Chapter

Antioxidant and Oxidative Stress

Betül Çalişkan and Ali Cengiz Çalişkan

Abstract

Antioxidants are compounds that eliminate oxidative stress in biological systems. Oxidative stress is caused by various radicals formed in the system as a result of oxygen entering the biological system. Structures with unpaired electron are either free radicals or radical ions. Antioxidants neutralize free radicals or radical ions due to the unpaired electron in their structure. The radical ions formed as a result of oxidation is removed from the system without damaging the biological system with the effect of antioxidants. There are many free radicals and radical ions. Among these radical groups are radical ions formed by oxygen which are important for biological systems. Antioxidants are responsible for the destruction of such radicals.

Keywords: antioxidant, oxidative stress, free radical, radical ions

1. Introduction

1.1 Oxidative stress

Oxidative stress is described as the disturbance of the balance between prooxidants (free radicals) and antioxidants. Oxidative stress occurs with the effect of free radicals and oxidants. Free radicals have unpaired electrons. Therefore, they create the oxidation process in the body. Oxidation causes an oxidative stress to occur. Oxidation processes and free radicals are constantly formed in the body. Oxidation is a process that can be harmful or beneficial. If the increase in free radicals is not balanced with antioxidants, the ground is prepared for the harmful process. It plays an important role in the development of diseases as it causes various damages. It creates DNA, lipid and protein damage.

Aging is an inherent mechanism existing in all living cells. There is a decline in organ functions progressively along with the age-relateddisease development. The twomost important theories related to aging are free radical and mitochondrial theories, and these have passed through the test of time. There is claim by such theories that a vicious cycle is generated within mitochondria wherein reactive oxygen species (ROS) is produced in increased amount thereby augmenting the damage potential [1–6].

The effect of oxidative stress and the interaction of aging and age-related diseases are shown in **Figure 1** [2].

Oxidative stress and disease development are shown in **Figure 2** [3].

Prooxidants are subtances that trigger oxidative stress. Prooxidants are reactive oxygen species (ROS). Prooxidants are studied in two groups. These are exogenous prooxidants and endogenous prooxidants. The exogenous prooxidants are studied in six groups. These are pathogens, drugs, toxicants, dietary ingredients, environmental pollution and climate. The endogenous prooxidants are studied

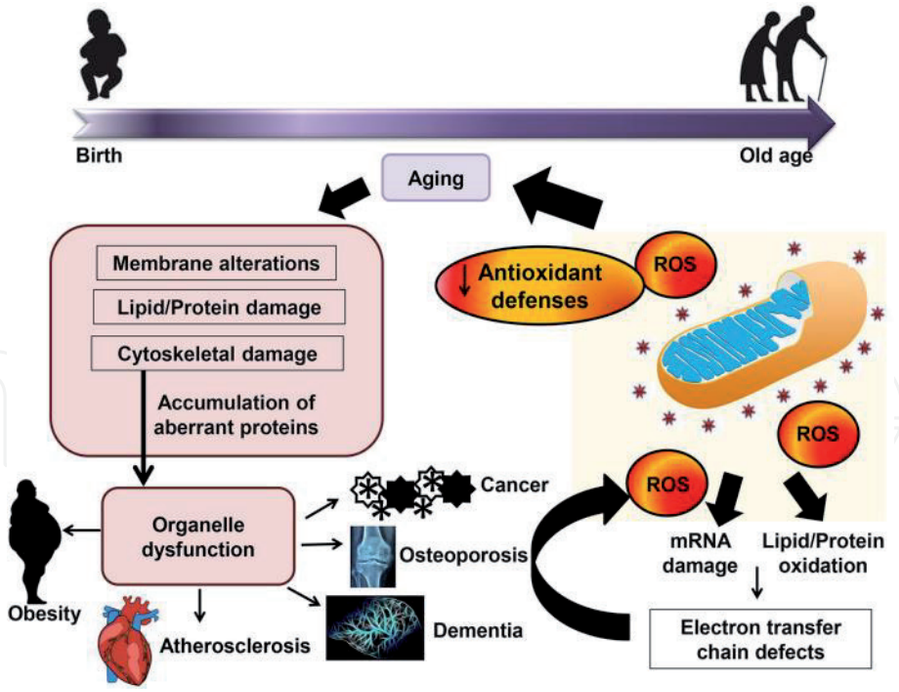

Figure 1.
Effect of oxidative stress and the interaction of aging and age-related diseases.

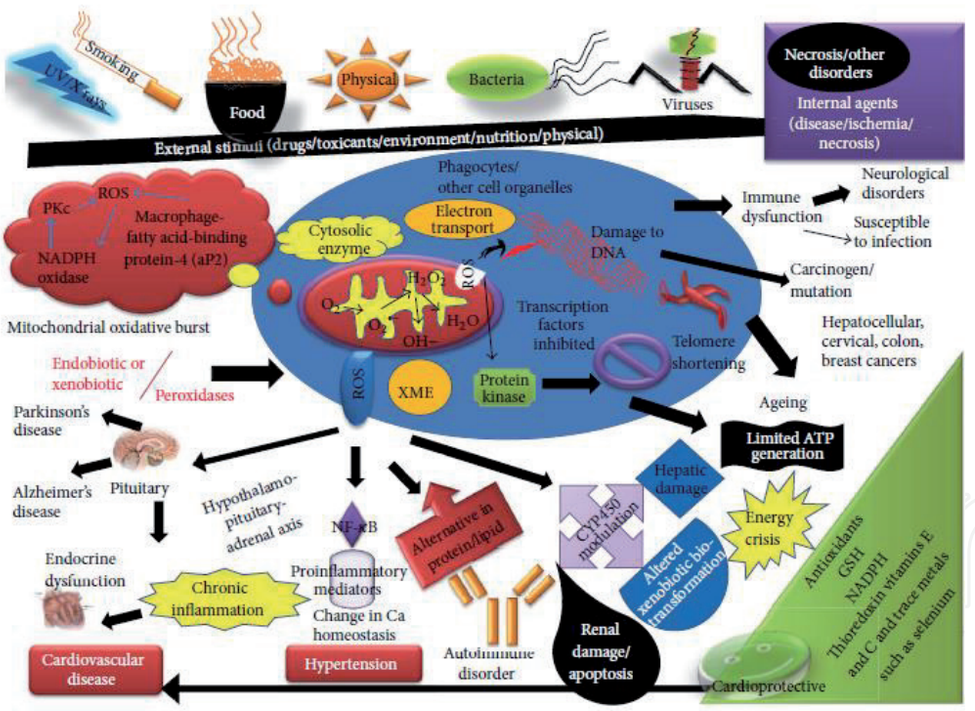

Figure 2.
Oxidative stress and disease development.

in seven groups. These are endogenous metabolites, drug metabolites, cellular metabolism, ion flux, anxiety, pathophysiology and ischemia.

Antioxidants are studied in two groups. These are endogenous antioxidants and exogenous antioxidants. Endogenous antioxdants are studied under two groups. These are enzymatic antioxidants and non-enzymatic antioxidants. Dietary antioxidants derived from fruits, vegetables and grains are exogenous antioxidants.

Contact of living cells with oxygen leads to the formation of reactive oxygen species. Reactive oxygen species are listed in **Table 1** [1–5].

$O_2^{\cdot-}$	Superoxide radical
O_2^{-2}	Peroxide
H_2O_2	Hydrogen peroxide
$HO^{\cdot}$	Hydroxyl radical
OH^-	Hydroxyl ion
$^1O_2$	Singlet oxygen
$HOO^{\cdot}$	Hydroperoxyl radical
$LOOH$	Alkylhydroperoxide
$LOO^{\cdot}$	Alkylperoxyl radical
$LO^{\cdot}$	Alkoxyl radical
ClO^-	Hypochlorite ion
$Fe^{4+}O$	Ferryl ion
$Fe^{5+}O$	Periferryl ion
$NO^{\cdot}$	Nitric oxide
$HOCl$	Hypochlorous acid
$GSOO^{\cdot}$	Glutathione thiylperoxyl radical
$GSO_2^{\cdot}$	Sulfonyl radical
$GSO^{\cdot}$	Sulfinyl radical
$GSO_2OO^{\cdot}$	Sulfonyl-peroxyl radical

Table 1.
Reactive oxygen species.

2. Prooxidants

Reactive oxygen species that cause oxidative stress are called prooxidants. Prooxidants occur for a variety of reasons. These may be internal or external causes. Prooxidants are of two types, exogenous and endogenous.

2.1 Exogenous prooxidants

2.1.1 Pathogens

Pathogens are divided into four groups. These are bacteria, virus, fungus and parasite.

2.1.2 Drugs

Common over-the-counter drug like analgesic (paracetamol) or anticancerous drug (methotrexate) causes oxidative stress.

2.1.3 Toxicants

Toxicants are the man-made harmful substances such as insecticides and many other industrial chemicals which are released to the environment by human activities. Carcinogens, mutagens, allergens, neurotoxin and endocrine disrupters are the different types of toxicants 2 [7]. As an external factor, various toxicants cause oxidative stress.

2.1.4 Dietary ingredients

Dietary ingredients are divided into four groups. These are lipids, carbohydrates, highly processed food and antioxidants.

2.1.5 Environmental pollution

Environmental pollution are divided into three groups. These are transition metals, pesticides and drug residues.

2.1.5.1 Transition metals

These are magnesium, iron, copper, zinc, and so forth.

2.1.5.2 Pesticides

These are BHC, DDT, and so forth.

2.1.5.3 Drug residues

Drug residues cause environmental pollution and trigger oxidative stress.

2.1.6 Climate

Climatic effects such as extreme heat, extreme cold etc. cause oxidative stress.

2.1.7 Cigarette smoke

Cigarette smoke accumulates neutrophils and macrophages in the lungs. Therefore, it is a factor that activates the oxidant mechanism in the body [8].

2.1.8 Ozone exposure

The exposure of the body's airways to ozone causes lipid peroxidation and neutrophil flow in the airway epithelium [9].

2.1.9 Hyperoxia

Hyperoxia is the condition in which the lungs and other tissues have higher oxygen levels. It causes reactive oxygen species (ROS) and reactive nitrogen species (RNS) to form in the body [10, 11].

2.1.10 Ionizing radiation

Ionizing radiation transforms hydroxyl radical, superoxide and organic radicals into hydrogen peroxide and organic hydroperoxides by the effect of O_2 . These hydroperoxide species react with redox active metal ions such as Fe and Cu. Thus, they cause oxidative stress [12, 13].

2.1.11 Heavy metal ions

Heavy metal ions such as cadmium, mercury, nickel, lead and arsenic cause reactive oxygen species in the body.

2.2 Endogenous prooxidants

2.2.1 Endogenous metabolites

Endogenous metabolites are defined as substrates or products of approximately one thousand nine hundred metabolic enzymes encoded in our genome [14–16]. There are several studies showing that most of these metabolites are toxic. These toxic metabolites are classified depending on the method of introducing toxicity to cells. They are expressed as ROS-producing metabolites, reactive metabolites, metabolite analogues, excitotoxins, and not established/unknown biology.

2.2.2 Drug metabolites

Drug metabolism is the term used to describe the biotransformation of pharmaceutical substances in the body so that they can be eliminated more easily. The majority of metabolic processes that involve drugs occur in the liver, as the enzymes that facilitate the reactions are concentrated there. The purpose of metabolism in the body is usually to change the chemical structure of the substance, to increase the ease with which it can be excreted from the body. Drugs are metabolized through various reactions including: Oxidation, reduction, hydrolysis, hydration, conjugation, condensation, isomerization [17].

2.2.3 Cellular metabolism

Cellular metabolism is chemical reactions that occur in living things. They are controlled biochemical reactions in metabolism. Biochemical reactions provide growth, proliferation and preservation of structures.

Thanks to the chemical reactions that occur in metabolism, one chemical is transformed into another chemical under the influence of various enzymes. Enzymes direct chemical processes in living things and are indispensable for living things. Enzymes design down to the finest detail the process of homeostasis called the cell's response to environmental changes.

Cellular metabolism is examined as two processes as anabolism and catabolism. Anabolism is referred to as the constitutive metabolic process. In other words, it is a metabolic process in which a cell uses energy to build various molecules such as enzymes and nucleic acids and to maintain the necessary vital activities. Anabolism consists of three basic stages: The first is the process of making precursors such as amino acids, monosaccharides, isoprenoids, and nucleotides. Second, it includes the process by which precursors such as amino acids, monosaccharides, isoprenoids, and nucleotides are activated to reactive forms. Third, it involves the process by which these precursors combine to form complex molecules.

Catabolism constitutes the second part of the metabolic process. It is the process by which complex molecules are broken down by the cell. Reactions in catabolism provide the energy and substances needed by reactions in anabolism. Catabolic reactions are generally exothermic reactions. Catabolism is divided into several subgroups. These are carbohydrate catabolism, fat catabolism and protein catabolism [18].

2.2.4 Ion flux

Ion channels are pore-forming proteins that warrant controlled and directed flux of ions through membranes. Temporal and spatial coordination of ion movements is essential for a wide range of physiological processes including the generation and propagation of the membrane action potential that is critical for

the biomechanical activity of muscle cells. Despite their well-established canonical electrophysiological functions in the heart, recent findings have demonstrated that ion channels also might feature ion flux independent functions during heart development and morphogenesis long before acting as ion-conducting pores [19].

2.2.5 Anxiety

Tension and apprehension cause anxiety. Anxiety disorders can cause low antioxidant defenses and increased oxidative damage to proteins, lipids and nucleic acids pores [20].

2.2.6 Pathophysiology

Pathophysiology means the examination of the causes of the disease, the various effects caused by the disease, and the abnormal changes in body functions that occur with the disease process. Research in the field of pathophysiology has often focused on physical, mental or psychophysiological states that are directly related to disease processes. Topics such as changes in the endocrine system, changes in certain neurotransmitters, or changes in inflammatory parameters related to the activity of the immune system are examples of research in the field of pathophysiology [21].

2.2.7 Ischemia

Ischemia is any reduction in blood flow resulting in decreased oxygen and nutrient supplies to a tissue. Ischemia may be reversible, in which case the affected tissue will recover if blood flow is restored, or it may be irreversible, resulting in tissue death [22].

2.2.8 Physical exercise

Several studies have demonstrated that intense physical exercise causes oxidative stress in animals and humans, being possibly related, for instance, to fatigue and tissue lesions [23].

2.2.9 Antioxidants

There are a number of reasons why high concentrations of antioxidants may be harmful. At high concentrations, antioxidants may act as pro-oxidants, increasing oxidation; protect dangerous cells (such as cancer cells) as well as healthy cells; reduce the health benefits of exercise; have unwanted side effects, such as nausea and headaches, or even reach toxic levels [1–5, 24].

3. Antioxidants

Antioxidants are examined under two headings as natural and synthetic. Natural antioxidants are examined in two groups as enzymatic and non-enzymatic antioxidants.

3.1 Synthetic antioxidants

Synthetic antioxidants make up only one analogue (type) of natural antioxidants and are developed to mimic the most effective analogue of the natural antioxidant. Butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ethoxyquin, propyl gallat and tertiary butylhydroxyquinone (TBHQ) are some of the synthetic antioxidants.

3.2 Natural antioxidants

3.2.1 Exogenous antioxidants

Exogenous antioxidants are prinicipal dietary antioxidants from fruits, vegetables and grains. Exogenous antioxidants are studied in ten groups.

3.2.1.1 Vitamins

Vitamins are examined in two groups as vitamin C and vitamin E.

3.2.1.2 Trace elements

Trace elements are examined in two groups as zinc and selenium.

3.2.1.3 Carotenoids

Carotenoids are examined in four groups as β-carotene, lycopene, lutein and zeaxanthin.

3.2.1.4 Phenolic acids

Chlorogenic acids, gallic acid, cafeic acid, etc. constitute phenolic acids.

3.2.1.5 Flavonols

Quercetin (and their glucosides), kaempferol (and their glucosides) and myricetin (and their glucosides) constitute flavonols.

3.2.1.6 Flavanols

Proanthocyanidins and catechins constitute flavanol.

3.2.1.7 Anthocyanidins

Cyanidin (and their glucosides) and pelagonidin (and their glucosides) constitute anthocyanidins.

3.2.1.8 Isoflavones

Genistein (and their glucosides), daidzein (and their glucosides) and glycitein (and their glucosides) constitute isoflavones.

3.2.1.9 Flavanones

Naringenin (and their glucosides), eriodictyol (and their glucosides) and hesperetin (and their glucosides) constitute flavanones.

3.2.1.10 Flavones

luteolin (and their glucosides) and apigenin (and their glucosides) constituteflavones.

The beneficial and harmful effects of exogenous antioxidants are shown in **Figure 3** [4].

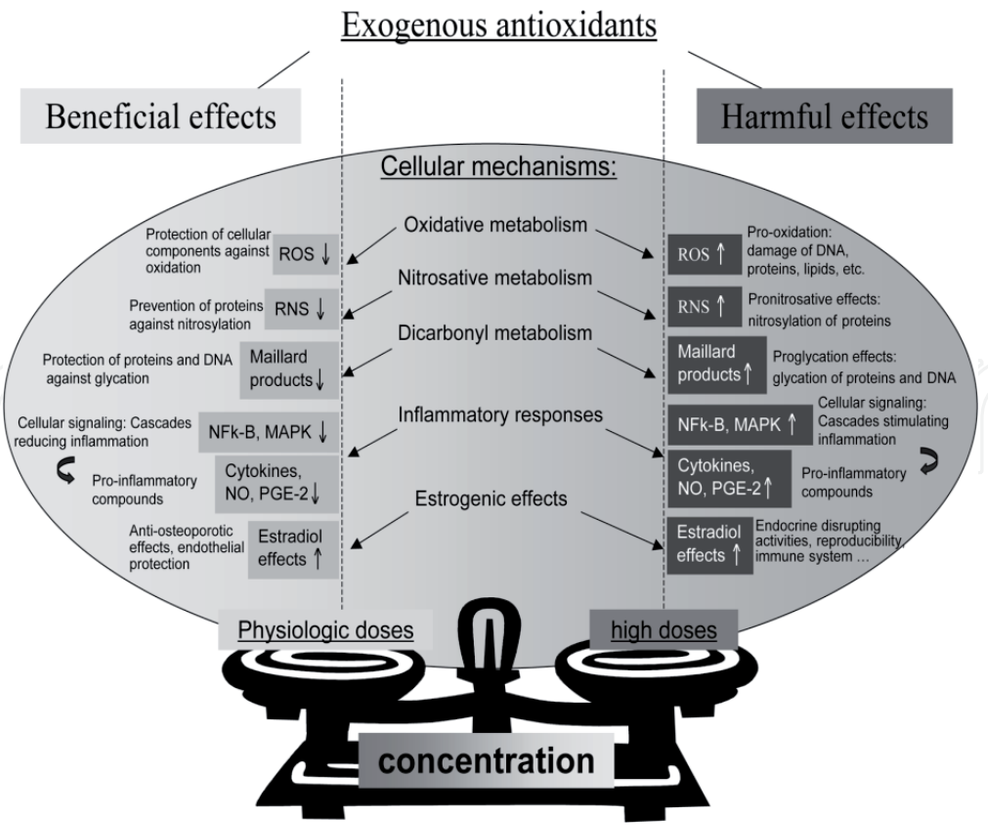

Figure 3.
Beneficial and harmful effects of exogenous antioxidants.

3.2.2 Endogenous antioxidants

Endogenous antioxidants are studied in two groups: enzymatic antioxidants and non-enzymatic antioxidants.

3.2.2.1 Enzymatic antioxidants

Enzymatic antioxidants are studied in five groups.

3.2.2.1.1 Superoxide dismutase (SOD)

Superoxide dismutase (SOD) is enzyme detoxifying superoxide radical ($O_2^{\cdot -}$).

3.2.2.1.2 Catalase (CAT) and glutathione peroxidase (GPx)

Catalase (CAT) and glutathione peroxidase (GPx) are enzymes involved in the detoxification of peroxides (CAT against H_2O_2 and GPx against both H_2O_2 and $ROOH$).

3.2.2.1.3 Glutathione reductase

Glutathione reductase is enzyme involved in the regeneration of glutathione.

3.2.2.1.4 Thioredoxin reductase

Thioredoxin reductase is enzyme involved in the protection against protein oxidation.

3.2.2.1.5 Glucose-6-phosphate dehydrogenase

Glucose-6-phosphate dehydrogenase is enzyme involved in the regeneration of NADPH.

3.2.2.2 Non-enzymatic antioxidants (principal intracellular reducing agents)

Glutathione (GSH), uric acid, lipoic acid, NADPH, coenzyme Q, albumin and bilirubin make up the non-enzymatic antioxidant class [1–5].

4. Conclusion

Oxidative stress is a condition that occurs with the increase of free radicals. Free radicals tend to increase in the body for various reasons. This situation may be caused by exogenous reasons or by various changes in the body (endogenous). As a result of the oxidation process in the body, reactive oxygen species (ROS) are formed. In addition to reactive oxygen species, reactive nitrogen species are also formed in the body. The oxidation process begins with the introduction of food into the body. Oxidation is a process that can be both beneficial and harmful. Oxidation triggers the formation of free radicals, ie reactive oxygen species. If antioxidants do not come into play as a balance element in the body, the increase in free radicals damages the body and causes the formation of the disease process. Depletion of various substances in the body due to age also triggers the formation of reactive oxygen species and the emergence of various diseases. Antioxidants can be various external substances, as well as various enzymes in the body and non-enzymatic substances in the body. With the effect of antioxidants, free radicals are prevented from causing DNA, lipid and protein damage.

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