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Superoxide anion radical: mechanism of action in food spoilage and as a cause of chronic diseases

Radical anión superóxido: mecanismo de acción en el deterioro de alimentos y como causa de enfermedades crónicas

Mendoza-Wilson, A.M, León-López, A.*

Centro de Investigación en Alimentación y Desarrollo, A.C. Coordinación de Tecnología de Alimentos de Origen Vegetal, Carretera Gustavo Enrique Astiazarán Rosas, No. 46, 83304, Hermosillo, Sonora, México.
mwilson@ciad.mx; arely.leon@ciad.mx*

Technological innovation: Superoxide radical action method in food products and degenerative diseases.

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Resumen

Cuando hay un desequilibrio entre antioxidantes y pro-oxidantes como especies reactivas de oxígeno (ROS), tiene lugar el estrés oxidativo. En ROS, el anión superóxido (O_2•-) es el más abundante, se considera un subproducto en la cadena de transporte de electrones, tiene una vida corta de 10^{-5}s y se forma por reducción de un electrón del oxígeno molecular. El O_2•- no es particularmente reactivo, sin embargo, es responsable de la formación de otros tipos de radicales como hidroxilo (•OH) e hidroperoxilo (•HO_2) y especies no radicales como el peróxido de hidrógeno (H_2O_2). También el O_2•- puede reaccionar con el óxido nítrico (NO) formando peroxinitrito (ONOO-) y peróxido de hidrógeno para obtener el radical hidroxilo (•OH), por lo que el anión superóxido es considerado como el radical primario. El O_2•- tiene la propiedad de oxidar macromoléculas biológicas importantes como ácidos nucleicos, lípidos y proteínas, aunque también el O_2•- actúa como agente reductor donando un electrón a metales como el hierro (Fe^{+2}) o el cobre (Cu^{+2}) en la reacción de Fenton. En los productos alimenticios, el superóxido O_2•- puede generarse cuando estos se someten durante su procesamiento a tratamientos como campos eléctricos pulsantes gamma, irradiación, óhmica y microondas, pero la principal fuente de

formación de superóxido en los alimentos son las reacciones oxidativas. La oxidación de lípidos en los alimentos provoca deterioro de la calidad, formación de compuestos nocivos para la salud, afecta negativamente las propiedades sensoriales en frutas, verduras, carnes y lácteos, reduciendo su vida útil produciendo su deterioro. En el cuerpo humano la formación de O_2•- es inevitable, porque se genera en las mitocondrias durante el proceso de respiración, pero también está implicado en el cáncer, artritis reumatoide, enfermedades cardiovasculares (aterosclerosis, hipertensión arterial e insuficiencia cardíaca) y neurodegenerativas (Alzheimer, Parkinson y epilepsia). El objetivo principal de esta revisión fue la recopilación de información relacionada con el mecanismo de acción del anión superóxido tanto como generador del deterioro en productos alimenticios y así como su acción en el cuerpo humano al ser responsable del desarrollo de algunas enfermedades.

Palabras clave: estrés oxidativo, anión superóxido, desperdicio de alimentos, enfermedades degenerativas.

Abstract

When there is an imbalance between antioxidant and pro-oxidants such as reactive oxygen species (ROS) the oxidative stress takes place. In ROS superoxide anion (O_2•-) is the most abundant, it is considered as a byproduct of electron transport chain, this radical has short lifetime of 10^{-5}s, and is formed by one-electron reduction of molecular oxygen. O_2•- is not particularly reactive, however it is responsible for the formation of other types of radical such as hydroxyl (•OH) and hydroperoxyl (•HO2) and non-radical species as hydrogen peroxide (H_2O_2). Also, O_2•- can react with nitric oxide (NO) to form peroxynitrite (ONOO-) and hydrogen peroxide to obtain the hydroxyl radical (-OH), so the superoxide anion is considered the primary radical. O_2•- tends to oxidize important biological macromolecules such as nucleic acids, lipids and proteins, but also acts as a reducing agent by donating an electron to metals like iron (Fe+2) or copper (Cu+2) during Fenton's reaction. In food products, superoxide O_2•- can be generated when these are subjected during processing to treatments such as pulsed gamma electric field, irradiation, ohmic and microwave**,** but the main source of superoxide formation in foods are oxidative reactions. Lipid oxidation in foods causes quality deterioration, formation of unhealthy compounds, and negatively affects sensory properties in fruits, vegetables, meat and dairy products, reducing their shelf life and causing food spoilage. In the human body, formation of O_2•- is inevitable, because it is generated in the mitochondria during the respiration process, but it is also implicated in cancer, rheumatoid arthritis, cardiovascular diseases (atherosclerosis, arterial hypertension and heart failure) and neurodegenerative diseases (Alzheimer, Parkinson and epilepsy). The main objective of this review is to collect information related to the mechanism of action of the superoxide anion both as a generator of spoilage in food products and its action in the human body by helping to the development of some diseases.

Key words: oxidative stress, superoxide anion, food spoilage, degenerative diseases.

Introduction

The formation of free radicals originates from essential metabolic processes in the human body but also from external sources such as x-rays exposure, smoking, pollution, chemicals, among others (1). However, when the endogenous antioxidant defense system is not enough to act against free radicals, the oxidative stress occurs and can generate damage in cellular components (polyunsaturated fatty acids, lipids, nucleic acids and carbohydrates). (2). Free radical that can be defined like small diffusible molecules that are highly reactive and unstable due to their unpaired electron, and their capacity to donate or accept an electron from other molecules. Reactive oxygen species (ROS) are included in these type of molecules. (3). ROS have been related to many chronic diseases including cancer, arthritis, hypertension, neurological disorders, atherosclerosis, infectious caries, gastrointestinal, cardiovascular, neurodegenerative, heart, periodontal, kidney diseases**,** among others (4-7). ROS like hydrogen peroxide, singlet oxygen (1O2), hydroxyl radical (OH), and superoxide radical anion (O_2•-), lead to biological damage (8). Compared with other ROS, superoxide radical anion O_2•-, is formed in the body by catalyzed reactions and/or as a result of nonenzymatic electron transfer, when the electron is converted to molecular oxygen. This type of ROS also participates in the formation of other toxic oxygen species, due to its longer lifetime and ability to move long distances in a cell. In biological systems, superoxide (O_2•-), generally participates in lipid peroxidation systems (2, 9). In contrast to living organism oxidation by free radical can causes spoilage in food products. Various types of free radicals can be generated by food spoilage, endogenous free radicals that are present during biological processes and exogenous free radicals that can be present during food processing. The nature and composition of this type of molecules can affect quality, sensory, physicochemical and sensory characteristics and also loss of nutrients generating toxic substances in the product. Food spoilage is a cause for concern during food processing and storage (10-13). Food spoilage and chronic diseases related to the presence of ROS specially superoxide are of major concern worldwide, causing economic losses and an enormous damage to public health. Therefore, an alternative to combat the presence of free radicals is the addition of natural antioxidants, which are substances that inhibit or delay undesired oxidation reactions, reducing the presence of free radicals in both food systems and in the human body (14, 15).

Oxidative stress and free radicals

Oxidative stress (SO) can be defined as a lack of balance between the pro-oxidant and the antioxidant species resulting in cellular injury and activation of pathological pathways which can cause many diseases (6, 16). Oxidative stress can contribute to diseases by the formation of ROS (reactive oxygen species) (17, 18). (19)**.** Depending of their source, ROS can be classified as: endogenous, when they are generated by mitochondria, cellular metabolism, organelle damage, inflammation and peroxisomes; and exogenous such as environmental pollution, smoking, light, hyperbaric oxygen, thermal shock and drugs (20, 21).

The biological relevant ROS can be divided into following categories:

I). - One electron reduction products: superoxide anion (O_2•−), hydroperoxyl radical (HO_2 •−) and hydroxyl radical (•OH).

II). – Two-electron reduction products of oxygen: hydrogen peroxide (H_2O_2).

III). - Paraffin peroxide homolysis products: alkoxy radical (RO•) and alkyl base peroxide (ROO•).

IV). - Excited oxygen, singlet oxygen and carbonyl compounds. Also, nitric oxide (NO), nitrous anhydride, nitrogen dioxide, nitroxyl anion, peroxynitrite, and nitrosoperoxycarbonate can be considered ROS molecules (22, 23). Although free radicals are very short-lived (on the order of a thousandth of a second), they are highly reactive and can cause damage to million molecules through this self-perpetuating process (Table 1) (24).

Table 1. Reactive oxygen species (ROS) calcification and stability. Modified from (25).

Radical	Half-life (s)	Biomolecule target
Superoxide anion O_2• −	10^{-5}	All biomolecules
Hydroperoxyl HO_2 •−	Unestable	
Hydroxyl radical •OH	10^{-9}	All biomolecules
Hydrogen peroxide H_2O_2	Stable	Polyunsaturated fatty acids (PUFAs)
Alkoxy RO•	10^{-6}	Polyunsaturated fatty acids (PUFAs)
Alkyl peroxide base ROO•	7	Polyunsaturated fatty acids (PUFAs)
Singlet oxygen $^1O_2$	10^{-6}	H^2O
Nitric oxide NO	1-10	Protein, lipids

Superoxide anion (O_2• −)

Under normal physiological conditions, superoxide anion is formed when oxygen accepts an electron and is not in itself particularly reactive. It is also considered as a byproduct in the electron transport chain (8, 26). O_2•− is a free radical produced at physiological pH because it contains an unpaired electron and is a negatively charged species. Furthermore, it is produced during normal aerobic metabolism and constitutes physiological intracellular metabolite (27). The formation and rate of superoxide is related to electrons present on the chain, which can increase under conditions like hyperoxia (excess supply of O_2 in tissues and organs), rising glucose and diabetes. Nevertheless, O_2•− can also be generated through leakage of electrons in the short chain of endoplasmic reticulum (20). Superoxide anion is responsible for the formation of hydroxyl (•OH) and hydroperoxyl (•HO_2), hydrogen peroxide (H_2O_2) and hydroxyl radical (28). Additionally, O_2•− can interact with nitric oxide (NO) forming peroxynitrite (ONOO-) and hydrogen peroxide to obtained hydroxyl radical (•OH), or can be converted by superoxide dismutase (SOD) enzyme action in hydrogen peroxide (20, 29, 30). O_2•- is a ROS highly reactive with: [Fe–S] clusters favoring H_2O_2 release which is a radical membrane-diffusible and longer-lasting; also with Fe_2+ generating •OH by the Fenton reaction (Figure 1) and with superoxide dismutase (SOD) forming enzyme H_2O_2 and O_2 by dismutation of the superoxide (Figure 1) (29).

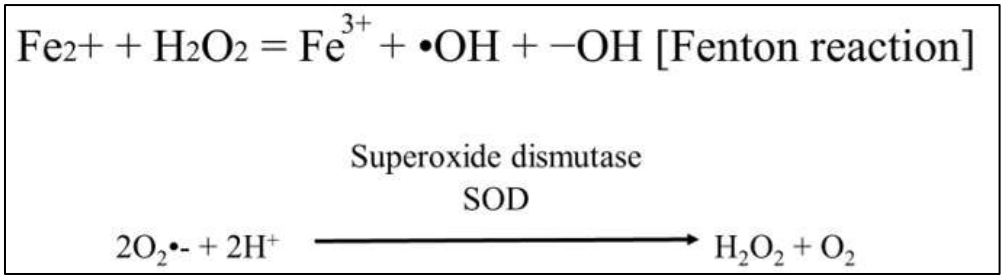

Figure 1. Superoxide anion is converted to another free racial H2O2 hydrogen peroxide by superoxide dismutase (31).

Superoxide action in food systems

The formation of reactive oxygen species (ROS) can be present during the process and storage of food products. Among other sources of ROS and ROS-production in food are bleaching agents, disinfectants and detergents (32). It is extremely important to control the formation of ROS in food products to improve their quality. ROS like hydrogen peroxide and superoxide anion are important precursors for hydroxyl radical and singlet oxygen, the most important ROS generate in food products (32, 33). Sometimes O_2•- acts as a reducing agent donating an electron to metals such as iron (Fe_{+2}) or copper (Cu_{+2}) in Fenton's reaction (34, 35). Under conditions of overproduction and depletion of its scavengers, O_2•- can interact with -SH groups of almost proteins and enzymes and inactivate them, it can also deplete glutathione and acts as initiator of oxidative events presenting the Haber–Weiss reaction as a critical component (36, 37). Superoxide by itself is consider relatively harmless because it does not react with some biomolecules, however it can start pathways of redox reactions producing the formation of highly reactive oxygen species (38).

The formation of superoxide anion radical O_2•- can be carried out by the spontaneous oxidation of several compounds of biological importance like sulfite, thiols, hydroxydopamine, catecholamines, hemoglobin, tetrahydropteridines, and electron carriers (flavins and quinones, nicotinamide adenine nucleotides, menadione, and ferredoxin). Another source of O_2•- is when, the electrons carries after being reduced by enzymatic, chemical or photo chemical action, spontaneously can re-oxidize forming this radical (39, 40). O_2•- can be produced in food products by enzymes as xanthine oxidase, nicotinamide adenine dinucleotide phosphate oxidase, dihydroorotate oxidase, aldehyde oxidase and also through photoactivation of tetrapyrroles like hemoglobin and chlorophyll, or even by applying irradiation that allows hydrated electrons to reduce triplet oxygen (33, 41). In products whit presence of unsaturated fatty acids (UFAs) superoxide anion cannot be by itself an oxidation initiator, because its reduction potential to abstract hydrogen from UFAs is low (42). However, in lipids O_2•- radical can reduce transition metals to a highly active state promoting oxidation. It can also form hydroperoxide radicals which have the potential to extract hydrogen from UFAs by protonated at low pH (40). In food products, superoxide O_2•- can be formed when products are subject to different treatments as pulsed gamma electric field, irradiation, ohmic and microwave during processing, still , the main source of superoxide formation in food is oxidative reactions (33). The damage of oxidation is not limited to high-fat foods like vegetable oils, proteins (dairy and meat products) and pigments (vegetables) compounds such as tocopherols, thiols and ascorbic acid can also be subject to this oxidation process (13, 32,

43)**.** In food oxidative reactions can affect valuable nutrients directly, generating undesirable odors and flavors or even toxic compounds, affecting the sensorial and physiochemical properties of the product (13).

Lipid oxidation

Superoxide O_2•- is considered an important intermediate that causes oxygen toxicity and leads via active oxygen species (hydroxyl radicals) to lipid oxidation, but the presence of the enzyme superoxide dismutase can eliminate it (44, 45). Lipids present in food products can provide texture and flavor to the products but they are also the most chemically unstable components, because they participate in oxidative reactions. Lipid oxidation can be defined as a complex chain reaction process of free radicals (Figure 2) (46, 47). The increase of unsaturated groups (double bonds) increases lipid oxidation which presents three mechanisms: free radical oxidation (autoxidation), photooxidation, thermal and enzymatic oxidation, being autoxidation the most common among all the process of oxidation (38). Autoxidation is the process that leads natural degradation in fats and oils by action of reactive species of oxygen like superoxide and it is the most common process of deterioration/damage in food (45). The reaction generally initiated by exposure to metalloprotein catalysts, metal ions, radiation, ionization, or heat of lipids. The classical route of autoxidation includes initiation reactions in which the production of lipid free radicals (Figure 3), propagation and termination (production of non-radical products) reactions takes place(36, 38).

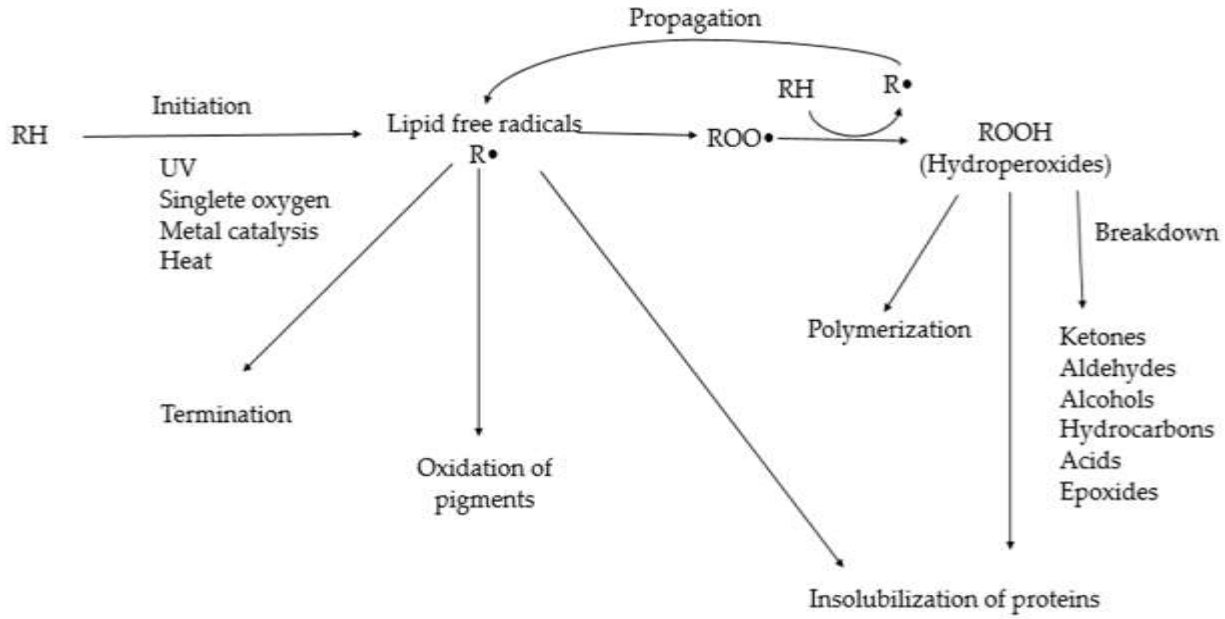

Figure 2. General autoxidation process in lipids. Modified from (36).

Initiation: some initiators (ROS, UV light, heat, metals) affect unsaturated lipids producing free radicals by losing a hydrogen atom (36, 48).

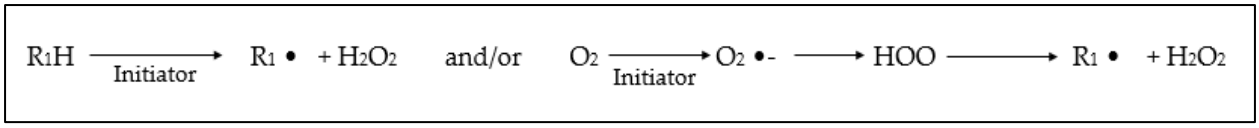

Figure 3. Initiation reaction of the classic route of autoxidation (36).

Propagation (figure 4): lipid radicals react with oxygen to form peroxyl radicals, which are chain carriers of the progressive reaction attacking a new lipid molecule (29, 49).

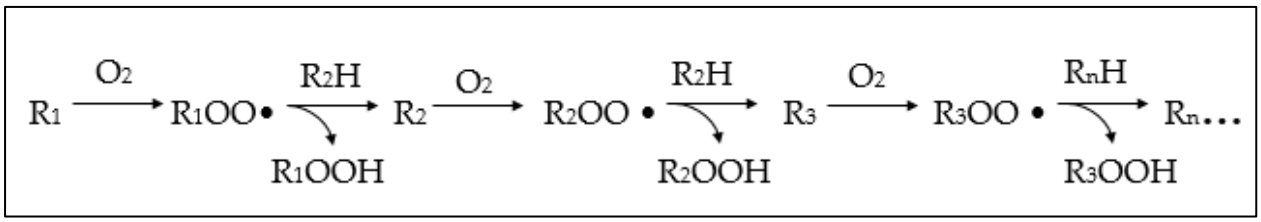

Figure 4. Propagation reaction in autoxidation (36).

Termination (figure 5): In this last stage the two radical interaction may lead to the formation of non-radical and the termination of the free radical chain (36, 45, 50).

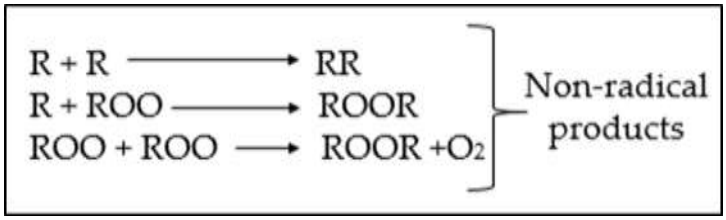

Figure 5. Termination of the route of autoxidation (36).

Lipid oxidation in food causes quality deterioration, formation of unhealthy compounds, negatively affects sensory properties of foods and is an important contributor to reduced shelf life and food spoilage, being a challenge for food scientists and the industry (46, 51). It can effect and causes deterioration of meat and dairy products, fruits and vegetable crops (36).

This phenomenon in meat and meat products affect quality because of the production of changes in taste, odor, color and texture, induces the development of toxic compounds and reduces shelf life. Additionally it has a negative influence on protein solubility and water holding capacity and it lowers the bioavailability of some nutrients (52)**.** Meat products with higher concentrations of myoglobin**,** as beef meat products, are more susceptible to lipid oxidation, being the target of metal ions (in free or hemeproteins form), which can donate electrons leading to increased rates of free radical production (53). Lipid oxidation in meat products depends on the type of product and type of process used to produced them, like cooked products, as sausages (53-55); source of meat as chicken (52, 56, 57); rabbit (46, 58, 59); pork (60, 61) and also type of packing applied to the products (modified atmosphere, vacuum, oxygen permeable, active packaging and others). In addition, storage conditions (time and temperature) can also accelerate lipid oxidation (62-64).

An integral part of human diet and nutrition come from milk and dairy products, because they are a great source of proteins, calcium, amino acids, vitamins fat and essential fat

acids, which are involved in several physiological and biochemical functions (65). Lipid oxidation is one of the principal reasons for milk and dairy products spoilage, which impairs their nutritional and sensory quality. Oxidative stability of milk and dairy products depends mainly of fatty acid composition, metal ion contamination, processing, packaging and storage (65). Polyunsaturated fatty acids (PUFA´s) are the most sensitive compounds present in milk and dairy products to autoxidation, the main product generated in this process are the hydroperoxides (66). Hydroperoxides are highly reactive compounds that break down easily in hydrocarbons, aldehydes, alcohols, ketones and other non-volatile compounds. The hydroxyperoxides generated in lipid oxidation are responsible for off-flavors, and may also interact with other essential nutrients as vitamins in raw milk (43). Some others factors that influence lipid oxidation in milk and dairy products are the temperature in thermal treatment**,** such as ultra-pasteurization (UHT) (67); the type of product, as dairy powders (68)**,** cheese (69) and the storage process since dairy materials and products are exposed to oxygen that is either dissolved or present within the headspace of tanks or packages (70). However, cow´s milk proteins (casein and whey proteins) have been reported to inhibit lipid oxidation via chelation of transition metal ions or scavenging of free radicals, helping to decrease or avoid lipid oxidation in milk and dairy products (43, 70).

Fruits and vegetables are indispensable in the human diet. They are rich in nutrients as vitamins and also contain an important amount of antioxidants**,** mainly polyphenols and flavonoids, which represent a benefit to human health (71). However, fresh fruits and vegetables are subject to deteriorate quickly and easily during postharvest, transportation and storage, affecting their quality, generating spoiled food and a significant loss of their economic value (72). A poor postharvest, storage and/or distribution of fruits and vegetables generate a rapid spoilage producing loss of water and microbiological damage. This water loss can cause cell damage inducing a higher respiration rate, increasing ROS production including superoxide O_2•-, hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH) mainly, that leads to rapid occurrence of molecular and physiological damage. The generation of reactive oxygen species as superoxide depletes the antioxidants present naturally in fruits and vegetables through an excess of reduction-oxidation reactions (73-75). Superoxide O_2•- plays an important role in ripening climacteric fruits (apple, pear, banana, plum, melon, avocado, kiwi, tomato, mango, peach, quince, watermelon, papaya and others) because during in the oxidative process, the O_2•- production rate increased postharvest (76, 77). Although in fruits and vegetables the first line of ROS-scavenging is the superoxide dismutase (SOD) which converts O_2•- into oxygen and H_2O_2. It plays an important role in ripening process (76, 78)**.** Some studies have demonstrated that storage temperature could directly affect the production of superoxide O_2•-**,** and consequently affect the respiration, transpiration, oxidation of some nutrients present in fruits (79-81) and vegetables (74, 82, 83) such as pigments, vitamin A, vitamin E, vitamin C, and flavonoids (72, 80).

Maillard reaction

The Maillard reaction can be defined as a chemical reaction that reduces sugars by reaction between amino acids, resulting in the browning of foods which is responsible for the generation of color, taste and potentially toxic compounds during food processing (24, 84). Many factors can have influence this reaction like light irradiation, temperature, pH initial, water activity, presence of amino groups and oxygen, also by the action of ROS

superoxide anion O_2•- and peroxide H_2O_2 in presence of unsaturated fatty acids (84, 85). During the autooxidation of sugars in Maillard reaction, superoxide anion is generated, to which brownish pigments of Maillard glycation are due. (86-88).

The Maillard reaction involves three main stages:

I.-Initial: sugars and the amines are condensed to form unstable Schiff base compounds which are converted to N-substituted glycosylamines by cyclization. These form aldoses generating 1-amino-1-deoxyketoses (Amadori compounds), while those from ketoses form 2-amino-2-deoxyaldoses (Heyns compounds). Amadori and Heynes compounds do not lead to brown color however, the nutritional value reduces because the availability of amino acids decreases (89).

II.- Intermediates: Amadori and Heynes compounds are decomposed by different routes, at acid pH furfural or hydroxymethylfurfural is generated and at alkaline pH reductone compounds are generated. The yellowish color, flavor and reducing power increase (90).

III.-Final: the formation of brown-colored, nitrogen-containing melanoidins (high-molecular weight polymerized products) take place under different reaction as condensation, rearrangement, retro-aldolization and isomerization (85).

The Maillard reaction and lipid oxidation are interrelated because the products of each reaction can modify the other. Therefore, the products generated in lipids oxidation can modify the Maillard reaction promoting or even preventing it, due to the formation of compounds different from those commonly formed in the absence of lipids (12, 24).

Superoxide radical O_2•- not only causes food spoilage, because it is present in reactions such as lipid oxidation and Maillard reaction, generating disagreeable taste, odor, and color in food during processing and storage, but it also has negative effect in human health, being responsible for some chronic diseases as cancer, arthritis, cardiovascular and neurodegenerative diseases Figure 3.

Superoxide action in the human body and chronic diseases

It has long been known that the action of the superoxide radical O_2•- in human diseases (Figure 6), plays a vital part in normal biological processes. O_2•- formation in the body is inevitable and is released by cells involved in immune defense and others types of cells**,** and O_2•- is also involved in a large number of physiological processes as cellular malignacy, tumor proliferation, and malignant cell death (91-93).

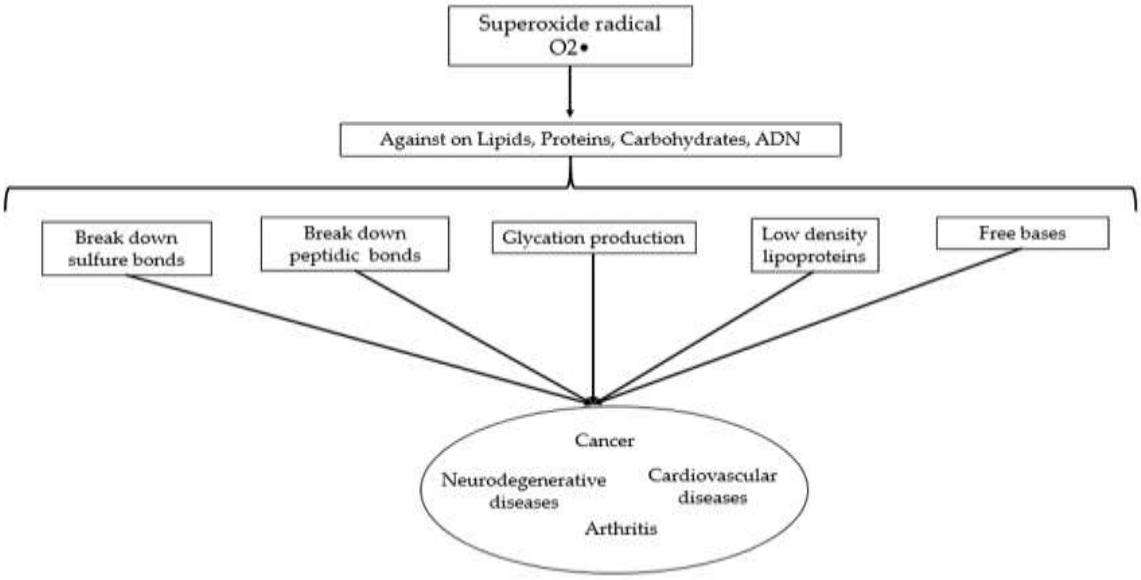

Figure 6. Superoxide radical and chronical diseases (94).

Cancer

Cancer is one of the main causes of death worldwide and it constitutes a group of varied diseases that share common features (95). Cancer cells are generated by different pathways, resulting in uncontrolled cell proliferation. These cells also present high levels of reactive oxygen species (ROS) (96). When the amount of ROS produced is higher than the antioxidant response, damage in lipids, proteins and nucleic acids occurs, causing genetic and/or epigenetic alterations that lead to the initiation of carcinogenesis (97). The oxidative stress produced by ROS can cause changes in gene expression, cell proliferation and apoptosis**,** playing an important role in initiation and progression of tumors, driving cancer progression and tumorigenesis (98, 99).

The relationship of ROS, and specifically superoxide anion O_2•- with cancer initiation and progression is because it can cause oxidative damage such as DNA damage and mutations**,** including single-strand breaks, double strand breaks, rearrangement of DNA sequence, gene amplification, and the activation of oncogenes (100). Superoxide is one of most toxic reactive oxygen species**,** capable of altering function and promoting death of cells (101). Mitochondria is the major producer of O_2•- in normal and cancer cells (Figure 7) during the respiratory chain (102)**.** It is composed of complexes I to V. From I-IV are electron transport complexes that use oxygen as a last electron acceptor and complex V is the ATP synthase. O_2•- is generated in complex I under conditions of a high proton motive force (reverse electron transport mechanism) and complex III when mitochondria were treated with antimycin as an inhibitor (102, 103). Additionally, in the mitochondria, superoxide is produced in membrane-bound NADPH oxidase complex (Figure 5), which catalyze the generation of intracellular and extracellular O_2•- from oxygen and NADPH (104)**.** The major defense against superoxide in the body is the enzyme superoxide Dismutase (SOD) which catalyze the conversion of O_2•- to hydrogen peroxide (102, 104). Cancer cells have a need for ATP, that is required as a support for their anabolic processes involved in cell growth and proliferation, and also induce mutations in mitochondrial enzymes which can generate high superoxide production (105).

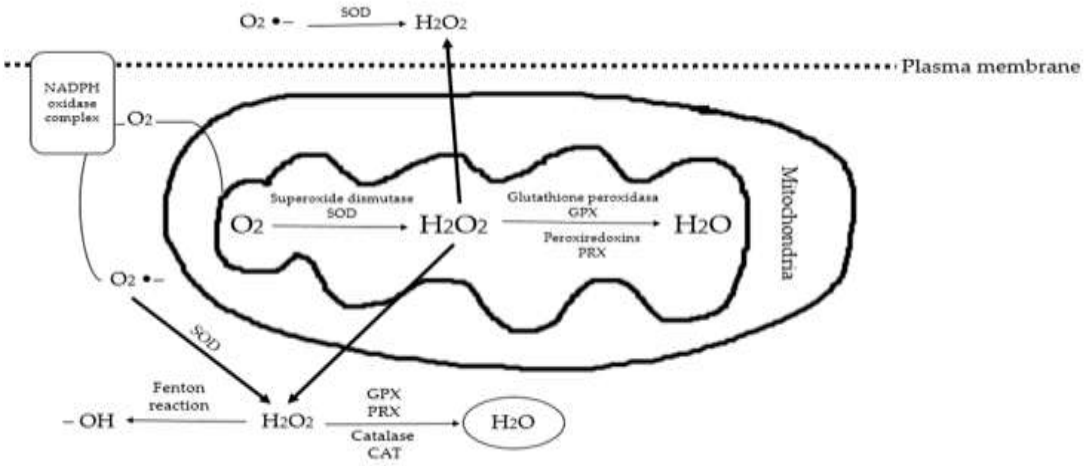

Figure 7. The major source of superoxide anion radical is the mitochondria during respiration process (104).

Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a disease that can occurs at any age and it is present in 1% of the population, however, it affects 2 to 3 times more women than men causing morbidity and disability (106, 107). RA is a chronic and progressive autoimmune disease, with the characteristic being chronic joint inflammation of synovial joints that causes progressive cartilage and bone damage (21, 108)**.** RA is disease with different genetic and environment causes. Oxidative stress has an essential role in pathophysiology of rheumatoid arthritis, because an altered antioxidant system can cause the presence of high levels of lipid peroxidation in serum and synovial fluid (21, 59). The production of reactive oxygen species is a result of inflammation leading cartilage and bone destruction in rheumatoid arthritis (108, 109). The principal ROS associated with the noticeable inflammation in RA patients is the superoxide anion, as some studies have demonstrated (110-112). O_2•- and others radicals of oxygen and nitrogen decrease the synthesis of collagen and proteoglycans producing the deterioration of the cartilage (113). One way in which O_2•- acts to produce AR is by nitration, it reacts with nitric oxide (•NO) producing proxynitrite (ONOO-). This radical is formed by a fast radical-radical reaction, which means that •NO overcomes superoxide dismutase (SOD) which catalyze the dismutation of superoxide (Figure 8) (112, 114). Additionally, superoxide dismutase reacts the superoxide O_2•- to peroxide and this radical by the action of catalase and glutathione reductase**,** is converted to water. The peroxide generates by dismutation of O_2•- is converted to hydroxyl radical in presence of ferrous ions and other transition metals (Fenton reaction). Hydroxyl reacts with lipids, proteins and nucleic acids**,** quickly damage them resulting in severe pathogenesis of rheumatoid arthritis. The peroxide is also converted to hypochlorous acid in neutrophils by the action of myeloperoxidase and form the damaging singlet oxygen radical (112, 113, 115)**.** The neutrophils have a NADPH oxidase (isozyme family) in their plasma membrane, when the neutrophils are activated by the immune complexes in an inflammatory site, this enzyme catalyzes the production of O_2•− which is dismutated to H_2O_2, aggravating inflammatory processes and causing tissue damage (116, 117). NADPH oxidase is present not only in neutrophils but also in phagocytes and endothelial cells, and these cells play an important role in the development and initiation of the inflammatory response in AR (113).

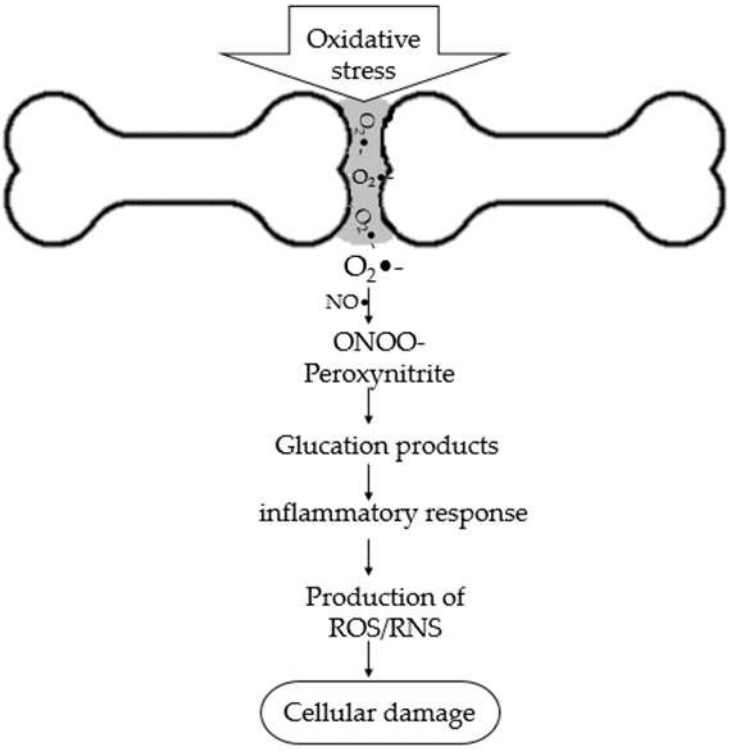

Figure 8. Oxidative stress and superoxido anion action in AR.

Cardiovascular diseases

Oxygen is essential for life, however, it represents a paradox in living organism because approximately 2% of inhaled O_2 generates ROS, which lead the oxidative stress (118). Increased oxidative stress and ROS production (oxygen species, superoxide anions, hydroxyl radicals) are related to cardiovascular diseases (CVD) like atherosclerosis (119-121), arterial hypertension (54, 122, 123), cardiac abnormalities and heart failure (28, 31, 124). However, cardiovascular diseases are complex entities and multifactorial pathophysiologic mechanisms (125-127). From $O_2^{\bullet-}$ a series of reaction are triggered that favor the formation of toxic derivatives that have prevalence in oxidative damage generating CVD (Figure 9) (128).

Atherosclerosis is a chronic inflammatory disease with multifactorial and latent causes leading cardiovascular diseases worldwide, it results in the accumulation of lipid and the hardening of the arteries, and usually stemming from hyperlipidemia and lipid oxidation (76, 129). Superoxide anion is a promoter of lipid peroxidation, which is of chain reaction nature, where one lipid is altered ant it can promote the peroxidation of adjacent lipids (130). In atherosclerosis diseases lipid peroxidation occurs when $O_2^{\bullet-}$ acts again low density lipoprotein LDL like cholesterol, when these oxidized lipoproteins in the arterial wall stimulates the inflammatory response generating from unsaturated lipids products (lipid peroxides) and then change to aldehyde products (malondialdehyde hexanone and other compounds) that produce apoptosis of vascular cells**,** apoptosis of vascular cells which determines the vulnerability of the plaque increasing the development and progression of atherosclerotic lesions (76, 131-133). Some studies have been

demonstrated the action of superoxide anion in the atherosclerosis generation (134-136).

The exaggerated vascular production of O_2•− generates arterial hypertension because it has an effect in endothelial cells (major component of the innermost layer of blood vessels), whose functions are mainly the maintenance of blood flow, regulation of inflammation, the immune response and neovascularization , also these cells represent a natural barrier and serve to maintain the bloodstream separate from extravascular tissues (137-139). Superoxide produces endothelial dysfunction that is a decrease in the vasorelaxant capacity that has implications in blood pressure which is a relevant pathophysiological alteration of human arterial hypertension (140-142). In the other hand superoxide anion induces death by apoptosis of cardiomyocytes, which are cardiac muscle cells whose mission is to produce the pumping of blood through the contraction and relaxation of the cardiac ventricles in the heart (54, 122, 123).

A heart failure can be generated by ischemic heart disease, myocardial and infarction ischemia-reperfusion phenomenon and they are related by an increase of superoxide presence due to the decreased activity of superoxide dismutase and other antioxidant enzymes such as catalase and glutathione peroxidase (31, 141). The ischemic heart disease occurs when some enzymatic changes are present like the one associated to xanthine dehydrogenase, an enzyme present in the in the endothelium, which function is purifying xanthines through the formation of uric acid. When the enzyme changes to oxidized form produced by ischemia, it generates the radical O2•-. Although this is not the only source of superoxide in cardiac tissue, the membrane NADPH oxidase of smooth muscle cells has the ability to generate O2•- in vascular cells leading to inflammation (133).

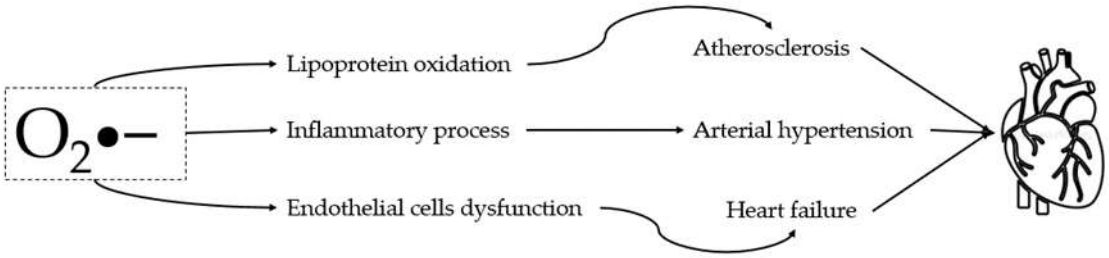

Figure 9. Superoxide anion O_2•− action to generate cardiovascular diseases.

Neurodegenerative diseases

The brain contains about 1011–1012 neurons protected by many neuroglial cells, cell membranes of the brain are rich in polyunsaturated fatty acids (PUFA). Also, the brain consumes around 20% of the bodily oxygen to maintain its high metabolic rate, making it susceptible to damage by ROS (hydrogen peroxide, superoxide anion, etc.) and reactive nitrogen species RNS (nitric oxide), generating deteriorating effect compared to other tissues, causing neurodegenerative diseases (Figure 10). (143-145). Neurodegenerative diseases (ND) can be defined as a collection of multiple disorders in which the deterioration of motor or cognitive function leads to a slow and progressive neural cell death and also neuronal dysfunction, being a chronic, progressive, devastating and incurable diseases prevalent in aging populations (146-148). The Superoxide radical participate in some neurodegenerative diseases in different ways like inactivating iron and sulfur

containing enzymes, initiating lipid peroxidation of polyunsaturated fatty acids (PUFA), reacting with carbonyl compounds, halogenated carbons and nitric oxide to generate more highly reactive radicals as peroxynitrite ONOO–.O_2•– activates the formation of mitochondrial permeability pore, which is considered as a point of no return in apoptosis (94, 144, 145, 149). Some of the most common neurodegenerative diseases related with superoxide radical expressed in this review are Alzheimer´s disease, Parkinson´s disease and epilepsy (114).

Alzheimer disease (AD) is an aging neurodegenerative disorder, characterized by progressive loss of memory and cognitive functions, resulting in severe dementia. Oxidative stress and ROS presence are related to this disease. ROS and specifically superoxide anion acts deteriorating biomolecules as proteins, lipids and DNA causing neurodegeneration (cognitive deficit and memory loss) related to AD (144, 148, 150, 151). Superoxide interacts with other molecules to generate hypochlorous acid, which is an oxidant that can damage biomolecules such as DNA and also generates the hydroxyl radical through the Fenton reaction, which is very reactive with a short half-life, but a very high reaction rate (70, 152, 153). With organic and inorganic molecules within the cell, including DNA, lipids, amino acid proteins, and metals. In addition, superoxide through NADPH oxidase, which is found in the brain vasculature and is produced by glial cells, producing large amounts of H_2O_2, which generates a progression in AD (154, 155).

Parkinson's disease (PD) is a neurodegenerative condition that affects the central, peripheral, and enteric human nervous systems. The typical clinical features involve a movement disorder consisting of bradykinesia, resting tremor, and rigidity; this pathological process progresses slowly but involves multiple neuronal systems (156, 157). PD increases its prevalence with age, between 85 and 89 years of age, the causes of PD are unknown, however it has been related to genetic and environmental risk factors (158). Has been hypothesized that oxidative stress contributes to Parkinson´s disease, because it promotes the production of ROS which lead to mitochondrial dysfunction, dopamine metabolism and neuroinflammation resulting in degeneration of nigrostriatal dopaminergic neurons which have the mission to produce the neurotransmitter dopamine that enables the activation of certain brain structures and areas which function related to movement (159-161). Among ROS the superoxide anion O_2•- is usually referred to as “primary” and is the is the initiator of reactions that generate radicals such as H_2O_2 and OONO- that cause neuron damage. Based on this, in the early stages of PD, when an increased dopamine turnover is present, it generates excessive H_2O_2 -which is inactivated by glutathione in a reaction normally catalyzed by glutathione peroxidase (162-164). Nevertheless, if the glutathione system is deficient, the peroxide radical may be converted by the Fenton reaction to OH- a highly reactive radical which initiates lipid peroxidation and cell death. Superoxide also can react with nitric oxide to generate ONOO− that is related to neuroinflammation, contributing to the progression of the disease because of the degenerative process in the brain (162, 165, 166).

Epilepsy affects over 50 million people worldwide, being one of the most common neurological disorders. It is characterized by recurrent, unpredictable, and typically unprovoked seizures causing significant co-morbidities or even death, it also has an impact on patient’s quality of life due to the stigmatization and social issues (167-169). Epilepsy can be genetic caused by diverse

mechanisms such as channelopathies, chromosomal abnormalities, alterations of genes associated with brain malformations, and mutations in mitochondrial DNA; or acquired resulting from traumatic brain injury, stroke, infection or an insult to the brain such as a prolonged seizure. Literature shows evidence that apoptosis, neuroinflammation and oxidative stress are factors involved in pathogenesis of epileptogenesis (process by which epilepsy develops) (170-174**).** Epileptic seizures are a very complex spontaneous and recurrent psychological process where oxidative stress leading to mitochondrial dysfunction that contributes to glutamate-induced excitotoxicity and later apoptosis in neurons, and death of hippocampal neurons, being quite recurrent in cases of epilepsy, contributing to cognitive dysfunction (167, 169). During the occurrence and development of epilepsy the superoxide anion $O_2^{\bullet-}$ is continuously producing peroxidation of lipids which causes changes in neurotransmitter release and uptake and ion channels expression**,** resulting in neuronal hyperexcitability. In addition, $O_2^{\bullet-}$ produced during an epilepsy episode reacts immediately with nitric oxide producing the radical ONOO- which has as a target DNA, lipids and proteins producing cell death. The ONOO- formed by superoxide reaction is used as indicator for the early diagnosis of epilepsy (167, 170, 171, 175). However, the human body has an antioxidant system that helps to maintain the balance of the radical presence like the superoxide anion (169). In this system, non-enzymatic compounds (Vitamins A, C, E) and enzymatic compounds (catalase, glutathione peroxidase and superoxide dismutase) are present. Some studies have suggested that ions as zinc and copper present in Cu-Zn superoxide dismutase that catalyzes the dismutation of superoxide anion $O_2^{\bullet-}$, to molecular oxygen or hydrogen peroxide (they react rapidly and destroy many important biological molecules), act as signaling ions in nervous system and are released from certain synaptic terminals of neurons, so that if the antioxidant system is effected during a seizure the presence of $O_2^{\bullet-}$ might have incidence in evolution of epilepsy induced brain damage (5, 176-178).

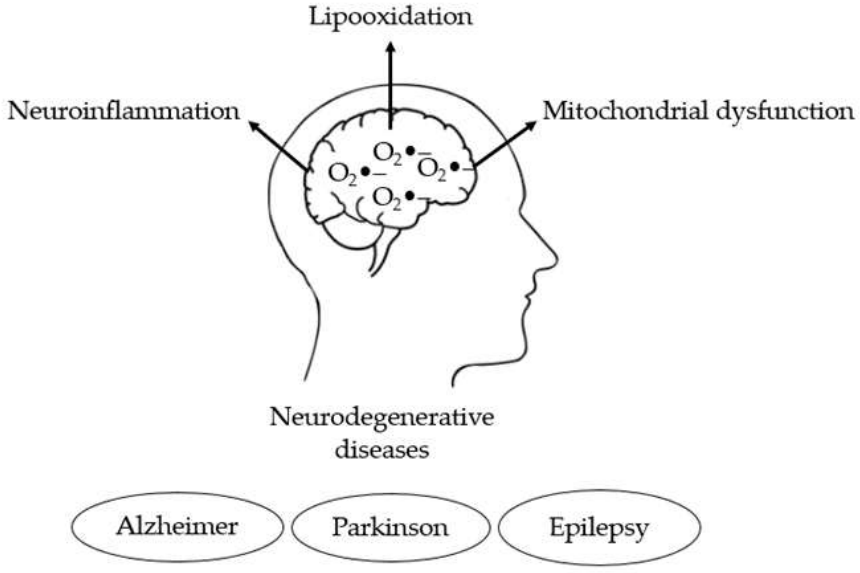

Figure 10. Superoxide anion promoted of neurodegenerative diseases.

Conclusions

Superoxide anion radical is one of the most dangerous reactive oxygen species, because it not only generates food spoilage by lipid oxidation and Maillard reaction, but also O_2•- is related to biological processes, that involves a high number of physiological processes. Superoxide radical anion can promote DNA damage and mutation related to cancer cell formation. This radical play an important role in development and initiation of inflammatory response in rheumatoid arthritis. In cardiovascular diseases O_2•- is involved in atherosclerosis, hypertension and heart failure. Superoxide radical participates in some neurodegenerative diseases as Alzheimer´s, Parkinson's and epilepsy by initiating lipid peroxidation of polyunsaturated fatty acids present in neurons. Knowing and understanding formation and action of superoxide radical will be important to development antioxidants to prevent its propagation.

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