]. Thus, vitamin E accomplishes its role in membrane preservation against free radical damage promoted by low-density lipoproteins. It can positively alter the oxidative stress biomarkers, improves erythropoiesis or can lower the necessary erythropoietin dose [205]. It has been assessed that by the intake of high-dose vitamin E supplements, an inhibition of proatherogenic processes can be achieved, by the release of superoxide radical anions and IL-1β by activated monocytes, lipid oxidation, platelet aggregation, in vivo smooth muscle cell proliferation, and monocyte adhesion to the endothelium. Vitamin E contributes to stabilizing atherosclerotic plaque [206,207].

2.3.2.3. Carotenoids: beta-carotene. Beta-carotene is a highly effective singlet oxygen physical quencher, the latter being responsible for UV light-damage of skin, cataract, macular degeneration, and whose addition to diene structures results in endoperoxides [141,208–210]. The role of beta-carotene in systemic photoprotection, originating from its antioxidant properties, is counterparted by some reported prooxidant effects [67].

Research studies have focused towards another potent carotenoid, lycopene, and its presence in plasma and serum has been reversely associated with cancer risk [211–217]. Comparable correlations have been established for markers of cardiovascular diseases, osteoporosis, cognitive function, and body weight [218–225]. It has been settled that 40 g tomato paste incorporates an approximate lycopene amount of 16 mg and that consumption for a period longer than 8 weeks has beneficial effects in UV-induced erythema [226–228]. Bell peppers proved able to prevent cataract, owing to the presence of beta carotene and vitamin C [185].

It has been found that the antioxidant activity of *lycopene* is superior to that of *beta*-carotene and *alpha*–tocopherol [229,230]. The preventative tasks of lycopene [231] are founded on its enhanced singlet oxygen quenching ability [232], which proved the best of all 600 natural carotenoids [229] and are also due to its structure: as it is represented by a tetraterpene hydrocarbon polyene, possessing eleven conjugated and two unconjugated double bonds, it can readily interact with electrophilic reagents, which implies an enhanced reactivity versus oxygen and oxygenated free radical species [232]. Carotenoids can undergo reaction with free radicals following three possible mechanisms: electron transfer, hydrogen abstraction and radical addition [233]. The scavenging potential of lycopene towards nitrogen dioxide, as well as thiyl and sulphonyl radicals has been confirmed previously [234]. It has been assessed that lycopene and torulene possess better reactivity than beta-carotene versus peroxyl radicals [235]. The C5 position has been established as the major ‴OOH addition site. Lycopene has also been confirmed as able to scavenge peroxynitrite, noted for its damaging oxidizing potential, in vitro and in vivo [236–238]. It was described that this reaction may lead to oxidized lycopene products endowed with biological activity [239]. It was postulated that lycopene might improve the cell's antioxidant protection by regenerating both vitamin E and C from their correspondent radical forms, on the basis of its capacity to reduce the δ-tocopheryl radical [240]. When tocopherols are not present in the reaction environment, the radical cations derived from lycopene react, to finally yield stable products [234]. Skin lycopene has been confirmed more susceptible to UV light stress than beta–carotene [229,230].

2.3.2.4. Phenolic antioxidants

2.3.2.4.1. Stilbene derivatives: resveratrol. Resveratrol has been classified as antioxidant, cyclooxygenase inhibitor, as phytoalexin, peroxisome proliferator-activated receptor stimulator, endothelial nitric oxide synthase inducer, as well as silent mating type information regulation 2 homolog 1 activator [241].

The most significant sources are represented by grape skins and red wine. This stilbene derivative traps reactive oxygen species, acts as a metal chelator and modulates enzyme activity [242,243]. Both red wine and resveratrol proved able to decrease lipid peroxidation in the hippocampus of diabetic rats. These antioxidant properties exhibited in this brain region were certified by an increased catalase activity [243].

2.3.2.4.2. Phenolic acids (benzoic and cinnamic acid derivatives). The results of a comparative investigation proved the ability of gallic acid and its esters to scavenge hypochlorous acid and to decrease the peroxidation of oxidated brain phospholipids in ethanol solution. Studies on their interaction with trichloromethyl peroxyl radical proved weaker reactivity of gallic acid, in comparison to methyl, propyl, or lauryl gallate. A moderate inhibition of the reaction of superoxide radical anion with cythochrome c was noticed for gallic acid and its esters, indicated by the lowered values of the respective rate constants. Despite these findings supporting antioxidant activity, gallic acid esters escalated damage of HO· sensitive deoxyribose, in the presence of the ferric – EDTA complex, showing prooxidant behavior in the presence of transition metal complexes [244].

Hydroxycinnamic acid derivatives act as chain-breaking antioxidants, able to scavenge free radicals due to their hydrogen-donating ability, with subsequent stabilization of the resulting phenoxyl radical [245].

Chlorogenic acid, ester of caffeic and quinic acid, is one of the most effective free radical scavengers encountered in eggplant [185,246]. Beneficial effects assigned to chlorogenic acid often used as model phenolic antioxidant, refer to antimutagenic, antimicrobial, anti-low density lipoproteins and antiviral activities [246].

Comparative investigations on the antioxidant strength of phenolic non-flavonoid compounds present in diet, focused on chlorogenic acid and caffeic acid. Kinetic studies showed the ability to quench superoxide and hydroxyl radicals. Chlorogenic acid

determined the inhibition of chain lipid peroxidation, by trapping peroxyl radical. It was also established that chlorogenic acid can quickly react with peroxynitrite, in a concentration and pH dependent mode [247].

2.3.2.4.3. Flavonoids. Quercetin and rutin represent two of the most studied flavonoids. Their antioxidant behavior in lipid peroxidation systems, has been investigated and compared to that proper to other flavonoids [248–254]. Quercetin and rutin, but also apigenin and naringin emphasized antioxidant activity manifested against superoxide radical anion [255–257]. Hesperidin, naringenin, and naringin, mainly present in citrus, exhibited low antioxidant activity in lipid peroxidation systems [251,252,255].

Quercetin inhibits the cytotoxicity and the macrophage oxidative alterations of low density lipoproteins by preserving the alpha-tocopherol level and delaying the onset of lipid peroxidation [258]. At elevated levels, quercetin and rutin protect against cell damage caused by oxidized LDL, by inhibiting lipoprotein oxidation. At low concentrations, they provide direct protection of the cells from the cytotoxicity of oxidized LDL [259]. It is believed that quercetin inhibitive influence against xanthine oxidase activity occurs in a competitive manner [260]. Compared with other influences on oxidant enzymes, quercetin can as well inhibit cyclooxygenase and lipooxygenase [253,256,258,261]. Apigenin, kaempferol, naringenin, and rutin also proved inhibitors of lipooxygenase [253,261,262]. Rutin exhibited a moderate preventative activity versus hydrogen peroxide – induced oxyhemoglobin oxidation and heme loss [263].

Nevertheless, flavonoids may show prooxidant activity: in the presence of Fe^{3+}-EDTA at pH 7.40 and for a 100 mM concentration value, quercetin promotes hydroxyl radical generation from H_2O_2, as proved by the deoxyribose assay [264]. Kaempferol can cause DNA degradation and lipid peroxidation in rat liver [265]. These pro-oxidant effects exhibited in physiological media, occur in the presence of transition metal cations.

Nasunin, the anthocyanin present in the peel of eggplant, purple radish, red turnip, and red cabbage, captures reactive oxygenated species, such as hydrogen peroxide, hydroxyl and superoxide and prevents Fenton hydroxyl radical generation, assumingly by chelating ferrous ions [185,266,267]. Thus, nasunin intervention results in beneficial consequences: protecting cholesterol from peroxidation, preventing cellular injury responsible for cancer and lowering free radical damage in joints [185].

A comparative investigation on the peroxyl radical scavenging activity of phenolics present in grape seeds or skins, pointed to the following classification: resveratrol > catechin > epicatechin = gallocatechin > gallic acid = ellagic acid. The three major phenolics present in grape seeds imparted less than 26% of the antioxidant capacity assessed as oxygen radical absorbance capacity, relying on the corrected concentrations of gallic acid, catechin, and epicatechin in grape byproducts. The Authors concluded that dimeric, trimeric, oligomeric, or polymeric procyanidins are mostly responsible for the high antioxidant capacity of grape seeds [268].

A recent study of the flavonoids' propensity to undergo oxidation, relying on their quenching ability towards DPPH·, led to the following classification given by the antioxidant capacity indexes IC_{30} and IC_{50}: 5,6,7-trihydroxy flavone > 4,5,7 trihydroxy-flavanone > 6-hydroxy flavanone > 6-methoxy flavanone > 6-methyl flavone > flavone. Hence, flavones presenting three hydroxyl groups are endowed with the strongest antioxidant ability, whereas simple flavone possesses the weakest antioxidant power. These results were validated by UV-Visible spectrometry [269].

A cyclic voltammetric investigation of the wine phenolics electro-oxidation, proved that phenolics presenting an ortho-diphenol group (catechin, epicatechin, quercetin, gallic, caffeic and tannic acids) and morin are characterized by the greatest antioxidant power and are oxidized at about 400 mV. Phenolics with lower reducing ability, that do not have an ortho-diphenol structure, such as ferulic acid, trans-resveratrol, malvin, as well as vanillic and p-coumaric acids, are subject to slower oxidation, as they present a solitary phenol moiety, in many cases close to a methoxy function. Anthocyanins impart the occurrence of a peak at 650 mV. Phenolics that gave the first peak in the 370–470 mV range can be subject to a second oxidation at around 800 mV: catechin and epicatechin due to the meta-diphenol groups on the A-ring, quercetin owing to the hydroxyl group on the C-ring, and gallic acid due to the third –OH group next to the orthodiphenol structure previously oxidized [270].

Despite the confirmed capacity of polyphenols as recognized antioxidants due to scavenging ROS, phenolics, flavonoids and non-flavonoids may exhibit pro-oxidant activity in the presence of transition metals such as iron or copper, by chelating, reducing them, and subsequently enabling them to form free radicals from interaction with peroxides. It has been suggested that the phenoxyl radicals resulted from hydrogen donation by antioxidants with an ortho-diphenol structure, may have pro-oxidative potential, eliciting ROS generation [271].

$$Ph - O^{-\bullet} + O_2 \rightarrow Ph = O + O_2^{-\bullet}$$

$$Ph - OH + O_2^{-\bullet} + H^+ \rightarrow Ph - O^{-\bullet} + H_2O_2$$

Auto-oxidation may also occur, resulting in further ROS occurrence [271]:

$$Ph - OH + O_2 \rightarrow Ph - O^{-\bullet} + O_2^{-\bullet} + H^+$$

2.3.2.5. Oil lecithins. Oil lecithins (rapeseed, soy, sunflower, oleic, palm, walnut, fish oils and lard), well recognized for their emulsifier properties have been tested for antioxidant properties [272] and it has been established that phospholipids can follow various antioxidative mechanisms: metal chelating properties have been assigned to the amino groups of phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine and to the sugar moiety of phosphatidyl inositol [273–275]. An oxygen barrier effect was noted as well for the mentioned phospholipids at oil/water interfaces, resulting in a protective action against oxygen attack [276]. Phospholipids can donate a hydrogen atom from the $-NH_2$ group, leading to the regeneration of phenolic antioxidants. The most effective synergism is exhibited in the presence of α or γ-tocopherols [277]. Nevertheless, this synergism is negatively affected by high linoleic acid amounts [272]. It was also suggested that hydroxyl and amino groups of phosphatidyl ethanolamine imparted antiradical properties to oil lecithins [278,279].

2.3.2.6. Acetylcysteine. The antioxidant properties of the *acetylcysteine* drug are due to its behavior as free radical scavenger. Moreover, the improvement of the cell's antioxidant capacity, as well as of the coronary and peripheral vascular functions were particularly assigned to the reactive sulfhydryl group [280]. It has been also reported that acetylcysteine diminishes the plasma levels of both 8-isoprostane and oxidized low density lipo-proteins, and lowers anemia [281].

2.3.2.7. Exogenous selenium. Selenium-enriched broccoli was demonstrated to diminish colon cancer and mammary tumors in animal studies [187,188]. When grown in selenium rich soils, onion

and garlic can also store selenium as selenocysteine and selenoproteins [185].

Studies were focused towards comparing organic and mineral selenium supplementation: it has been established that sodium selenite supplementation (50 μg of selenium daily for 28 days) is able to modulate glutathione peroxidase activities through transient and acute modifications in lymphocyte, granulocyte and platelet phospholipid-hydroperoxide glutathione peroxidase activity (GPx4), noticed by day 7 or 14 of sodium selenite intake. In lymphocytes of selenomethionine-treated persons, such modifications arised by day 7 of treatment. It has been stated that the temporary enhanced trigger of the activity of GPx4, a highly stable enzyme which proved often unused in selenium-deficient animal models, may point towards its quality as a marker of acute selenium requirement in humans. Cytosolic glutathione peroxidase (GPx1) activity in the mentioned blood cells exhibited continuous increase during supplementation [282].

The investigation of the effects of sodium selenite and selenomethionine supplementation on meat quality, selenium distribution, and antioxidant status in broilers was performed. Glutathione peroxidase activity in serum and in the investigated organs presented a significant increase in dietary Se supplementation. Sodium selenite determined a better increase of the glutathione peroxidase activities in pancreas and breast muscle than selenomethionine. The additional Se supplementation determined a significant increase in superoxide dismutase activities in tissues (except for kidney). Nevertheless, selenomethionine showed a better capacity to elicit an increase of the total antioxidant capacity than sodium selenite, except for kidney [283].

2.3.2.8. Zinc. Zinc is well known for its role as cofactor of superoxide dismutase, previously presented at *endogenous antioxidants*. With respect to its potential anti-inflammatory and *exogenous* antioxidant role as a *supplement*, it was shown that for subjects receiving zinc supplementation (45 mg zinc as gluconate), plasma levels of lipid peroxidation products (such as hydroxyalkenals or malondialdehyde) and DNA adducts diminished with respect to the placebo group. Lipopolysaccharide-stimulated mononuclear cells from zinc-supplemented subjects, presented lowered mRNA for TNF-α and IL-1β, in comparison to placebo [284].

In a study directed towards assessing to the capacity of zinc to inhibit lipid peroxidation in liposomes and using various oxidation initiators, it was shown that zinc only prevented Cu^{2+} and Fe^{2+}-initiated lipid oxidation. The inhibition of iron-induced lipid oxidation by either α-tocopherol or epicatechin was optimized in the presence of zinc: namely, the mixture of α-tocopherol (0.01 mol %), epicatechin (0.5 μM) and zinc (5–50 μM) almost thoroughly prevented Fe^{2+}-promoted lipid oxidation at 25 μM ferrous ion concentration. The protective action of zinc against iron-initiated lipid oxidation was due to the ability to block negatively charged sites with iron binding capacity [285].

3. Critical view on the oxidant-antioxidant balance

While redox biology implies a slight increment of the reactive oxygenated species level, meant to activate signaling pathways, oxidative stress involves elevated ROS amounts, resulting in the impairment of nucleic acids, protein or lipids [286]. Although it has been confirmed that fruits and vegetables represent secure sources of antioxidant vitamin amounts lowering oxidative stress, it has been reported that high antioxidant supplementation can prove unsafe [287]. The results of randomized controlled trials referring to beta carotene, vitamins A, C, E and selenium supplementation, did not show preventive effects on cancer incidence [288]. For the particular case of gastrointestinal tract cancers, it has been found that beta carotene, vitamin A, and vitamin E supplements were without beneficial effect and increased all-cause mortality [289,290]. Vitamin C and selenium had no proved (either increase or decrease) effect on mortality [291].

Antioxidant supplements administered individually or in specific combinations did not exert any influence on the incidence of oesophageal, gastric, colorectal, or pancreatic cancers when compared to placebo/control. Combinations of β-carotene and vitamin A, or β-carotene, vitamin C, and vitamin E did not considerably change the prevalence of hepatocellular carcinoma [290].

In accordance with the results of trials meta-analysis [292], the use of supplements with beta-carotene and vitamin A (as beta-carotene's metabolite endowed with biological activity) should not be encouraged, as these compounds are linked to all-cause mortality and cardiovascular death. Moreover, because of the lack of mechanistic informations sustaining the effectiveness of vitamin E, it has been concluded that its regular use should be discouraged [292]. It has been found that antioxidant supplements cannot be corroborated with reduced all-cause mortality. Beta carotene, vitamin E, and high vitamin A doses may be even associated with increased all-cause mortality. Therefore, the authors suggested that the use of antioxidant supplements does not represent a primary or a secondary preventive measure [293].

The results of a large trial [294] showed that daily natural-source vitamin E supplementation did not induce any improvement in cardiovascular conditions or cancer (general cancer, breast or colon cancer). Therefore, vitamin E supplementation for cardiovascular disease or cancer prevention among healthy women is not avisable [294].

The antioxidant supplementation resulted from the belief that people exposed to enhanced oxidative stress have elevated antioxidant requirements [295]. The questionable effects may be associated with the differences in functionality and composition between natural sources and synthetic ones [296]. For instance, synthetic alpha-tocopherol (all-racemic alpha-tocopherol), composed of equal amounts of 8 different stereoisomers, is different from its natural form (RRR-alpha-tocopherol) [297]. Also, there are differences between their biological activities [297,298]. Although the role of beta-carotene against cancer initiation has been reported [299], this compound has also been confirmed to behave as prooxidant under condition of oxidative stress, such as the one caused by smoking: oxidation of beta-carotene and DNA oxidative damage are induced, that eventually lead to lung cancer [288,300].

Trials on antioxidant supplementation prove differences in the results reported, that are justified by the type of subjects addressed (with general or high-risk), the different supplement doses (nutritional amounts or higher), the number of antioxidants administered and assayed, and the type of intake (single or in balanced combination). It has been noticed that a particular antioxidant vitamin administered at elevated doses in subjects prone to high pathology risk (such as smokers, asbestos-exposed subjects), may not result in significant beneficial effects and can even have negative outcomes [301].

The processes underlying these effects have been investigated and it has been asserted that antioxidant supplementation, although depleting the reactive oxygenated species, may interfere with the immune's system activity or with defense mechanisms responsible for elimination of impaired cells, apoptosis and detoxification. The antioxidative or prooxidative activities were confirmed as dose dependent [9,291]. Also, antioxidant supplementation might have interdependency, the compounds exhibit their effectiveness when administered in mixtures, and this implies reciprocal influences [301].

While diet usually provides secure vitamin amounts, elevated antioxidant supplementation may change the physiological balance between ROS generation and removal. Moreover, the cell's defense mechanisms (endogenous systems and repair processes), under conditions of enhanced activation, use important energy amounts, too great for ensuring thorough protection against oxidative decline during the whole life-span [9]. Recent studies stipulated that triggering endogenous systems by some prooxidants may even be more beneficial than antioxidant supplementation [302]. It is believed that a series of elements such as polyunsaturated fat, exercise and mild alcohol intake, that are part of the heart-healthy lifestyle, become prooxidant [303].

4. Conclusions

Oxidative stress results from an excessive reactive oxygen species generation, and consists in an imbalance of oxidative to reducing species, being also better defined as a perturbation of redox signalling. The action of reactive oxygenated/nitrogenated species (superoxide anion radical, hydroxyl, alkoxyl, lipid peroxyl radicals, nitric oxide and peroxynitrite) results in alterations and function modulations of key biomolecules.

The marker of DNA damage is represented by 8-hydroxydeoxyguanosine. The oxidative attack on lipids also results in reactive aldehydes, such as malondialdehyde and 4-hydroxynonenal, but also isoprostanes. Oxidation of thiol groups takes mainly account on protein oxidative damage, along with carbonylation that leads to advanced glycation end products. Side-chain oxidation, backbone fragmentation, unfolding and misfolding, with activity loss, may also occur in protein structure.

The oxidative insults of the components of lipid membranes are involved in the mechanism of neurodegeneration, cancer, cardiovascular or inflammatory diseases. It has been confirmed that excessive reactive oxygenated species production may lead to overexpression of oncogene genes or to formation or mutagen compounds, can promote pro-atherogenic activity, and is related to senile plaque occurrence or inflammation.

In many cases, the results of oxidative injury caused by reactive oxygenated species, become themselves sources of oxidative stress: the damaging of the membranes and protein structure can further promote ROS propagation, leading to enhanced oxidative impairment.

Antioxidant intervention consists in radical chain breaking through hydrogen donation, quenching singlet oxygen, peroxide decomposing, oxidative enzyme inhibition or UV radiation absorbtion.

The endogenous antioxidant defense system (antioxidant enzymes, uric acid, bilirubin, metal-binding proteins like ferritin, transferrin, lactoferrin, ceruloplasmin) is complemented by the intervention of exogenous antioxidants present in diet or in nutritional supplements (ascorbic acid, tocopherols, carotenoids, phenolics – flavonoids and nonflavonoids).

Nevertheless, it has been suggested that the organisms can keep constant their level of oxidative stress, irrespective of the intake of antioxidant supplements. It has been stated that antioxidant supplementation proves its effectiveness if the initial oxidative stress is above normal or above the individual's stabilized level.

Antioxidants may exhibit beneficial mutual influences like the synergism of synthetic phenolic antioxidants, or the regeneration of tocopherol from its oxidized form, tocopheroxyl radical, by reduced coenzyme Q or vitamin C.

In some cases, such as the presence of transition metal cations or lipid hydroperoxides, antioxidants may exhibit pro-oxidative effects, it that they become part of redox systems causing reactive oxygenated species generation, particularly hydroxyl radicals.

Conflicts of interest

There are no conflicts of interest involved, and no fundings supporting this paper.

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