

Antioxidants for the prevention of chronic degenerative diseases: A Biochemical, nutritional, and functional perspective

Morachis-Valdez, Ana Gabriela
Rosales-Martínez, María del Carmen
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ISBN: 978-607-8948-68-0
ECORFAN Publishing Label: 607-8948
Control Number B: 2025-07
Classification B (2025): 251125-0104

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Antioxidants for the prevention of chronic degenerative diseases: A Biochemical, nutritional, and functional perspective

The Book will offer selected contributions from researchers of the Universidad Autónoma del Estado de México in its area Food Sciences. In addition to having a complete evaluation, by the coordinators of the Universidad Autónoma del Estado de México, of the quality and punctuality in its chapters, each individual contribution was refereed with international standards [V|LEX, RESEARCH GATE, MENDELEY, GOOGLE SCHOLAR y REDIB]. The Book thus proposes to the academic community recent reports on new progress in the most interesting and promising areas of Biology, Chemistry and Life Sciences.

Antioxidants for the prevention of chronic degenerative diseases: A Biochemical, nutritional, and functional perspective

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Noviembre 2025

<https://doi.org/10.35429/B.2025.7.1.154>



Contet

Abstract	2
Resumen	2
Introduction	3
Chapter 1. Oxidative stress	4
1.1. Free radicals and reactive oxygen species	4
1.1.1. Free radicals	4
1.1.2. Non-free radicals	6
1.1.3. Reactive oxygen species	6
1.1.4. Reactive nitrogen species	7
1.2.1. Production sources.	7
1.1.2.1. Properties of radicals	11
1.1.2.1.1. Superoxide radical	11
1.1.2.1.2. Hydrogen peroxide radical	11
1.1.2.1.3. Hydroxyl radical	12
1.1.2.1.4. Singlet radical ($^1\text{O}_2$)	12
1.1.2.1.5. Peroxyl radical	13
1.1.2.1.6. Ozone radical	13
1.1.2.1.7. Nitric oxide radical	13
1.2. Oxidative stress	15
1.2.1. Nitro-oxidative stress	18
1.3. Lipoperoxidation	18
1.3.1. Carbonylated proteins	21
Chapter 2. Chronic degenerative diseases	24
2.1. Alzheimer's disease	24
2.2. Parkinson's disease	27
2.3. Amyotrophic lateral sclerosis	29
2.4. Cardiovascular diseases	31
2.5. Liver Diseases	35
2.6. Diabetes	41
2.7. Cancer	46
2.8. Physical activity	50
Chapter 3 Antioxidants	54
3.1. Endogenous antioxidants	55
3.1.1. Superoxide dismutase	55
3.1.2. Catalase	57
3.1.3. Glutathione	60
3.2. Exogenous antioxidants	62
3.2.1. Polyphenols	62



3.2.2. Flavonoids	67
3.2.3. Carotenoids	73
3.3. Vitamins	76
3.3.1. Vitamin C	76
3.3.2. Vitamin E (α -tocopherol)	79
3.4. Minerals	81
3.4.1. Selenium	82
3.4.2. Zinc	84
3.4.3. Melatonin	87
Chapter 4. Extraction, Identification, and Quantification of Antioxidant Compounds	90
4.1. Extraction of Antioxidants	90
4.2. Identification of antioxidants	90
4.3. Quantification of antioxidants	93
4.4. Antioxidant Activity	93
Conclusions	96
Recommendations	97
Declarations	97
Abbreviations	97
References	100

Antioxidants for the prevention of chronic degenerative diseases: A Biochemical, nutritional, and functional perspective

Antioxidantes en la prevención de enfermedades crónico-degenerativas: Un enfoque bioquímico, nutricional y funcional

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Field: Life sciences

Discipline: Biochemistry

Subdiscipline: Food biochemistry

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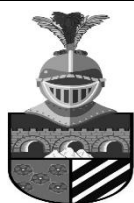
This research contributes to Science and Technology by integrating biochemical, nutritional, and functional perspectives to elucidate how dietary antioxidants mitigate oxidative stress and prevent chronic degenerative diseases such as Alzheimer's, Parkinson's, diabetes, cardiovascular, and liver disorders. The main scientific advancement lies in systematizing biochemical mechanisms of endogenous and exogenous antioxidants—superoxide dismutase, catalase, glutathione peroxidase, vitamins, polyphenols, and carotenoids—supported by validated analytical and bibliographic evidence. To apply this research toward universal knowledge, it is essential to understand the balance between reactive oxygen species and cellular antioxidant defenses, as well as methodological reproducibility in biochemical and nutritional studies. The principal conclusions emphasize that antioxidant-rich diets can reduce cellular damage, promote healthy aging, and serve as a preventive strategy for oxidative-stress-related pathologies. The author team includes three PhD researchers and two postdoctoral fellows, with two holding SECIHTI postdoctoral grants, all from the Universidad Autónoma del Estado de México (UAEMéx), a State Public Institution. Together, the authors have generated 2,134 citations in the last year, highlighting the research visibility and academic impact. The most frequent keywords defining the scope of this work are antioxidants, oxidative stress, chronic degenerative diseases, functional foods, bioactive compounds, and nutritional biochemistry, representing the interdisciplinary axis of this scientific contribution.

Area: Dissemination and universal access to science

Citation: Morachis-Valdez, Ana Gabriela, Rosales-Martínez, María del Carmen, Dublán-García, Octavio and Saucedo-Vence, Karinne. 2025. Antioxidants for the prevention of chronic degenerative diseases: A Biochemical, nutritional, and functional perspective. 1-154. ECORFAN.

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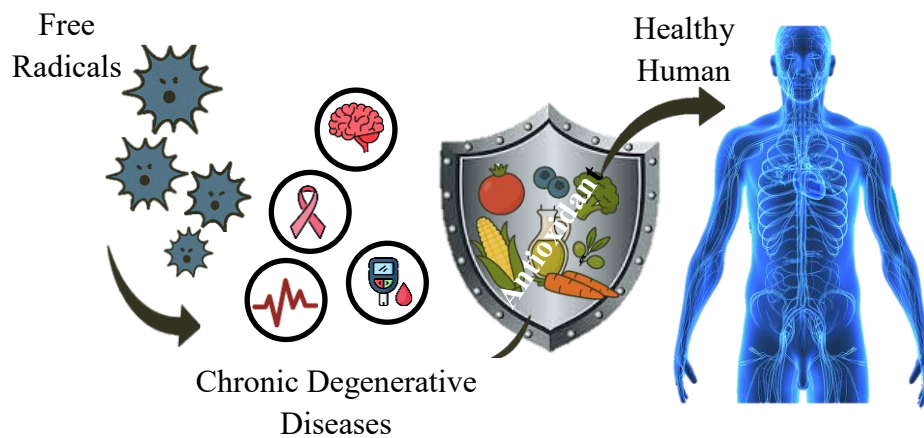
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Abstract

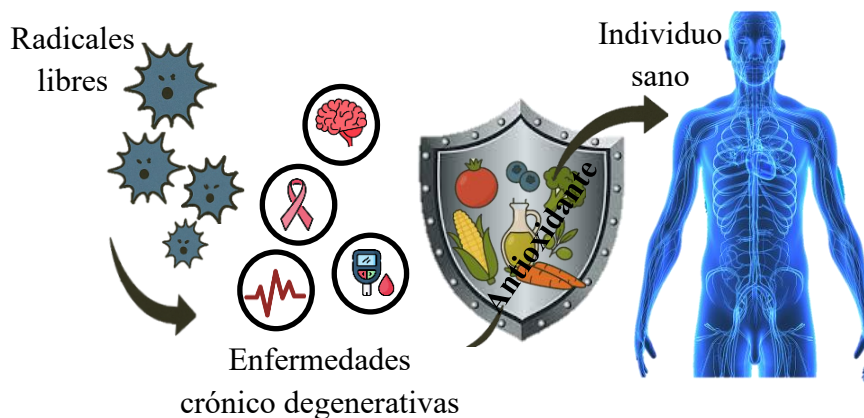
This research analyzes the effect of antioxidants found in foods on the prevention and progression of chronic degenerative diseases such as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, cardiovascular diseases, liver conditions, diabetes, and cancer. These pathologies are closely related to oxidative stress, a process caused by the imbalance between reactive oxygen species and the body's antioxidant defense mechanisms. The study reviews the role of endogenous antioxidants (such as superoxide dismutase, catalase, and glutathione peroxidase) and exogenous antioxidants (including vitamins, polyphenols, carotenoids, and minerals), as well as their natural dietary sources. Through a documentary and analytical approach, it describes the biochemical mechanisms of cellular damage and emphasizes the relevance of antioxidant-rich diets as a preventive strategy. This work presents an integrative perspective that links nutrition, biochemistry, and public health, highlighting the importance of adopting healthy eating habits to reduce the risk of diseases associated with cellular aging and modern lifestyle factors



Antioxidants, Oxidative stress, Chronic degenerative diseases

Resumen

La presente investigación analiza el efecto de los antioxidantes presentes en los alimentos sobre la prevención y progresión de enfermedades crónico-degenerativas como Alzheimer, Parkinson, esclerosis lateral amiotrófica, enfermedades cardiovasculares, hepáticas, diabetes y cáncer. Estas patologías están estrechamente relacionadas con el estrés oxidativo, un proceso provocado por el desequilibrio entre especies reactivas de oxígeno y los mecanismos antioxidantes del organismo. El estudio revisa la acción de los antioxidantes endógenos (como superóxido dismutasa, catalasa y glutatión peroxidasa) y exógenos (vitaminas, polifenoles, carotenoides y minerales), así como sus fuentes naturales. Mediante un enfoque documental y analítico, se describen los mecanismos bioquímicos del daño celular y la relevancia de una dieta rica en antioxidantes como estrategia preventiva. El trabajo propone una visión integradora que vincula nutrición, bioquímica y salud pública, y destaca la importancia de adoptar hábitos alimenticios saludables para reducir el riesgo de enfermedades asociadas al envejecimiento celular y al estilo de vida.



Antioxidantes, Estrés oxidativo, Enfermedades Crónico-Degenerativas

Introduction

Chronic degenerative diseases (CDDs) represent one of the main public health challenges today. Their progressive, incurable nature and high prevalence have generated great scientific interest in understanding the factors that cause them and how to prevent their progression. In this context, oxidative stress (OS) has been identified as a central pathophysiological mechanism in the onset and progression of diseases such as Alzheimer's, Parkinson's, cardiovascular disease, diabetes, and cancer, among others. OS is caused by an imbalance between Reactive Oxygen Species (ROS) and the body's antioxidant systems, leading to cell damage, premature ageing, and organ dysfunction.

Faced with this challenge, the hypothesis has emerged that a diet rich in natural antioxidants from fruits, vegetables, and other functional foods can counteract the harmful effects of OS, thereby reducing the risk and progression of these diseases. This approach is proposed as a complementary, non-invasive and accessible alternative, with clear advantages over conventional pharmacological treatments, as it focuses on prevention through diet, without generating adverse side effects.

The added value of this research lies in its interdisciplinary and up-to-date approach, which integrates knowledge of biochemistry, nutrition, medicine and food technology. Unlike other approaches that analyse the effects of antioxidants in isolation, this work studies their action from a molecular and systemic perspective, considering genetic, environmental and lifestyle factors.

Chapter 1. Oxidative stress

1.1. Free radicals and reactive oxygen species

The oxygen molecule (O_2) is the second most important component in the Earth's atmosphere and is essential for the life of many organisms, including humans, as it is necessary for vital processes such as cellular respiration (Ortiz & Medina, 2020). O_2 , which despite its radical nature is stable and not very active on its own, needs to be activated by metal ions such as iron and copper (Hernández *et al.*, 2020). It has a dual nature with beneficial and toxic effects inherent to its structure and ability to undergo chemical reactions. Among its beneficial effects is the metabolism of fats, proteins, and carbohydrates to generate energy (basi *et al.*, 2022). On the other hand, toxic effects appear when O_2 undergoes changes in its structure due to partial reductions or transfer of excitation energies. Furthermore, if its pressure is excessive, it tends to produce reactive oxygen species (ROS), which are classified as radicals and non-radicals (Singh *et al.*, 2019; Ortiz & Medina, 2020; Rodríguez *et al.*, 2021). It is estimated that 1-5% of the O_2 captured by the lungs is converted into reactive species (Castillo & Salazar-Lugo, 2018).

O_2 has a high oxidation-reduction (redox) potential, is a strong oxidising agent and electron (e^-) acceptor. Oxidation is any process in which there is a loss of e^- , uptake of O_2 or transfer of hydrogen (dehydrogenation) (Eq. 1), and reduction is the process in which e^- are acquired or O_2 atoms are eliminated (Eq. 2); every oxidation process is always accompanied by a reduction process. (Viada *et al.*, 2017; Cruz-Rodríguez & López-Solís, 2021).



In the univalent reduction process, O_2 undergoes four successive reductions with e^- , accepting them one at a time until it forms water (H_2O). However, this addition of e^- leads to the formation of e-reduction intermediates, also called EROs. As shown in Figure 1, the addition of the first e^- generates the superoxide radical ($O_2^{\bullet-}$); adding the second e^- plus two protons (H^+ ions) yields hydrogen peroxide (H_2O_2); adding the third yields the hydroxyl radical ($\bullet OH$); finally, adding the fourth e^- plus two H^+ produces the H_2O molecule. (Arancibia-Hernández *et al.*, 2022).

Box 1

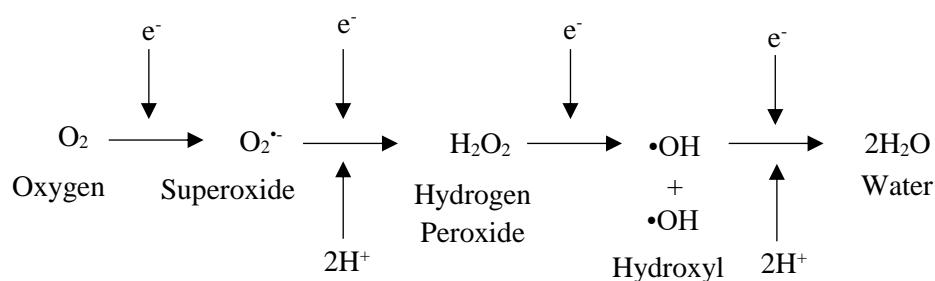


Figure 1

Univalent reduction of oxygen

Arancibia-Hernández et al. (2022)

1.1.1. Free radicals

Cells continuously generate highly unstable molecules called RLs as a fundamental part of their metabolic processes (Estrada & Iglesias, 2017). RLs are atoms or molecules capable of existing independently (hence the term 'free') that have one or more unpaired electrons in the outer orbital of their atomic structure (hence the term 'radical'), making them highly unstable molecules with great reactive power and a very short half-life (Viada *et al.*, 2017; Radi, R., 2018; Cruz-Rodríguez & López-Solís, 2021; Rodríguez *et al.*, 2021). This causes them to interact rapidly with other molecules in their vicinity, from which they steal an e^- , oxidising them and producing changes in their chemical composition or structure, thus losing their specific function in the cell, in order to achieve a stable electronic configuration (Arteche *et al.*, 2018; Gutiérrez *et al.*, 2018; Mora *et al.*, 2019).

These radicals can be produced in cells by donating or accepting a single e^- from other molecules, behaving as oxidants or reductants, all of which leads to structural and/or functional changes with significant repercussions at the cellular, tissue and organic levels (Fig. 2) (Liguori *et al.*, 2018; Rodríguez *et al.*, 2021).

The unpaired e^- of a fR is denoted by a dot on the atom or group where it predominantly resides, for example, hydrogen atom ($\bullet H$), hydroxyl ($\bullet OH$), among others. In oxygen radicals, the unpaired electron is mainly located in an O_2 atom, as in superoxide ($O_2\bullet^-$), hydroxyl ($\bullet OH$), etc. (Moldogazieva *et al.*, 2019; Jakubczyk *et al.*, 2020; Martemucci *et al.*, 2022).

Box 2

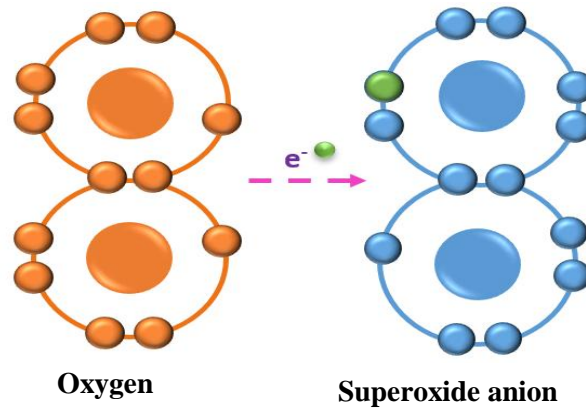


Figure 2

Formation of the superoxide free radical from oxygen in the electron transport chain

Guija-Guerra & Guija-Poma (2023)

The life of an FR is extremely fast, its aggressiveness and destructive activity occurring in fractions of a millisecond, but it has the ability to react with everything around it, causing significant damage to molecules and cell membranes. This brief interval is also necessary for the acquisition of the complementary e^- for the stabilisation of its electrical charge (Castillo & Salazar-Lugo, 2018; Hernández *et al.*, 2020).

Due to their high reactivity, RLs tend to capture an e^- from other atoms or molecules in order to achieve electrochemical stability, being capable of initiating a chain reaction by forming other RLs, as they do not have a specific receptor, which gives them the ability to indiscriminately attack living cells and tissues in their attempt to capture the e^- they lack (Fig. 3). (Arteche *et al.*, 2018; Gutiérrez *et al.*, 2018; Mora *et al.*, 2019).

Box 3

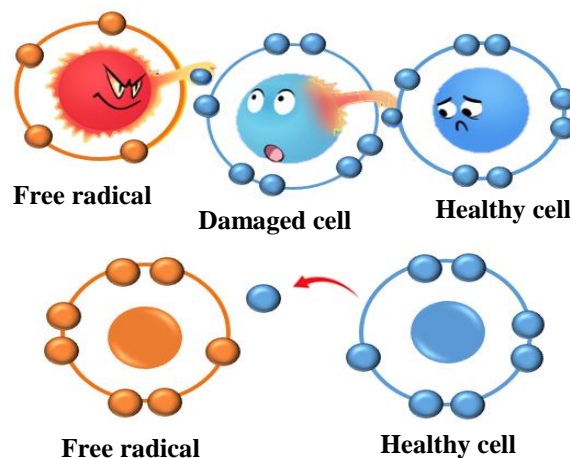


Figure 3

Formation and action of free radicals. A) Chain reaction; B) Electron transfer
Own Elaboration

RLs play a dual role in living beings because they have both beneficial and harmful effects. The beneficial effects manifest themselves at low or moderate concentrations, acting as second messengers in cell signaling (a process in which the cell responds to external substances by means of molecules that are inside or on the surface of the cell), cellular responses to a harmful or damaging agent (noxa), such as a toxic substance, as occurs in the defense against infectious agents and the induction of mitogenic responses (Losada-Barreiro & Bravo-Díaz, 2017; Lolas, 2020; Di Meo *et al.*, 2022).

On the other hand, when there is an overproduction of RL, harmful effects are generated, such as a decrease in antioxidant defences or an excess of pro-oxidants, which are substances that can produce O₂ by-products of metabolism (RL) that increase EO, causing potential biological damage and damage to macromolecules such as lipids, proteins, carbohydrates, and nucleic acids, thus altering the normal intracellular redox balance, which leads to oxidative damage and tissue dysfunction (Losada-Barreiro & Bravo-Díaz, 2017; Konno *et al.*, 2021; Di Meo *et al.*, 2022).

1.1.2. Non-free radicals

Not all reactive species originating from reactions with O₂ are RLs, but they are highly reactive species, which is why non-free radicals exist. As their name suggests, they are reactive species that are not RLs per se, as they do not have unpaired electrons, but they have the ability to easily lead to oxidative reactions, forming RLs (Castillo & Salazar-Lugo, 2018; Arancibia-Hernández *et al.*, 2022).

FR formation occurs through three mechanisms: the first is by e⁻ transfer, in which an e⁻ is transmitted from one molecule to another; the second is through the loss of an e⁻ in a molecule; and the third is through the homolytic rupture of a covalent bond in any molecule, such that each resulting fragment retains one of the unpaired e⁻ in the bond (Mora *et al.*, 2019; Jamshidi-Kia *et al.*, 2020; Tvrdá & Benko, 2020).

As a product of normal cellular metabolism, different types of FR are generated, which have biological functions essential for cellular development. Among the most common and important are O₂-centred radicals known as ROS and nitrogen-centred molecules known as reactive nitrogen species (RNS) (Liguori *et al.*, 2018; Meñaca-Guerrero *et al.*, 2020; Luna-Ortiz *et al.*, 2024).

1.1.3. Reactive oxygen species

ROS are a group of chemicals generated in the body by the partial reduction of O₂ in the cell through the transfer of an e⁻ during the oxidative phosphorylation pathway, mainly (Ortiz & Medina, 2020; Revilla, E.M., 2021). They are characterised by being unstable, capable of existing independently and being highly reactive with different molecules in the cell due to the presence of one or more unpaired valence electrons (Jakubczyk *et al.*, 2020; Curieses *et al.*, 2023).

The term ROS is used to include RLs and non-radicals, which are the most abundant reactive species in aerobic living organisms and are formed inside and outside cells. A basal concentration of ROS is essential for participating in various important cellular activities such as gene transcription, signal transduction, respiration, and immune response. Without the generation of these, the cell could not function normally (Di Meo & Venditti, 2020).

However, when there is overproduction, they can cause oxidative damage to cellular macromolecules such as lipids, proteins, and DNA, causing irreversible chemical reactions that affect their functioning, necrosis, and OES, leading to apoptotic cell death (Arteche *et al.*, 2018; Liu *et al.*, 2021; Senoner & Dichtl, 2019).

The harmful aspect is not that ROS are generated in the body, as this is a phenomenon that occurs in normal situations, but rather that there is an imbalance between their production and elimination, which is what determines the onset of disease (León *et al.*, 2018). Among the most common ROS are O₂•⁻, H₂O₂, •OH, singlet oxygen (¹O₂), ozone (O₃), and ROO• (Table 1) (Carvajal, C., 2019; Rudrapal *et al.*, 2022).

1.1.4. Reactive nitrogen species

RNS are redox-active molecules derived from nitrogen. Like ROS, they can have beneficial or harmful effects depending on their concentration and the context in which they are produced (Di Meo & Venditti, 2020). At normal concentrations, they have biological activity and can play important roles in cell signalling and immune response. Conversely, at high concentrations, they cause toxicity to cellular macromolecules such as DNA, lipids, and proteins, causing oxidative stress, which contributes to the loss of neuronal cells (Aggarwal *et al.*, 2022).

There are ROS that may or may not be FR and are produced constitutively. Among the most common are nitric oxide ($\bullet\text{NO}$), peroxyxynitrite (ONOO^-), nitrous anhydride (N_2O_3), among others (Table 1) (Luna-Ortiz *et al.*, 2024).

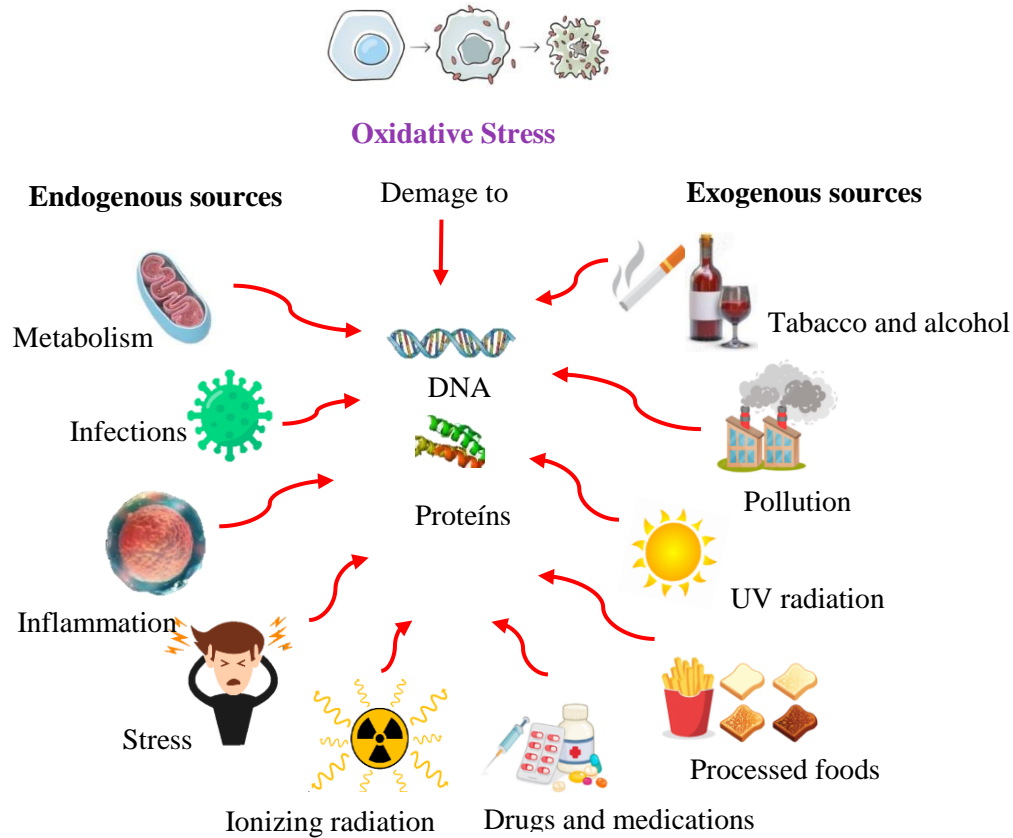
$\bullet\text{NO}$ is the most important ROS because it is a signalling molecule involved in numerous biological processes, participating in blood pressure control, platelet aggregation inhibition, and neurotransmission processes. (Sahay & Gupta, 2017; Sies *et al.*, 2017).

Box 4			
Table 1			
Main reactive oxygen and nitrogen species			
Reactive Oxygen Species			
Radicals		Non-Radicals	
Name	Formula	Name	Formula
Superoxide	$\text{O}_2^{\bullet-}$	Singlet oxygen	$^1\text{O}_2$
Hydroxyl	$\bullet\text{OH}$	Hydrogen peroxide	H_2O_2
Peroxyl	$\text{ROO}\bullet$	Ozone	O_3
Alkoxy	$\text{RO}\bullet$	Hypochlorous acid	HOCl
Hydroperoxyl	$\text{HO}_2\bullet$	Hypo-bromous acid	HOBr
Reactive Nitrogen Species			
Radicals		Non-Radicals	
Nitric oxide	$\bullet\text{NO}$	Peroxyxynitrite	ONOO^-
Nitrogen dioxide	$\text{NO}_2\bullet$	Nitrous acid	HNO_2
		Dinitrogen trioxide	N_2O_3
		Dinitrogen tetroxide	N_2O_4
		Peroxyxynitrous acid	ONOOH

Carvajal, C. (2019)

1.2.1. Production sources.

ROS can originate from two sources: endogenous and exogenous. Among endogenous sources, ROS generation occurs in various parts of the cell, particularly in organelles with high O_2 requirements, such as mitochondria, peroxisomes, phagocytes, endoplasmic reticulum (ER), leukocytes, lysosomes, microsomes, neutrophils, macrophages, and the cell or cytoplasmic membrane (Fig. 4) (Aguilar-Paredes *et al.*, 2018; Rudrapal *et al.*, 2022; Vasconcelos-de Dios *et al.*, 2022), while in exogenous sources they are generated as by-products in the degradation or metabolism of exogenous compounds after being absorbed by the body through the consumption of tobacco, alcohol, drugs and toxic agents, chemical additives in processed foods, cooking methods (smoking or reuse of oils), metabolism of a wide range of drugs and use of stimulants (Ortiz & Medina, 2020; Rudrapal *et al.*, 2022), or as a result of exposure to certain factors such as environmental pollution, ionising radiation, X-rays, gamma rays, ultraviolet radiation, O_3 , carbon monoxide, xenobiotics such as pesticides, herbicides and fungicides, cadmium, lead, arsenic, iron and mercury ions, hydrocarbons produced by anthropogenic activity, infections, prolonged stress conditions and intense physical exercise, all of which will induce cell damage (Fig. 4). (Viada *et al.*, 2017; Moldogazieva *et al.*, 2019; Jakubczyk *et al.*, 2020; Meñaca-Guerrero *et al.*, 2020; Revilla, E.M., 2021).

Box 5

Figure 4

Main endogenous and exogenous sources of reactive oxygen species production

Own Elaboration

There are several natural pathways in the human body capable of producing ROS. Mitochondria are the main source of ROS production at the cellular level. This occurs through the electron transport chain (ETC) by means of oxidative phosphorylation, which is the most important pathway of ROS generation in the body, as it is through this pathway that cellular respiration and the generation of adenosine triphosphate (ATP), which is the fundamental energy molecule in cells generated by the transfer of e⁻ (Nolfi-Donagan *et al.*, 2020; Angelova *et al.*, 2021; Park & Yang, 2021; Montero, M., 2023). The ETC consists of four enzyme complexes and two e⁻ transporters, NADH dehydrogenase (complex I), succinate dehydrogenase (complex II), cytochrome c oxidoreductase complex (complex III), cytochrome c oxidase (COX, complex IV), non-protein e⁻ transporter ubiquinone, and e⁻ transporter cytochrome c (Cyt c) (Kalpage *et al.*, 2020).

The process of oxidative phosphorylation encompasses both e⁻ transport along the ETC and ATP synthesis. During this process, O₂ acts as the final electron acceptor and is reduced to H₂O in order to obtain energy (Hernández *et al.*, 2019). This pathway uses most of the O₂ in the human body, between 80 and 90% of a person's consumption (Losada-Barreiro & Bravo-Díaz, 2017).

The events leading to oxidative phosphorylation are as follows:

1.- e⁻ transport: the flow of e⁻ in the CTE of the inner membrane of the mitochondrion is derived from the oxidation of respiratory substrates such as NADH, succinate and activated fatty acids; during this process, e⁻ are transferred through a series of protein complexes, releasing energy in the form of an H⁺ gradient (Cunha-Oliveira *et al.*, 2020). However, around 1 to 5% of O₂ inevitably does not follow the normal transfer order and undergoes monovalent reduction by the e⁻ leaving the respiratory chain, through complexes I and III, leading to the formation of ROS as a fundamental part of its metabolic processes through various mechanisms (León *et al.*, 2018; Ortiz & Medina, 2020), with the addition of an e⁻ to a stable molecule being the most common, forming the O₂•⁻ radical, which can then be dismutated and catalysed by SOD to form H₂O₂, which can generate even more radicals such as •OH by partial reduction (Aguilar-Paredes *et al.*, 2018; Hernández *et al.*, 2019; Chen *et al.*, 2020; Nolfi-Donagan *et al.*, 2020). Likewise, O₂ can react with •NO to form ERNs such as ONOO⁻, N₂O₃, etc. (Fig. 5) (Smith *et al.*, 2019).

2.- Formation of H^+ gradient: e^- transfer leads to the pumping or translocation of H^+ from the mitochondrial matrix to the intermembrane space by complex V, creating an H^+ gradient to generate the energy necessary for ATP synthesis, which occurs in the third step (Hernández *et al.*, 2020). The three respiratory complexes that participate as ‘pumps’ in the generation of the electrochemical gradient are complexes I, III, and IV, which pump or translocate 4, 4, and 2 H^+ , respectively (Fig. 5) (Matus *et al.*, 2021).

3.- ATP synthesis: the energy stored in the H^+ gradient is used to drive ATP synthesis through the enzyme ATP synthase, which couples the entry of H^+ to the flow of adenosine diphosphate (ADP) to ATP. This step involves a process where the membrane domain facilitates the flow of H^+ back into the mitochondrial matrix, a process that is coupled with the formation of ATP (Fig. 5) (Matus *et al.*, 2021). It is important to mention that oxidative phosphorylation also plays a role in the regulation of apoptosis and cell differentiation. However, as a source of energy and ROS, it causes mitochondrial dysfunction, which can contribute to decreased energy levels and excessive O_2 generation, as well as leading to higher rates of mutations in mitochondrial DNA (mtDNA), exacerbating the deterioration of the oxidative phosphorylation system. (Jiménez, 2019).

Box 6

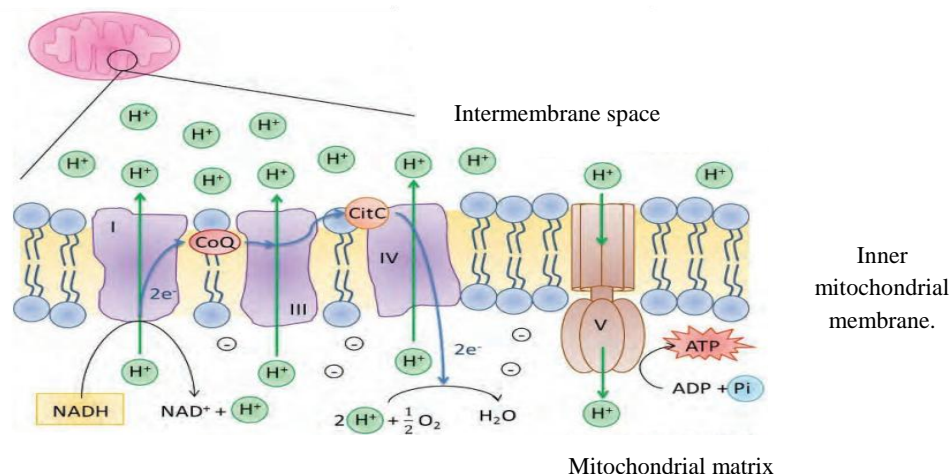


Figure 5

Oxidative phosphorylation in the electron transport chain

Matus et al. (2021)

Peroxisomes are cellular organelles that play an important role in lipid metabolism, but their main function is the degradation of peroxides, in which they convert H_2O_2 into H_2O and O_2 . However, in situations where H_2O_2 is not dismutated by the peroxisomal system, inevitable cell damage can occur. Although the main function of peroxisomes is the degradation of peroxides, their activity can also lead to the production of ROS, especially H_2O_2 (Corrales & Muñoz, 2012; Sarmiento, 2020).

Leukocytes have the enzyme NADPH oxidase in their membranes, which is responsible for generating O_2^- and, in the presence of iron, this can be transformed into the highly toxic radical $\bullet OH$. This situation is particularly evident in inflammatory processes (Hernández *et al.*, 2020).

Beneficial ROS are produced in phagocytes during phagocytosis, as they constitute the first line of defence against pathogens, but at this level, an oxidative ‘explosion’ occurs in which large amounts of ROS such as O_2^- , 1O_2 , H_2O_2 and $\bullet OH$ are produced with the aim of destroying infected cells (Estrada & Iglesias, 2017; Revilla, E.M., 2021).

In the endoplasmic reticulum (ER), ROS are generated through cellular activities such as e^- transport, whose function is related to the metabolism of xenobiotics and the introduction of double bonds in fatty acids (Carvajal, C., 2019), in enzymatic activities in which oxidases, reductases, cytochrome P450, b5 and diamine oxidase generate them as a by-product of normal metabolic activities, and in the incorrect formation or misfolding of proteins, which is also associated with ER stress (Tvrdá & Benko, 2020; Konno *et al.*, 2021).

Other cellular sources capable of generating ROS are neutrophils and macrophages, cells belonging to the immune system that, when activated by various signalling proteins or other cells, produce ROS and use them to combat invading organisms such as bacteria (Ortiz & Medina, 2020).

Oxidants can also come from outside the body, either directly or as a result of the metabolism of certain substances. Of the exogenous sources of ROS, tobacco is one of the main generators (León *et al.*, 2018). It is composed of a wide variety of toxic substances, nicotine being one of the most dangerous and addictive, and also includes pro-oxidant substances and radical compounds, with carbonyls and ROS being the main oxidants (Sosa *et al.*, 2022).

Smoke, a product of tobacco combustion, contains a complex mixture of chemicals and carries a wide variety of ROS centred on carbon, O₂ and nitrogen that can damage macromolecules. It can be classified into two phases according to the size of its components: tar phase and gas phase, both of which produce large amounts of FR directly and indirectly (Shein & Jeschke, 2019; Caliri *et al.*, 2021). Among the most common RLs present in tobacco smoke are O₂•⁻, H₂O₂, and •OH, which cause OS and alterations in redox homeostasis (Caliri *et al.*, 2021; Sosa *et al.*, 2022).

Chronic intake of high concentrations of alcohol generates ROS due to the metabolism of ethanol, which is converted to acetaldehyde by the enzyme alcohol dehydrogenase and cytochrome P450 2E1 (CYP2E1), a highly toxic product (Tsermpini *et al.*, 2022). The oxidative metabolism of ethanol releases small amounts of O₂•⁻, however, high doses of ethanol induce CYP2E1, increasing O₂ consumption and thus generating large amounts of O₂•⁻. It also produces H₂O₂, which can damage tissue, and •NO, which in turn forms ONOO⁻ (Borrelli *et al.*, 2018; Díaz-Soto & Calderín-Miranda, 2020; Tsermpini *et al.*, 2022), causing OS in cells by inducing morphological and functional alterations in target organs such as the brain (Metro *et al.*, 2022).

Ambient air pollution is a complex and heterogeneous mixture of particulate matter (PM) and gaseous components that vary according to season, source, and atmospheric conditions. They are anthropogenic in origin, such as energy, car exhaust, combustion, mining, industrial sources, fine dust from the earth, road and tyre abrasion, construction work, and agricultural sources (Gangwar *et al.*, 2020). PM has the ability to generate ROS and RNS such as O₂•⁻ and •NO, which react with each other to form highly reactive ONOO⁻, causing EO, inflammation, and tissue damage (Rao *et al.*, 2018).

Among gaseous pollutants, O₃ is a powerful and important oxidant because it has greater effects on health, as it is a secondary pollutant generated by chemical reactions between •NO and volatile organic compounds in the presence of sunlight (Gangwar *et al.*, 2020; Bello-Medina *et al.*, 2022).

Stress is defined as the reaction to stimuli that may be perceived as threatening. It is our body's natural response to unfavourable or demanding changes in our environment as a measure to cope with and overcome these challenges to our well-being (Juszczuk *et al.*, 2021). Depending on the stressor and the severity of its effects, stress can be beneficial or harmful. When stress is exacerbated, it can cause harmful alterations in the brain, lead to cellular stress, induce pro-inflammatory mechanisms that lead to EO, accelerate biological ageing, and promote oxidative damage (Bisht *et al.*, 2018).

Other influencing factors are pharmaceuticals and drugs. Pharmaceuticals have toxic effects on various organ systems depending on the type and route of administration. Drug addiction has been associated with direct and indirect effects of these substances, causing changes in brain function, alterations in neurotransmitter systems, and neurotoxicity, which is linked to OST (Pavlek *et al.*, 2020). Their abuse promotes the release of dopamine (DA), which oxidises or metabolises rapidly, generating ROS such as O₂•⁻ and H₂O₂, which cause adverse effects such as EO, neuroinflammation, and neurotoxicity, altering mitochondrial function. (Berríos-Cárcamo *et al.*, 2020; Jitcă *et al.*, 2021).

1.1.2.1. Properties of radicals

1.1.2.1.1. Superoxide radical

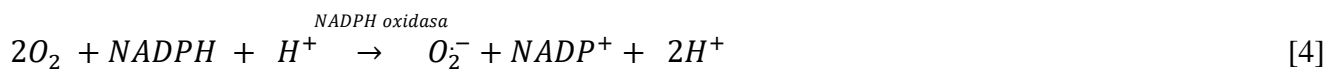
The $O_2^{\cdot-}$ It is the most important radical, its formation is one of the first species generated by various cellular systems, and it is considered the "primary" ROS because it triggers a cascade of ROS when interacting with other molecules to generate "secondary" ROS, either directly or indirectly through processes catalysed by enzymes or metals. The biological impact of these molecules is determined by the amount of ROS, cellular defences, and cellular adaptability. (Curieses *et al.*, 2023).

The $O_2^{\cdot-}$ It is formed by reactions in the ETC, enzymatic processes (by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX)), auto-oxidation reactions, and extracellular reactions. It occurs mainly in the respiratory chain from the first univalent reduction of O_2 by the transfer of an e^- in respiratory complexes I and III, generating a highly reactive and relatively unstable molecule with a half-life of approximately 5 milliseconds. (Curieses *et al.*, 2023; He *et al.*, 2023).

2% of the e^- escape along the CTE and react directly with the O_2 consumed by the mitochondria, reducing around 5% of it to produce $O_2^{\cdot-}$ instead of an H_2O molecule. (Ec. 3) (Lozano-Picazo & Fernández-Belda, 2018; Tirichen *et al.*, 2021).



In enzymatic processes, oxidised NADPH (NOX) is an enzyme located in the membrane that has the property of oxidising the coenzyme NADPH. It is considered an important source of FR production, particularly $O_2^{\cdot-}$, due to the transfer of e^- from NADPH to O_2 , which is partially reduced (Eq. 4). (Guija-Guerra & Guija-Poma, 2023; He *et al.*, 2023)



There are elements that promote the formation of RL, such as transition metals, since as they change their valence state, they lose or gain electrons. Most transition metals have the ability to function in various oxidation states, such as auto-oxidation. This reaction occurs due to the presence of certain transition metals, such as iron and copper, because O_2 alone is not reactive enough to initiate the process (Corrales & Muñoz, 2012).

The redox state of the transition metal is more important for pro-oxidant activity than its concentration. Fe^{2+} is a stronger pro-oxidant than Fe^{3+} and has the property of reacting with O_2 to form the $O_2^{\cdot-}$ radical (Eq. 5). However, it only has pro-oxidant activity in the presence of a reducing agent. (Guija-Guerra & Guija-Poma, 2023).



1.1.2.1.2. Hydrogen peroxide radical

$O_2^{\cdot-}$ can be converted into H_2O_2 by superoxide dismutase (SOD) (Nayak *et al.*, 2018; Singh *et al.*, 2019), $O_2^{\cdot-}$ is an unstable radical that undergoes a dismutation process (a reaction in which RLs generate non-radical products) where two $O_2^{\cdot-}$ ions react, one oxidising to O_2 and the other reducing to H_2O_2 through the action of SOD (Eq. 6) (Hancock, 2021).



H_2O_2 is not considered a FR because it lacks unpaired e^- , however, it is aggressive enough to be considered an ERO (Sies *et al.*, 2017). It can act as a mild oxidant or reducing agent, does not easily oxidise most biological molecules such as lipids, DNA and proteins, is relatively stable, making it less reactive, but it has high lipophilicity, which allows it to diffuse easily through membranes. It has a relatively long half-life and is considered the main reactive species in the redox regulation of biological activities such as intracellular signalling. As an essential mediator, it is considered an important ROS because, like $O_2^{\cdot-}$, it can give rise to other 'secondary' ROS (Carrillo *et al.*, 2016).

H₂O₂ is an important compound in RLs because it can be easily broken down and eliminated by enzymes such as CAT, GPx and peroxiredoxin, converting it into H₂O. It can also be used as a signalling molecule (Martemucci *et al.*, 2022). On the other hand, in larger quantities it is also more toxic and induces the oxidation of nearby biomolecules. Furthermore, it has the ability to generate •OH radicals through reactions catalysed by reactive transition metal ions, such as the Fenton and Haber-Weiss reactions (Angelova *et al.*, 2021; Jávega, 2022). Therefore, H₂O₂ is considered an important immediate precursor (Hernández *et al.*, 2020).

1.1.2.1.3. Hydroxyl radical

•OH is considered the most toxic radical due to its high reactivity. It is capable of causing irreversible damage by reacting immediately with any compound in its vicinity at the site where it is produced, thus limiting its diffusion capacity (Cenini *et al.*, 2020; Arancibia-Hernández *et al.*, 2022). Because it does not cross the membrane, it can react with and damage biological molecules, including DNA, proteins, lipids, and carbohydrates (Jávega, 2022). It has an extremely short lifetime of approximately 1 microsecond (Prado, 2019).

•OH is produced by various reactions, including the Haber-Weiss reaction and the Fenton reaction, the latter being the most important in its formation. Likewise, transition metals are important for the formation of •OH in cells (Nayak *et al.*, 2018; Hancock, 2021).

The Haber-Weiss reaction can be described in two reactions, the first occurring between two RLs, where O₂^{•-} can react with H₂O₂ and, in the presence of Fe as a catalyst, form •OH (Eq. 7) (Carrillo *et al.*, 2016; Prado, 2019; Hancock, 2021).



The second reaction occurs in the presence of a transition metal, especially iron, in which Fe³⁺ is reduced by O₂^{•-}, producing Fe²⁺ and O₂ (Eq. 8). (Prado, 2019).



In the Fenton reaction, Fe²⁺ reacts with H₂O₂, oxidising to Fe³⁺ and simultaneously generating •OH and hydroxyl anion (OH⁻) (Eq. 9). (Crotty *et al.*, 2017; Lozano-Picazo & Fernández-Belda, 2018; Guija-Guerra & Guija-Poma, 2023).



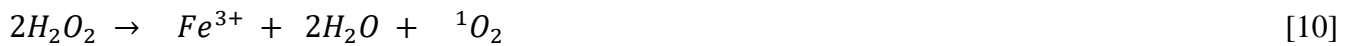
1.1.2.1.4. Singlet radical (¹O₂)

Triplet oxygen (³O₂) is the most abundant form of O₂, which is the oxygen we breathe. It has a ‘spin restriction’ to prevent it from reacting with most organic molecules. However, when the two unpaired electrons of ³O₂ enter two different orbitals, the result is a powerful oxidant called singlet oxygen (¹O₂) (Edge & Truscott, 2021; Martemucci *et al.*, 2022).

¹O₂ is a product of the activation of O₂ in an electronically excited state with high energy and electrophilic properties (Sies *et al.*, 2017; Díaz-Ramírez, 2020; Wang *et al.*, 2024). It is not considered a radical because it does not contain unpaired electrons, However, it is a strong oxidising agent due to its high reactivity caused by the elimination of the ‘spin constraint’ (Di Meo & Venditti, 2020), making it a potential aggressor when it occurs within the cell, causing damage to DNA, cholesterol and proteins, which leads to toxic and mutagenic effects and tissue damage.

Conversely, it can play a role in generating cellular signals to modify gene expression and can be used to combat cancer cells and various pathogens such as microbes and viruses (Lutkus *et al.*, 2019). It is characterised by a very short half-life, although it has a high diffusion capacity and is permeable to membranes (Jávega, 2022). ¹O₂ can exist in two states. First, after activation, O₂ is excited to the delta state (1Δg). Second, it can reach an even higher state, known as the sigma excited state (1εg). The 1Δg state is highly reactive and is usually generated by the activation of neutrophils and eosinophils (Tvrdá & Benko, 2020).

1O_2 can be generated by different processes such as advanced oxidation, chemical decomposition, activation of neutrophils and eosinophils in response to inflammation, photocatalysis and photosensitisation in the natural environment, with oxidation being the most common. It can also be produced by the decomposition of H_2O_2 in an aqueous medium (Eq. 10), which is one of the most commonly used methods for producing it. (Wang *et al.*, 2024).



1.1.2.1.5. Peroxyl radical

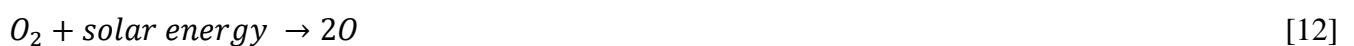
The peroxyl radical ($ROO\cdot$) is possibly the most abundant radical in biological systems. However, it is not as reactive as other ROS. It is formed as a result of oxidative damage to lipids, carbohydrates, and DNA, originating from the addition of O_2 to any hydrocarbon radical (Eq. 11) and has a relatively long half-life. (Ortiz & Medina, 2020; Jávega, 2022).



$ROO\cdot$ produce lipid peroxidation by removing an H from the methylene group ($-CH_2-$) of the chain, thus forming a peroxide radical ($ROOR$) with the O_2 in a chain reaction and increasing peroxidation along the carbon structure (Prado, 2019). Likewise, these reactions can generate new RLs, such as $1O_2$, and can promote tumour development. (Tvrđá & Benko, 2020).

1.1.2.1.6. Ozone radical

Ozone (O_3) is one of the most significant air pollutants. It is an allotropic form of O_2 characterised by being a triatomic molecule containing three O_2 atoms, resulting in an unstable form with high oxidising power due to its mesomeric structure (Alonso *et al.*, 2023). Although it is not a radical per se, it is a much stronger oxidising agent than O_2 and slightly less reactive than $\cdot OH$ (Di Mauro *et al.*, 2019; Martemucci *et al.*, 2022). It is produced by the photodissociation of the O_2 molecule, which generates two monoatomic oxygen atoms (Eq. 12), which subsequently react with O_2 . (Eq. 13) (Braidy *et al.*, 2017).



O_3 has both beneficial and toxic effects. Among its beneficial effects, it acts as an agent capable of effectively modulating the OE by maintaining the balance between pro-oxidants, antioxidants, and inflammation (Alonso *et al.*, 2023). Its toxic effects include the formation of ROS and other reactive intermediates, which are formed by oxidising biomolecules such as proteins, lipids and nucleic acids, causing lipid oxidation, enzyme inactivation, DNA destruction and cell apoptosis (Braidy *et al.*, 2017; Di Mauro *et al.*, 2019). A high dose of O_3 causes OS due to its ability to produce RL. (Braidy *et al.*, 2017).

1.1.2.1.7. Nitric oxide radical

NO is a molecule composed of oxygen and nitrogen that has an unpaired electron in its outer orbital. It has unique characteristics as a neurotransmitter, vasodilator, facilitator of neuronal excitability, regulator of mitochondrial respiration, stimulator of smooth muscle synthesis, and controller of enzymatic activity through protein nitrosylation (Sahay & Gupta, 2017; Gutiérrez *et al.*, 2018; Poderoso *et al.*, 2019).

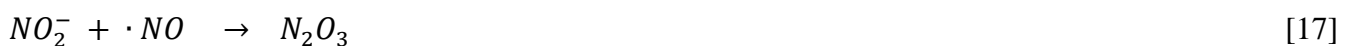
NO is a radical characterised by being a small, neutral, hydrophobic and low-reactivity molecule, which makes it stable and capable of diffusing easily through the cytoplasm and plasma membrane (Kumar *et al.*, 2017; Edge & Truscott, 2021), and has a relatively short half-life of around 0.1 to 10 seconds (Möller *et al.*, 2019).

NO is synthesised in different tissues through an enzymatic reaction catalysed by nitric oxide synthase (NOS), which is present in three isoforms: neuronal NOS (nNOS), which is found in the nervous system and is necessary for neuronal signalling; endothelial NOS (eNOS), which, as its name suggests, is located in the endothelium and is essential for vasodilation and blood pressure control; and inducible NOS (iNOS), which is produced by astrocytes and microglia as a first step of the immune system when some type of damage to nerve tissue is detected (Chen *et al.*, 2017; Miranda & Guerrero, 2021).

NO is also produced from L-arginine, dinucleotide phosphate (NADPH) and O₂ by enzymes of the NOS family (Ec. 14) (Kumar *et al.*, 2017; Cinelli *et al.*, 2020; Kamm *et al.*, 2019). There is another production pathway involving the reduction of nitrite (NO₂⁻) and nitrate (NO₃⁻), which can be absorbed from exogenous sources or synthesised endogenously from L-arginine and O₂ in reactions catalysed by NOS (Ec.15). (Kamm *et al.*, 2019).



There is also the auto-oxidation reaction in which NO reacts with O₂ to form secondary species, which are oxidants, nitrosants or nitrating agents, including nitrogen dioxide (NO₂⁻) (Eq. 16), dinitrogen trioxide (N₂O₃) (Eq. 17), nitroxyl (HNO) (Eq. 18) and ONOO⁻ (Eq. 19). (Möller *et al.*, 2019).



Like other FR molecules, the biological action of •NO depends on its cellular concentration. When produced at low concentrations, it acts as a signalling molecule; however, at high concentrations, it causes cellular damage, triggering nitro-oxidative stress. (Asgher *et al.*, 2017; Cinelli *et al.*, 2020; Holotiuk *et al.*, 2019).

1.1.2.1.8. Peroxynitrite radical

Excessive production of O₂⁻ leads to the rapid ‘inactivation’ of •NO through a reaction that produces an unusual and reactive peroxide, ONOO⁻ (Eq. 19) (Tirichen *et al.*, 2021; Piacenza *et al.*, 2022).

ONOO⁻ is a reactive species with one or two electrons, characterised by being a strongly oxidising and nitrating radical. It can oxidise lipids, proteins and DNA, producing modulations in cell signalling, mitochondrial dysfunction and oxidative damage, leading to cell death, necrosis and apoptosis (Radi, R., 2018; Sarmiento, 2020; Tirichen *et al.*, 2021).

It is also considered a harmful agent with cytotoxic properties, as it limits the bioavailability of •NO in cerebral vessels for the transduction of physiological signals and alters its biological effects towards nitrooxidative processes such as protein and tyrosine nitration (Poderoso *et al.*, 2019; Piacenza *et al.*, 2022). On the other hand, ONOO⁻ can react rapidly to form secondary radicals such as carbon trioxide (CO₃•-) and NO₂• (Eq. 20). (Möller *et al.*, 2019).



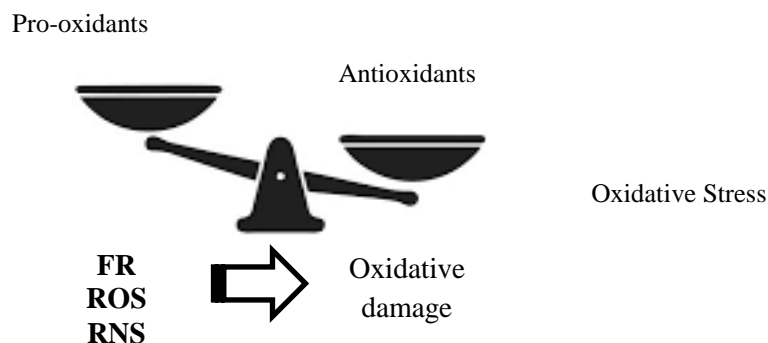
Box 7**Table 2**

Description of the main reactive oxygen species (origin and reactivity)).

Reactive species	Symbol	Half-life (s)	Origin and reactivity
Superoxide	$O_2^{\bullet-}$	10^{-4}	Metabolic product of oxidative phosphorylation generated in the mitochondria, vascular system, among others..
Hydrogen peroxide	$\bullet OH$	10^{-9}	Highly reactive, generated during iron overload and various reactions in the body..
Hydrogen peroxide	H_2O_2	Stable	Generated in the body as a product of the O_2 reaction catalysed by superoxide dismutase and through a large number of reactions..
Peroxyl radical	$\bullet OOR$	Range of seconds	Formed as a result of oxidative damage to lipids, DNA and carbohydrates..
Organic hydroperoxide	$ROOH$	Stable	Product of oxidative damage to lipids, DNA, and carbohydrates; can react with transition metals and form new radicals..
Singlet oxygen	1O_2	10^{-6}	Highly reactive, formed during photosensitisation and chemical reactions.
Ozone	O_3	Range of seconds	Present in the atmosphere, it can react with various molecules..

*Ortiz & Medina (2020)***1.2. Oxidative stress**

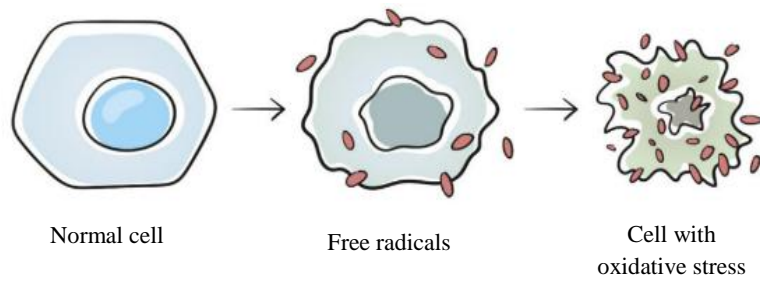
When excessive amounts of FR and oxidants are produced, a condition called OS occurs ([Jamshidi-Kia et al., 2020](#)). The term OS was defined by Helmut Sies in 1985 as an imbalance between oxidants (pro-oxidants) and antioxidant systems in favour of oxidants, leading to potential damage due to increased ERO production (Fig. 6). ([Ali et al., 2020](#); [Fernández & Zeledón, 2020](#); [Rodríguez et al., 2021](#))

Box 8**Figure 6**

Representation of oxidative stress

Barbosa et al. (2008)

OS is characterised by an imbalance in the homeostasis of pro-oxidants and antioxidants, causing deterioration and damage at the cellular, tissue and molecular levels (Fig. 7) ([Barbosa et al., 2008](#); [Yang et al., 2018](#); [Jakubczyk et al., 2020](#); [Park & Yang, 2021](#)). The impact of OS on the body will depend on the type of oxidant causing the stress, the site where it is occurring, its intensity, as well as the cell's ability to activate its antioxidant defence machinery and the ability of repair systems to repair the damage caused by the impact of ROS on the molecules that make up the cell. ([Castillo & Salazar-Lugo, 2018](#)).

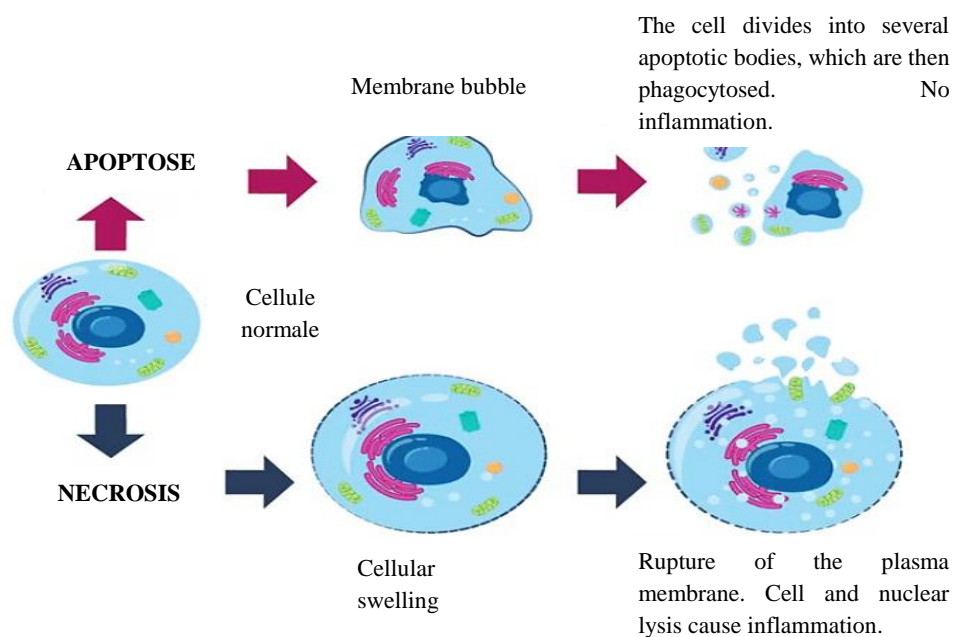
Box 9**Figure 7**

Cell damage caused by oxidative stress

Damien & Damien (2021)

Furthermore, OS leads to altered redox signalling and control, cellular and tissue oxidative damage, genetic mutation, and carcinogenesis (Jamshidi-Kia *et al.*, 2020; Meñaca-Guerrero *et al.*, 2020), causing irreversible modifications and oxidation in various biomolecules such as lipids (lipoperoxidation), proteins (carbonylation), and DNA (cellular senescence), preventing their proper functioning (Losada-Barreiro & Bravo-Díaz, 2017; Gutiérrez *et al.*, 2018). It also leads to disorders in cell membrane permeability, the formation of atheromatous plaques, protein fragmentation, glycosylations, mitochondrial dysfunction and even cell death (León *et al.*, 2018). Furthermore, OS and inflammation are closely related, as OS can cause inflammation, which in turn can induce OS, causing damage to the cell (Hernández *et al.*, 2019).

OS plays a fundamental role in various processes of neuronal death, such as necrosis and apoptosis (Fig. 8). Necrosis is unprogrammed cell death because it occurs accidentally when cells cannot combat stress that extends beyond their tolerance level and therefore cannot be regulated (Chen *et al.*, 2018). They suffer loss of membrane integrity caused by lipid peroxidation, oxidative damage to DNA and structural proteins (Hernández *et al.*, 2019). On the other hand, apoptosis is the precise and programmed natural cell death that is essential for the maturation of the central nervous system (CNS). It is characterised by cell contraction, loss of potential and blister formation in the membrane, release of cytochrome C, loss of positional organelles, protein peroxidation, resulting in the dysfunction of ATP synthase and mitochondrial respiratory chain complexes and a decrease in the concentration of antioxidant mechanisms such as glutathione (GSH). (Chen *et al.*, 2018; Yang *et al.*, 2018).

Box 10**Figure 8**

Neuronal death processes and their characteristics

Proteintech 2023

Oxidative stress alters the structure and function of any organ (Aguilar-Paredes *et al.*, 2018). The brain is the organ most susceptible to OS for several reasons. First, it is the most active part of the body, consuming approximately 20% more O_2 than other parts of the body, a significant portion of which is transformed into ROS. Second, it produces specific neurochemical reactions that generate large amounts of ROS and RNS. Third, it has large amounts of lipids, which are susceptible to EO. Finally, with the ageing process, more metal ions with redox activity accumulate, which act as catalysts in the production of ROS and RNS, increasing LOX (Crotty *et al.*, 2017; Hemmati-Dinarvand *et al.*, 2019; Chang & Chen, 2020; Montero, M. 2023). Oxidative stress promotes the development and progression of inflammatory diseases such as AD, PD, ALS, CVD, liver disease, cancer, diabetes, obesity, and ageing, among others, because ROS affect multiple tissues (Fig. 9). (Tvrdá & Benko, 2020; Cruz-Rodríguez & López-Solís, 2021; Montero, M., 2023).

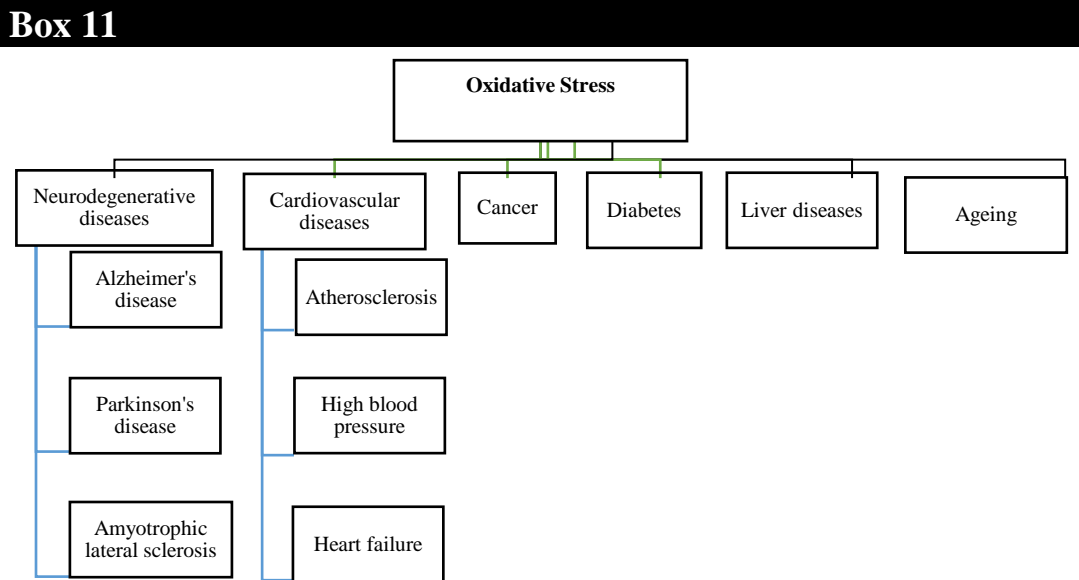


Figure 9

Diagram of the development of diseases caused by oxidative stress

Own Elaboration

The OS mechanism begins in the ETC due to poor O_2 transport, which is converted into ERO. The first FR formed by the reduction of O_2 is $O_2^{\bullet-}$, which is moderately toxic and can also be generated by enzymatic processes such as NADPH oxidase. Subsequently, through SOD, it is converted to H_2O_2 , which is a less reactive radical. Next, through CAT, it is converted into H_2O and O_2 . However, in larger quantities, H_2O_2 produces highly toxic $\bullet OH$ in the presence of Fe^{2+} through the Fenton reaction. Fe^{3+} can be recycled to Fe^{2+} through the Haber-Weiss reaction (see chapter 2.1.1.6.3). Finally, $\bullet OH$ is transformed into an FR and H_2O , which reacts with O_2 to form $ROO\bullet$ (Fig. 10). (Su *et al.*, 2019; Angelova *et al.*, 2021; Jávega, 2022).

Box 12

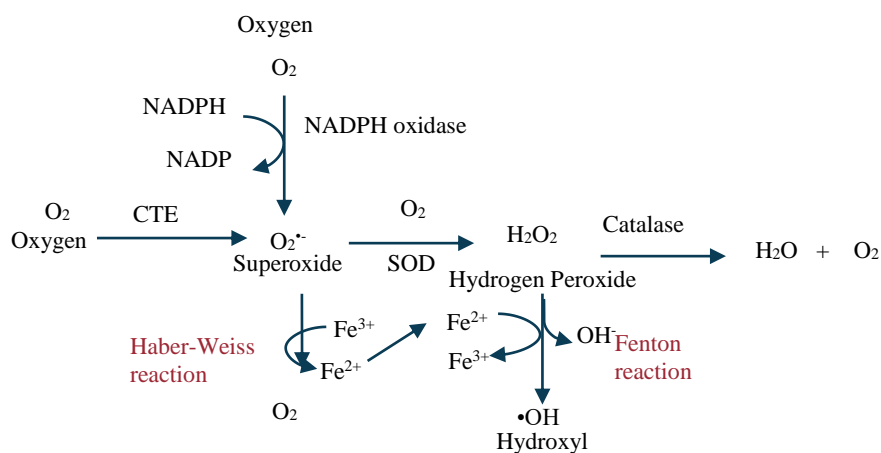


Figure 10

Oxidative stress mechanism

Own Elaboration

1.2.1. Nitro-oxidative stress

Nitro-oxidative stress (NOS) refers to the excessive or unregulated formation of $\bullet\text{NO}$ and ROS derived from it, together with the antioxidant system. It is mainly characterised by high cellular levels of ROS and O_2 (Morachis, 2014; Sahay & Gupta, 2017). ERNs can damage cells through various mechanisms: inactivation of the various complexes of the respiratory chain, damage to proteins and lipids, and inhibition of protein or DNA synthesis (Morachis, 2014). They also play an important physiological role in regulating the cardiovascular and neuronal systems, as well as in controlling the human immune response (Kamm *et al.*, 2019).

The EN mechanism begins when $\text{O}_2^{\bullet-}$ reacts with $\bullet\text{NO}$ to generate ONOO^- , a highly reactive ERN responsible for nitration and nitrosation, DNA oxidation, and lipid peroxidation. Subsequently, this can form N_2O_3 and HOONO . Then, a homolytic rupture of HOONO occurs, producing $\text{NO}_2\bullet$ and $\bullet\text{OH}$, which easily diffuse through membranes to mediate the oxidation and nitration of FAs (Fig. 11). (Rubbo, 2013; Gasparovic *et al.*, 2018).

Box 13

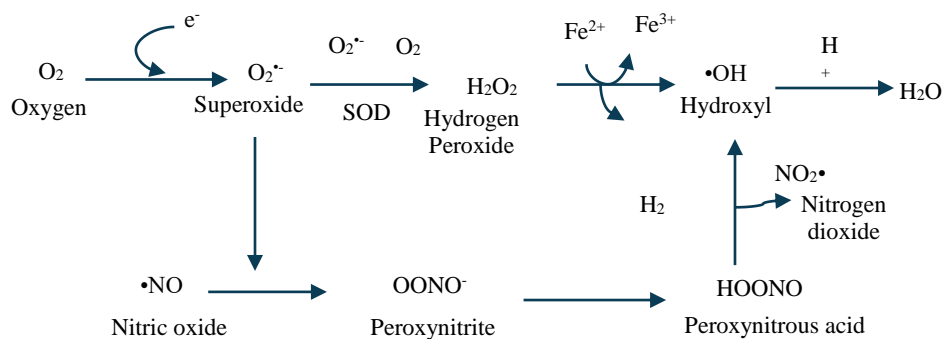


Figure 11

Nitro-oxidative stress mechanism

Castillo & Salazar (2018).

1.3. Lipoperoxidation

ERO and ERN have the ability to attack biomolecules such as lipids, proteins, and DNA (Spaas *et al.*, 2021). Lipids are the molecules most sensitive to the effects of RLs because they contain high levels of polyunsaturated fatty acids (PUFAs), making them particularly susceptible to oxidative damage caused by ROS, which is called ‘lipoperoxidation’ (LPO) (Guo *et al.*, 2018; Su *et al.*, 2019; Yalcinkaya *et al.*, 2019).

LPO is a complex process involving the oxidative degradation of lipids, which have a preference for fatty acids (FAs), especially PUFAs such as linoleic acid, arachidonic acid, docosahexaenoic acid, and eicosapentaenoic acid due to their instability and reactivity, as they contain carbon-carbon double bonds or carbon-hydrogen double bonds (Hauck *et al.*, 2019; Angelova *et al.*, 2021; Arce *et al.*, 2023). In this process, RLs capture electrons from lipids present in cell membranes or organelles, affecting their integrity and function (Vázquez *et al.*, 2019). The LPO mechanism begins when a RL, especially the $\bullet\text{OH}$ and $\text{ROO}\bullet$ radicals, attacks a double-bonded carbon molecule of an AGPI, causing its deprotonation and creating a chain reaction (López, 2019; Yaman & Ayhanci, 2021).

PUFAs are easily oxidised to lipid hydroperoxides, which are degraded into a variety of products. In addition, they can be converted into reactive RLs after reacting with other RLs, which are capable of initiating or propagating LPO chain reactions by attacking other lipid molecules (León *et al.*, 2018). The CNS is particularly susceptible to LPO due to the abundant presence of PUFAs in membranes, as well as its high O_2 consumption and iron levels (Spaas *et al.*, 2021).

LPO occurs through two pathways, non-enzymatic and enzymatic, in both cases the lipid molecule is oxidised after the formation of lipid radicals. Non-enzymatic LPO, also known as auto-oxidation, is iron-dependent peroxidation and ROS, especially $\cdot\text{OH}$ and $\cdot\text{OOH}$, which initiate oxidative chain reactions, which take place in three stages: initiation, propagation, and termination (Fig. 12). (Ursini & Maiorino, 2020; Yaman & Ayhanci, 2021).

Box 14

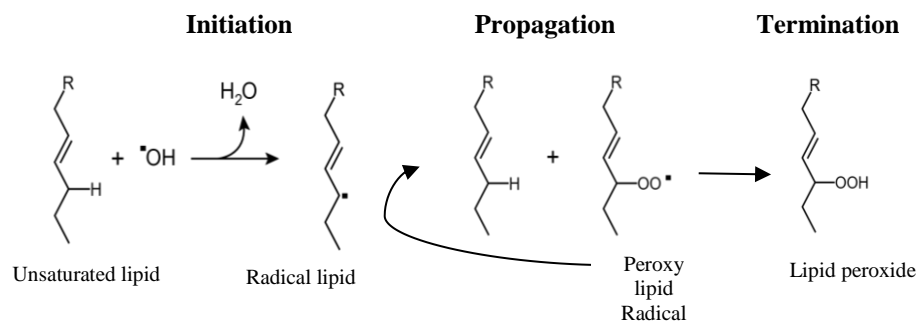


Figure 12

Lipoperoxidation process where three phases are observed: initiation, propagation and termination, starting from a polyunsaturated fatty acid

Aguilar-Paredes et al. (2018).

The initiation stage begins with the abstraction of a hydrogen atom from a phospholipid containing an AGPI by an ROS source such as $\cdot\text{OH}$, $\text{ROO}\cdot$ or $\text{RO}\cdot$ (Eq. 21) or by reacting with O_2 (Eq. 22), generating a carbon-centred radical ($\text{R}\cdot$). (Maiorino *et al.*, 2018; López, 2019).



The initiation stage is favoured when there is an increase in the number of double bonds in FAs, which is why PUFAs are more susceptible to oxidation (Aguilar-Paredes *et al.*, 2018).

In the propagation stage, $\text{R}\cdot$ readily reacts with O_2 to form $\text{ROO}\cdot$ (Eq. 23) (Su *et al.*, 2019), which is highly reactive and initiates a chain reaction, extracting an H^+ atom from an adjacent PUFA to form lipid hydroperoxides (ROOH) and a new radical (Eq. 24). (Aguilar-Paredes *et al.*, 2018; Ursini & Maiorino, 2020).



It is important to note that newly formed ROOH can subsequently decompose in the presence of free Fe and Cu through the Fenton reaction, leading to the formation of $\text{RO}\cdot$ and/or $\text{ROO}\cdot$, which initiates new chain reactions (Ursini & Maiorino, 2020).

In the termination stage, two radicals from the chain reaction react with each other in the absence of O_2 to form stable molecules, which stops the propagation of the chain reaction. (Ec. 25-27) (Maiorino *et al.*, 2018; Su *et al.*, 2019).



Enzymatic LPO is mainly catalysed by lipoxygenases (LOX) and cyclooxygenases (COX) (Gegotek & Skrzydlewska, 2022). Arachidonic and linoleic acids are the most abundant PUFAs that serve as substrates for LOX, using O₂ to form •OOH at different carbon positions in the acyl chains (Su et al., 2019).

LPO leads to the formation of various end products such as aldehydes, ketones, alkanes, carboxylic acids, and polymerisation products, which can be metabolised at the cellular level or diffuse from their initial locations and spread damage to other parts of the cell (Yaman & Ayhanci, 2021).

These products can be classified according to the modified lipid, isoprostanes/isofurans produced from the oxidation of arachidonic acid, which is present in all tissues, neuroprostans/neurofurans that come from the oxidation of docosahexaenoic acid, found in the grey matter of the brain, and di-homo-isoprostanes/dihomo-isofurans that originate from the oxidation of adrenic acid found in the white matter of the brain (Peña-Bautista et al., 2019).

The end products of LPO are peroxidised lipids, which, when degraded, generate new RLs and various reactive compounds that are mutagenic and cytotoxic, such as aldehydes, which are characterised by being highly reactive (Mora et al., 2019; Vázquez et al., 2019). Among the end products are malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), 4-hydroxyhexanal (Fig. 13), acrolein, and isoprostanes (Gegotek & Skrzydlewska, 2022; Hauck et al., 2019; Arce et al., 2023). These unstable molecules are called reactive carbonyl species (RCS), which can have beneficial and harmful effects. At low concentrations, they play an important role in cell physiology, including phospholipase activity and the stimulation of signalling cascades (Yalcinkaya et al., 2019; Angelova et al., 2021). However, at high concentrations, they directly affect the physical properties and functioning of the cell membrane, as they disrupt its lipid asymmetry, reducing its internal hydrophobicity and causing depolarisation and loss of integrity (Gegotek & Skrzydlewska, 2022), which can cause irreversible damage to cells, leading to inflammatory, necrotic, apoptotic, autophagy, ferroptosis and cell death processes. (Yalcinkaya et al., 2019; Arce et al., 2023).

Box 15

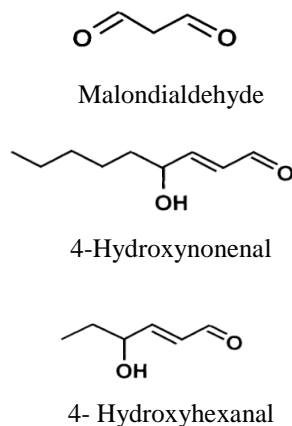


Figure 13

Chemical structures of the main aldehydes formed in lipoperoxidation.

Aguilar-Paredes et al. (2018).

MDA is the main product of LPO. It is a low molecular weight product resulting from the fragmentation of PUFAs by the action of RLs. It is a three-carbon dialdehyde found in the cell membrane and is used as a marker of OE. It is considered a toxic, mutagenic, and carcinogenic agent (López, 2019; Kehm et al., 2021). It is characterised by causing structural changes when oxidised, such as fragmentation, modification and adduct formation, especially in DNA and proteins (Yaman & Ayhanci, 2021).

Although many ROS have a half-life of less than a second, RSCAs can last for hours or even days and diffuse outside the cell, causing cellular damage and a variety of signalling effects (Spaas et al., 2021), thus causing oxidative stress and cell death, thereby contributing to the pathogenesis of various diseases such as AD, PD, ALS, among others (Angelova et al., 2021).

1.3.1. Carbonylated proteins

Proteins are targets of various post-translational modifications such as phosphorylation, methylation, acetylation, ubiquitination, LPO, glycosylation, and oxidation (Akagawa, 2021), the latter being the most important due to the variety of oxidation mechanisms and products, their rapid reaction rates with oxidants, and their abundance in cells, extracellular tissues, and body fluids (Gonos *et al.*, 2018; Kehm *et al.*, 2021).

Reversible and irreversible modifications can occur in protein oxidation. Reversible modifications are important in physiological processes and can serve as signalling mechanisms known as ‘redox signalling’, which activate antioxidant defences and involve the immune system in the cellular response to LO (Kehm *et al.*, 2021; Estévez *et al.*, 2022). On the other hand, irreversible modifications cause intracellular damage and deterioration in function (Akagawa, 2021).

ROS can cause oxidation of the amino acids that form proteins, producing various modifications such as the formation of carbonyl groups (=CO), which alter their structure, causing fragmentation, aggregation, and modification in the side chains of amino acids. In turn, this can alter their activity and function, increasing their susceptibility to degradation (Matamoros *et al.*, 2018; Tola *et al.*, 2021), thus affecting cellular processes and contributing to the development of diseases and disorders. This process is called ‘protein carbonylation’ (PC) (Hauck *et al.*, 2019).

PC is one of the main non-enzymatic and irreversible oxidative post-translational modifications induced by ROS and RNS (Rudzińska *et al.*, 2020). It is characterised by the addition of =CO (aldehydes or ketones), which are highly electrophilic and prone to nucleophilic attack, to the side chains of certain amino acids such as cysteine (Cys), lysine (Lys), histidine (His), methionine (Met), tyrosine (Tyr), arginine (Arg), proline (Pro) and threonine (Thr) (Fig. 14). (Hecker & Wagner, 2017; Martínez-Orgado, 2023; Muñoz *et al.*, 2022).

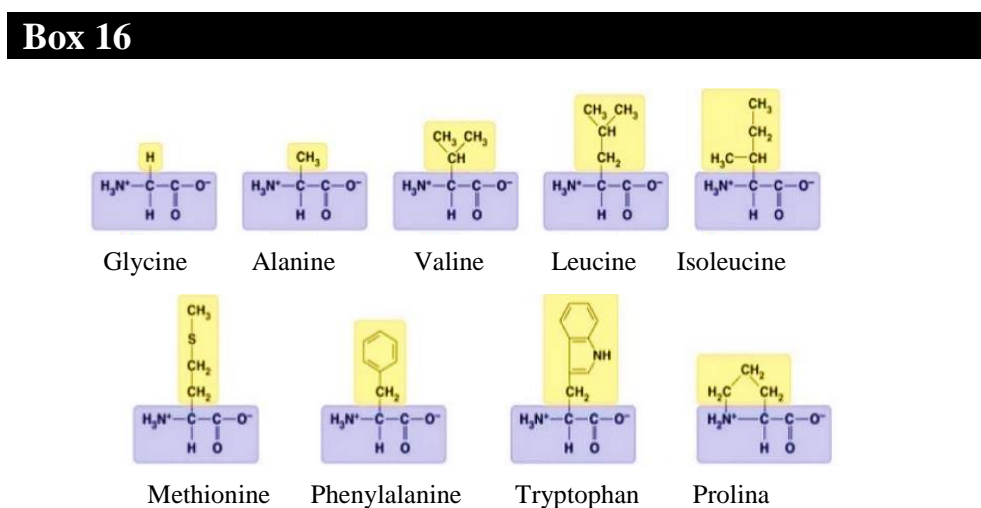


Figure 14

Structures of some amino acids
García-Allen (2025)

PC can occur through two mechanisms: oxidative (direct), in which direct oxidation of the side chains of Lys, Thr, Arg, and Pro residues occurs, induced by ERO (Fig. 15); or non-oxidative (indirect), promoted by OS by-products (Rodríguez-García *et al.*, 2020; Nair *et al.*, 2021; Muñoz *et al.*, 2022), leading to the formation of oxidative products, especially covalent lipid-protein adducts (Hauck *et al.*, 2019). On the other hand, the reaction of proteins with FR leads to the formation of protein radicals, specifically ROOH. (Gonos *et al.*, 2018).

Box 17

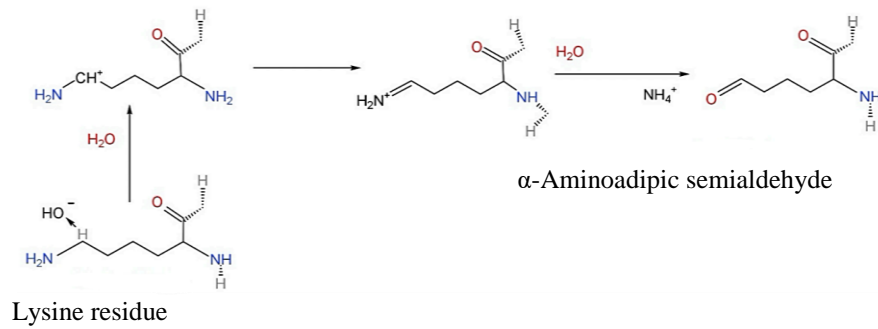


Figure 15

Protein carbonylation of lysine residue mediated by direct oxidation

Muñoz et al. (2022)

Reactive carbonyls can be generated from endogenous sources, mainly mitochondria and phagocytes, or through exogenous sources such as tobacco and food additives (Rudzińska *et al.*, 2020). The chemistry of PC is complex due to the different biomolecules involved, including lipid and sugar derivatives. Two main types of PC have been proposed, primary and secondary, reflecting how the modification occurs (Fig. 16) (Tola *et al.*, 2021). This depends on whether the carbonyls are formed in the proteins or introduced into the proteins after their formation (Estévez *et al.*, 2022).

Primary protein carbonylation involves the direct action of ROS or metal-catalysed oxidation (MCO) on amino acid side chains, leading to the formation of aldehydes or ketones (Rudzińska *et al.*, 2020; Sharma *et al.*, 2020). MCO is a common mechanism of PC in cells, occurring when Fe^{2+} (ionic metal) reacts with H_2O_2 and generates $\cdot\text{OH}$ through the Fenton reaction. These radicals induce the oxidation of Pro, Arg, Lys, and Thr to aldehydes or ketones, converting them into highly toxic carbonyl derivatives, which can oxidise almost any amino acid side chain (Matamoros *et al.*, 2018; Xiong & Guo, 2020).

Primary carbonylation can also occur, although to a much lesser extent, through α -amidation pathways (a process by which an amide group is added to the alpha carbon atom of an amino acid at the N-terminal end of the protein) or through the oxidation of glutamyl side chains (Rodríguez-García *et al.*, 2020). On the other hand, secondary carbonylation is formed from the oxidation of lipids, which are then introduced into proteins through covalent bonds, forming carbonyl-protein adducts (Estévez *et al.*, 2022). $=\text{CO}$ can be introduced into proteins indirectly through the non-oxidative covalent adduction of ERC to side chains of nucleophilic amino acids such as Lys, His, Cys, and Arg (Hecker & Wagner, 2017; Sharma *et al.*, 2020; Xiong & Guo, 2020).

PC can also be generated by non-enzymatic glycation reactions, in which a nucleophilic addition reaction occurs between the amino group (NH_2) of proteins and the $=\text{CO}$ of reducing sugars or their oxidation products (Rodríguez-García *et al.*, 2020; Martínez-Orgado, 2023). This post-translational modification is spontaneous, age-dependent, and affects the structure and function of various proteins. (Sharma *et al.*, 2020)

Box 18

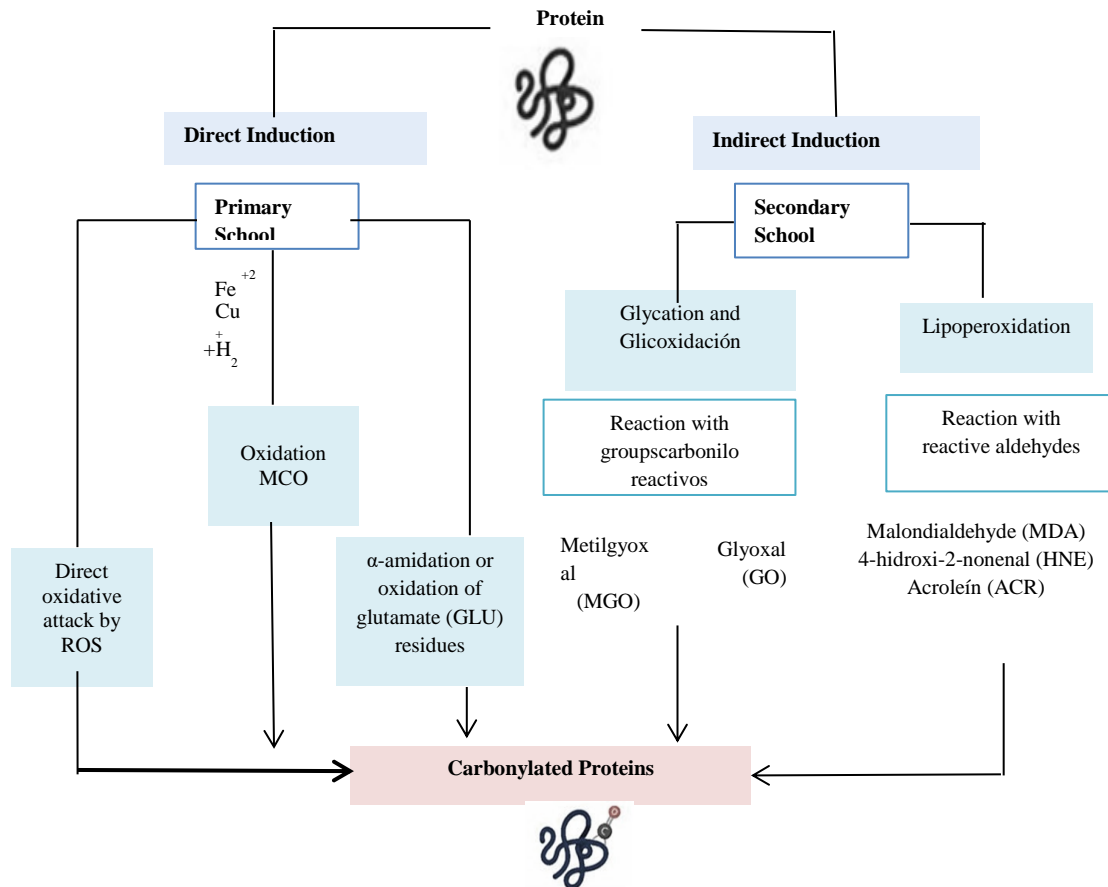


Figure 16

Schematic diagram of the classification of carbonyl protein production.

Rodríguez-García et al. (2020).

When PC tend to accumulate in the cell, they exert cytotoxic effects, can cause intracellular oxidative damage, deterioration of cellular functions, leading to tissue damage and ultimately cell death (Akagawa, 2021; Kehm et al., 2021). This is closely related to the ageing process and various pathologies and diseases such as diabetes, AD, PD, ALS, CVD, among others, which are characterised by the accumulation of carbonylated protein aggregates (Xiong & Guo, 2020; Martínez-Orgado, 2023; Muñoz et al., 2022).

The increase in PC is associated with an increase in cellular levels of ROS and multiple oxidation pathways, which is why it is considered an important biomarker for indicating the intensity of OS due to its nature, structural and functional ramifications, sensitivity, and availability for detection. (Nair et al., 2021; Tola et al., 2021).

Chapter 2. Chronic degenerative diseases

One of the great challenges currently facing humankind is the control of neurodegenerative diseases (NDs). Neurodegeneration is the process of progressive degeneration and neuronal death that compromises the proper functioning of the nervous system (Sienes *et al.*, 2022). CDDs are a group of pathological disorders characterised by the progressive loss of neurons associated with pathologically altered proteins that are deposited mainly in the brain and spinal cord.

They are distinguished by being chronic, untreatable and irreversible, and their typical physiological indicators are demyelination, loss of dendrites and neuronal death. As neuronal structures deteriorate, there is a gradual loss of cognitive (dementia) and/or motor (ataxia) abilities, causing mental deterioration, functional loss, and weakening, slowly and gradually physically degrading those who suffer from them, causing imbalances and conditions in organs and tissues. SDCs are more prevalent in the elderly, but they can also occur in patients of all ages (Kovacs, 2018; Rekatsina *et al.*, 2020).

Among the best-known ECDs that relate pathogenesis to the generation of ROS and RNS causing OS and affecting the CNS are AD, PD, ALS, and Huntington's disease. Other ECDs include diabetes, cancer, cardiovascular disease, liver disease, and ageing.

2.1. Alzheimer's disease

AD is one of the most common neurodegenerative diseases that alters mental development and disrupts neurocognitive function. It is defined as a chronic, late-onset, progressive, irreversible, and incurable disease. It is considered the leading cause of dementia, accounting for 50-75% of cases, causing a growing global health problem that affects activities of daily living and social functioning (Carril *et al.*, 2017; Srivastava *et al.*, 2021; Zhang *et al.*, 2021).

With its late onset and age dependence, AD is a disorder that mainly impacts old age, affecting more than 10% of people over 65 and around 50% of those over 85, and can last from 8 to 12 years (Zvěřová, 2019). According to statistical data, women are more likely to develop the disease because they live longer than men on average, and the risk increases further with age (Alzheimer's Association, 2017). Likewise, people with CVD, hypertension, obesity, and diabetes tend to have a higher risk of developing AD in the future (Srivastava *et al.*, 2021).

Currently, AD is recognised as a long-term process because its development and progression are slow. However, pathological changes occur years before (around 20 to 30 years) the first symptoms appear, making it one of the most problematic and costly diseases for society and considered a 'silent threat' (Zvěřová, 2019).

AD is characterised by progressive memory loss, deterioration of cognitive functions, functional capacity, and drastic changes in behaviour and personality (Barragán *et al.*, 2019). The main key pathological features are found in the brain tissue of AD patients, defined by the accumulation of β -amyloid peptide ($A\beta$) and neurofibrillary tangles, mainly in the hippocampus and cerebral cortex, where they form senile plaques outside the cells, and by the presence of hyperphosphorylated tau (p-tau), which clusters inside the cells as neurofibrillary tangles (NFTs), thus causing cognitive impairment and behavioural disorders (Joe & Ringman, 2019; Zhang *et al.*, 2021).

AD is classified into three identifiable clinical stages: mild (early), moderate, and severe, depending on the degree of cognitive impairment presented by the patient (Kumar *et al.*, 2018). The symptoms that stand out in the disease not only involve progressive and irreversible cognitive impairment, but also include neuropsychiatric symptoms called psychological and behavioural symptoms (Rekatsina *et al.*, 2020).

The mild or early stage involves symptoms such as memory loss, orientation, language, organisation, and planning. Memory loss is the main symptom of AD, usually beginning with short-term memory, while long-term memory is minimal or non-existent. Likewise, misplacing or losing objects is very common in these patients.

This is followed by deterioration in problem solving, judgement, executive functioning, lack of motivation and disorganisation, leading to difficulties in multitasking, motor dysfunction and abstract thinking. At this stage, the patient can live independently and continue to carry out their activities (Kumar *et al.*, 2018; Silva *et al.*, 2019).

In addition, these patients present psychological symptoms such as mood swings, depression, apathy, social withdrawal, irritability, and anxiety; behavioural symptoms such as wandering, restlessness, aggression, resistance to care, inappropriate sexual behaviours, and catastrophic reactions such as anger and verbal and physical aggression (Romero & Garrido, 2018). In the moderate stage, the disease is more advanced, usually the longest phase and can last for years. Patients experience difficulties with episodic memory, such as forgetting events, but may still remember essential and important details of their lives.

They also present neuropsychiatric symptoms such as mood and behaviour changes, mainly in difficult situations, severe anxiety, distrust, delusions, hallucinations (visual hallucinations being the most common), sleep disturbances, difficulty performing learned motor tasks (dyspraxia), misidentification and, occasionally, epileptic seizures, which are more common in young patients. require greater attention and assistance to carry out their daily activities and personal care (Barragán *et al.*, 2019; Zvěřová, 2019).

In the severe stage, patients lose the ability to manage their environment and movement, including the ability to walk and sit, and often become mute, incontinent, and bedridden. During this phase, various complications arise, such as immobility, deep vein thrombosis, malnutrition, and infections, which often become the direct cause of death. They also present neuropsychiatric symptoms such as irritability and impaired perception, aggressiveness, combativeness, shouting or hyperactivity, and these symptoms tend to worsen as the disease progresses, becoming stressful for both family members and carers, thus requiring immediate therapeutic intervention (Zverova, 2019).

Furthermore, AD can be classified into two stages according to the age of onset of the first symptoms: early-onset AD, if symptoms appear before the age of 65, accounting for approximately 4-6% of cases, and late-onset AD, if symptoms appear after the age of 65. These are further subdivided into familial AD, if there is a history of direct relatives and accounts for around 10% of cases, and sporadic AD, if there is no family history (Romano *et al.*, 2007).

Early-onset AD, also known as the cellular phase, develops simultaneously with the accumulation of β -amyloid, which in turn triggers the spread of tau pathology. This is not only a disease that occurs at an earlier age; it is estimated that between 60 and 80% of the risk of developing it is related to hereditary genetic factors, which are understood to be a family history, mainly inherited from a parent or grandparent who experienced the disease at an early age (between 40 and 50 years old).

It is also associated with one of three autosomal dominant mutations, amyloid precursor protein (APP), presenilin 1 (PSEN1) or presenilin 2 (PSEN2), with a prevalence of 0.8%, 1.1% and 13%, respectively, and can occur even after the age of 65. Likewise, alterations in the trigger receptor expressed in myeloid cell gene 2 (TREM2) increase the risk of developing AD (Romano *et al.*, 2007; McCartney *et al.*, 2018; Mendez, 2019; Silva *et al.*, 2019). On the other hand, late-onset AD is mainly associated with a polymorphism in the APOE gene (apolipoprotein E gene), especially the presence of the ϵ 4 allele (Silva *et al.*, 2019).

It is important to note that patients with early-onset AD may follow a more aggressive clinical course and tend to have a higher risk of premature death (Mendez, 2019). Conversely, there is no significant impact on predisposition to the disease if there is a positive family history of late-onset AD (Scheltens *et al.*, 2021).

The aetiology of the disease remains unknown; it is considered a complex multifactorial disorder resulting from genetic, environmental, acquired (diseases) and lifestyle risk factors. However, age is one of the most important risks for cognitive decline and AD (Cassidy *et al.*, 2020; Zhang *et al.*, 2021). As age advances, its prevalence increases by approximately 19% in people aged 75 to 84 and up to 30-35% in people over 85 (Armstrong, 2019).

Environmental risk factors are natural or chemical substances found in our environment that can cause damage to health. These factors include metals such as aluminium, iron, zinc, copper, and lead, and chemicals such as benzene, toluene, fertilisers, and insecticides. Metals play an important role in AD because they accumulate in the brain as we age (Armstrong, 2019; Singh *et al.*, 2019).

Acquired risk factors are considered one of the main risk factors for the progression of dementia, including CVD, diabetes, hypertension, obesity, depression, inflammatory processes, and atherosclerosis (Edwards *et al.*, 2019; Silva *et al.*, 2019). Traumatic brain injuries are also an important factor leading to the progression of AD (Katsumoto *et al.*, 2018).

Lifestyle risk factors include body mass index (BMI), smoking, and stress. Smoking is the main risk factor affecting the development of AD because it leads to cognitive impairment, which is reflected in an accelerated decline in verbal memory and a slowing of visual search speeds (Edwards *et al.*, 2019). Smoking is known to increase the generation of RL, causing OS and promoting pro-inflammatory action in the immune system. In addition, smoking can cause CVD, which increases the risk of AD (Silva *et al.*, 2019).

On the other hand, chronic stress is a risk factor, as it induces OS and neuroinflammation, further promoting the production of amyloid plaques. Therefore, improving stress regulation and emotion management can have a positive impact on cognition by reducing harmful psychological effects (Zhang *et al.*, 2021).

OFS is one of the main factors in the pathogenesis of AD, as excessive ROS production plays a key role in the accumulation and deposition of β -amyloid peptides, tau hyperphosphorylation and tangled formation, causing mitochondrial dysfunction, reduced ATP generation, extensive oxidative damage to nucleic acids leading to alterations in DNA structure and the onset of clinical dementia in AD (Fig. 17) (Cioffi *et al.*, 2019; Cassidy *et al.*, 2020).

Several pathways leading to OST are considered in the pathogenesis of AD. First, β -amyloid reduces O_2 to H_2O_2 in the presence of iron through the Fenton reaction. In addition, it has the ability to bind to CAT, thus limiting its antioxidant function against H_2O_2 . On the other hand, the tau protein is also affected by EO. It has been observed that 4-hydroxynonenal (HNE) aldehyde, a by-product of lipid peroxidation, can induce modifications in the conformation of tau, contributing to its abnormal hyperphosphorylation (Cheignon *et al.*, 2018; Misrani *et al.*, 2021).

On the other hand, the neurotoxicity of β -amyloid mediated by peroxides and membrane lipid peroxidation leads to cell death. In addition, it recruits and activates microglial cells (inflammatory cells), which in turn generate large amounts of ROS. Their overproduction originates in the respiratory reaction of microglia, triggered by cerebral inflammation caused by β -amyloid, causing the activation of the enzyme NADPH-PHOX, which transfers e^- from NADPH to O_2 , producing O_2^- . Microglia hyperactivation occurs through innate immune response receptors, such as Toll-like receptors 2 (TLR2), which are activated when they bind to β -amyloid, resulting in the overexpression of proinflammatory cytokines.

The enzyme cyclooxygenase 2 (COX 2), induced in the brain by these proinflammatory cytokines, such as interleukin 1β (IL- 1β) and tumour necrosis factor α (TNF- α), regulates prostaglandin 2 (PGE2) signalling in neurons and can activate the transcription of amyloid precursor protein in astrocytes. It also increases the release of glutamate, which causes excitotoxic neuronal damage by opening calcium ion channels, whose increase in the cytosol will activate a series of second messengers, such as phospholipase A_2 , calmodulin, calpain, and endonuclease, which ultimately leads to neuronal death (Cioffi *et al.*, 2019; Sacristán *et al.*, 2019).

Similarly, the insertion of β -amyloid as oligomers into the bilayer can lead to the development of ROS, thus initiating lipid peroxidation of membranes, followed by the oxidation of intracellular proteins and nucleic acids. (Misrani *et al.*, 2021).

Box 19

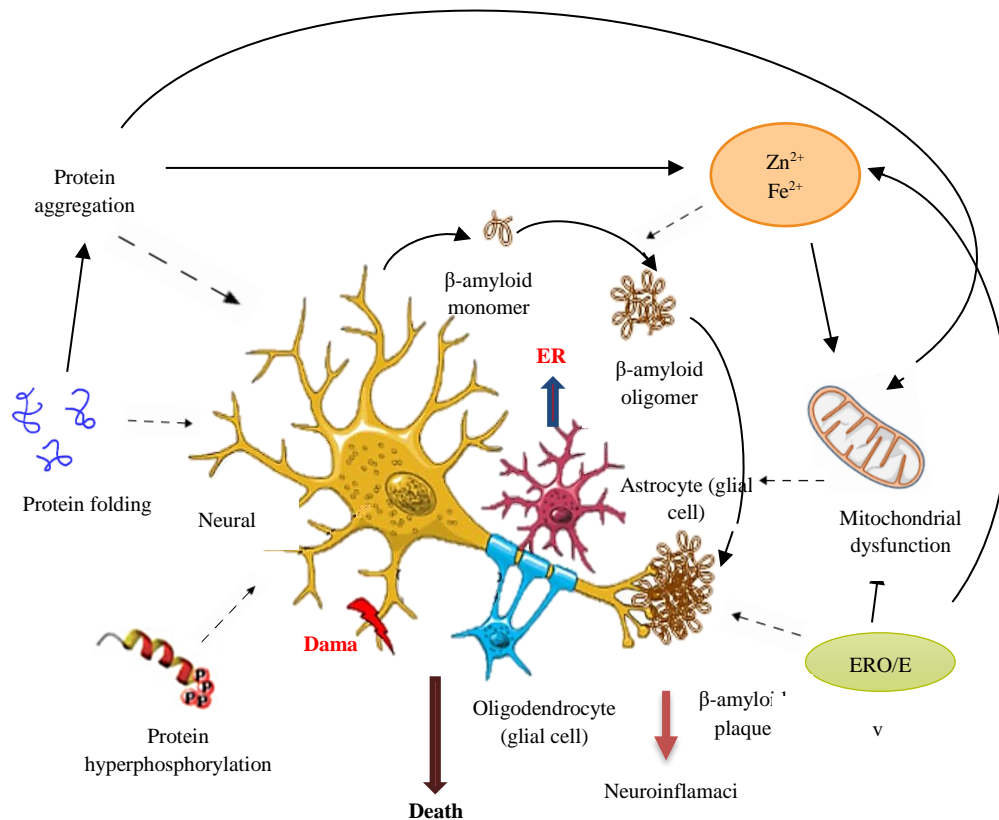


Figure 17

Oxidative stress in Alzheimer's disease

López et al., (2019).

2.2. Parkinson's disease

PD is the second most common neurodegenerative disease affecting the global population after AD, affecting more than 1% of the population over 60 years of age and more than 4% at the age of 85, and tends to occur more frequently in men (Percário *et al.*, 2020; Shen *et al.*, 2020; Dionísio *et al.*, 2021; Sienes *et al.*, 2022). It is a chronic disease characterised by progressive motor deterioration along with rigidity and/or tremors at rest, attributed to the loss of DA-producing neurons located specifically in a region of the midbrain called the substantia nigra, due to the appearance of intracellular inclusions called Lewy bodies in this substance, which are formed as the end product of a series of failures in cellular processes that produce abnormal folding of neurofilaments and proteins, including α -synuclein; the accumulation of these bodies has a neurotoxic effect, being the most common pathological finding in PD (Medeiros *et al.*, 2016; Jiang & Dickson, 2018; Hemmati-Dinarvand *et al.*, 2019; Fernández & Granados, 2020). It is estimated that between 50-90% of dopaminergic neurons are lost during the early stages of the disease, and as it progresses, there is minimal loss (Dionísio *et al.*, 2021).

PD patients present motor-related symptoms such as resting tremor, slow body movements (bradykinesia), muscle rigidity and postural instability, difficulty walking, changes in speech and writing (Wei *et al.*, 2018). In addition, they may experience olfactory deficits, sleep disorders with rapid eye movements, depression, constipation, and cognitive impairment (Chang & Chen, 2020; Dionísio *et al.*, 2021; Dorszewska *et al.*, 2021). PD has no specific cause; it is characterised by being multifactorial, with an interaction between extrinsic and intrinsic risk factors contributing to the development of this disease. Extrinsic factors can be modified, such as the environmental setting (use of pesticides, herbicides, exposure to organic chemicals, carbon monoxide, plant-derived toxins, and bacterial and viral infections; and heavy metals such as lead, copper, and manganese), lifestyles, and eating habits. In contrast, intrinsic factors cannot be modified, for example, genetic factors (age, race, and sex). There are also predisposing factors, which are environmental pollutants associated with traffic (nitrogen oxide and carbon dioxide); exposure to these factors can induce EO. Furthermore, it has been shown that ultrafine particles have the ability to penetrate the brain and act as neurotoxins, causing inflammatory processes (Singh *et al.*, 2019; Fernández & Granados, 2020).

The brain produces neurochemical reactions such as DA oxidation, which generate large amounts of ROS and RNS, and their overproduction increases OS in PD patients, thus playing an important role in the degeneration of dopaminergic neurons (Crotty *et al.*, 2017; Chang & Chen, 2020). Various sources and mechanisms responsible for ROS production have been identified, including the metabolic process of DA, mitochondrial dysfunction, the presence of iron, the activity of neuroinflammatory cells, calcium regulation, and ageing (Dias *et al.*, 2013).

Dopaminergic neurons tend to accumulate large amounts of ROS, derived from the enzymatic and non-enzymatic metabolism of DA. Its excessive accumulation is one of the main causes in the development of PD pathology, because dopaminergic neurons are more susceptible to various OS factors than other neurons (Dorszewska *et al.*, 2021). Macromolecules such as lipids, proteins, and nucleic acids undergo oxidation and accumulation in the brain tissues of PD patients. Mutations arising as a result of DNA oxidation can further aggravate the generation of ROS in the brains of people with the disease. Consequently, it can intensify neuronal loss due to defects in TET in the mitochondria, a decrease in antioxidants, and exposure to oxidised DA, which is toxic (Trist *et al.*, 2021; Dorszewska *et al.*, 2021).

Genetic products associated with PD, such as DJ-1, PINK1, parkin, alpha-synuclein, and LRRK2, have a complex impact on mitochondrial function, resulting in increased ROS production and susceptibility to OS (Blesa *et al.*, 2015). DA and its oxidised metabolites are involved in damage to dopaminergic neurons. These metabolites are characterised by an e- deficiency, becoming highly reactive and unstable species known as dopamine quinones (DAQs), which are non-specific cytotoxic molecules whose formation increases with the OST produced during PD. In addition, the increase in OS causes a deterioration in the functioning of the ubiquitin-proteasome system (UPS), which is one of the main mechanisms responsible for the degradation of multiple cellular proteins, mainly degrading misfolded or damaged proteins, further affecting cell survival. α -Synuclein is modified and its aggregation is accelerated. Neuroinflammatory mechanisms may contribute to the cascade of consequences that lead to cell death. On the other hand, environmental toxins impair mitochondrial function, increasing ROS production and causing protein aggregation, including α -synuclein (Fig. 18). (Guo *et al.*, 2018; Blesa *et al.*, 2015; Jiang & Dickson, 2018).

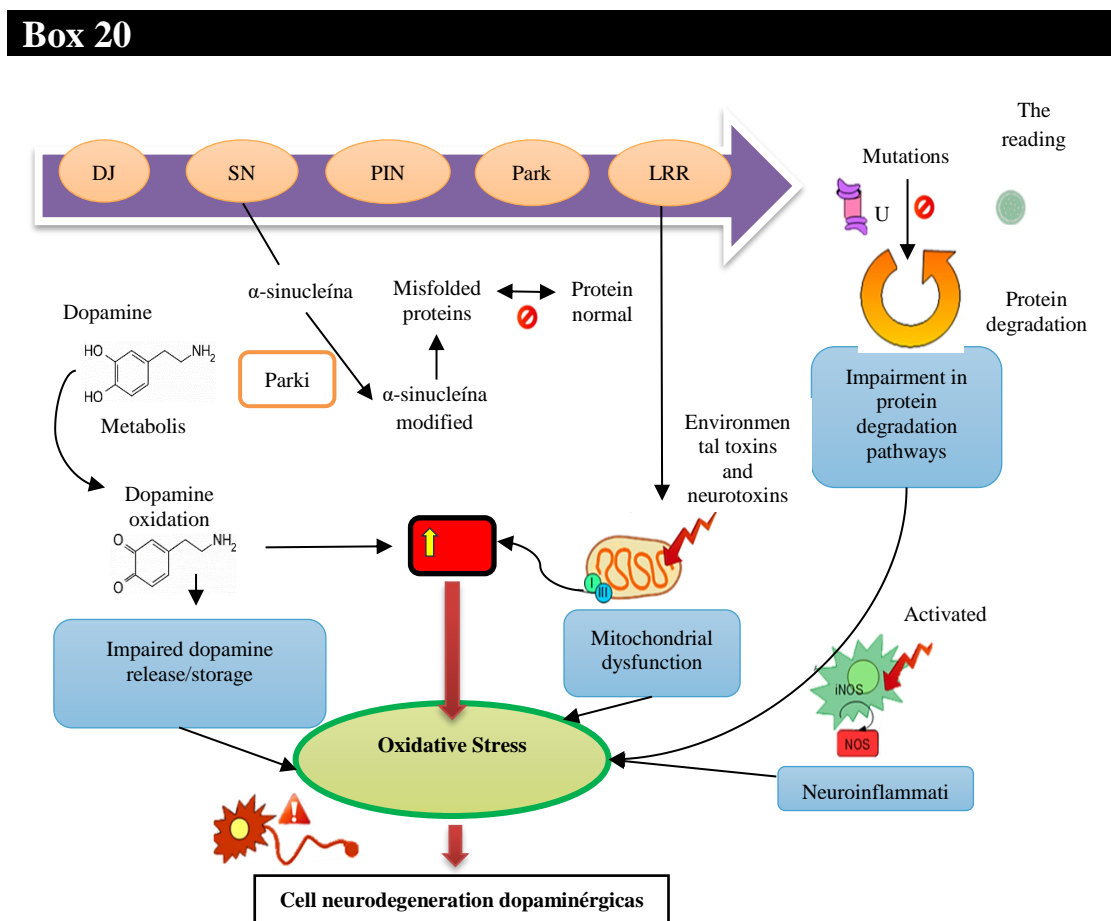


Figure 18

Oxidative stress in Parkinson's disease.

Blesa *et al.* (2015).

We use DA and some transition metals, such as Fe, Cu, Zn, Se, Al, and Mn, as trace elements that generate EO, because they participate in the process of neurodegeneration and aggravation of cellular damage (Sienes *et al.*, 2022).

Fe plays an important role in the oxidative transformations associated with the disease and is considered a risk factor, as it is present in different areas of the brain. Its presence at high levels aggravates the cellular damage that occurs in the substantia nigra due to PD (Jiang & Dickson, 2018; Singh *et al.*, 2019). Dopaminergic neurons, being rich in this metal, show high susceptibility to Fenton or Haber-Weiss reactions, generating $\bullet\text{OH}$ and, consequently, causing high EO, DNA damage and cell death by autophagy (Percário *et al.*, 2020).

2.3. Amyotrophic lateral sclerosis

Among the best-known neurodegenerative diseases is ALS, also known as motor neuron disease (MND), a progressive and fatal disease that affects motor neurons (nerve cells that control muscles). It is considered a disorder that causes rapid death within a few years of its onset and is characterised by the selective loss of upper motor neurons in the cerebral cortex and lower motor neurons located in the brainstem and spinal cord, which means that it affects the entire chain of neurons that extend from the cerebral cortex to the muscles (Park & Yang, 2021; Goutman *et al.*, 2022; Teleanu *et al.*, 2022). The average age of onset is between 50 and 65 years, but young patients can also be affected, with around 5% of cases occurring in people aged 30 or younger (Mathis *et al.*, 2019; Teleanu *et al.*, 2022). It is more common in men, and the disease may progress more rapidly in older patients (Oskarsson *et al.*, 2018).

ALS usually begins in a focal manner but eventually spreads to different parts of the body. The main cause of death is respiratory failure resulting from weakness of the respiratory muscles. On average, patients survive for 2 to 3 years after diagnosis, around 25% reach 5 years and between 5-10% manage to survive up to 10 years, due to the disease presenting more slowly (Ghasemi & Brown 2018; Smith *et al.*, 2019).

The central clinical phenotype is primarily related to the loss of upper and lower motor neurons; the loss of upper neurons leads to symptoms such as spasticity, clumsiness, rapid reflexes, and functional limitations, while the loss of lower motor neurons causes progressive muscle weakness, which generally begins in the muscles of the extremities and often affects the distal muscles rather than the proximal muscles, muscle atrophy, fasciculations, and cramps that progress to affect all extremities and bulbar muscles (swallowing and speech), ultimately leading to total or partial paralysis, contributing most significantly to mortality. Secondly, hyperreflexia is observed as a distinctive feature. In the more advanced stages of the disease, patients develop symptoms of shortness of breath (dyspnoea).

This causes most patients to die from respiratory failure (Ghasemi & Brown 2018; Oskarsson *et al.*, 2018; Longinetti & Fang, 2019; Obrador *et al.*, 2020). ALS is also considered a multisystem degeneration, as this disorder can also present additional symptoms that are not directly related to motor function, such as behavioural changes, cognitive dysfunction, frontotemporal dementia, and language problems (Mathis *et al.*, 2019).

The diagnosis of ALS is established through clinical evaluation, based on the detection of signs of upper and lower motor neurons in patients who present with steadily deteriorating muscle weakness and when no other cause can be found to explain this weakness. Unfortunately, this disease is often diagnosed up to a year after its onset (Masrori & Van Damme, 2020).

ALS cases are classified into two categories: familial and sporadic, depending on whether or not there is a clearly defined inherited genetic element (Cenini *et al.*, 2019; Mathis *et al.*, 2019). Familial ALS is usually inherited in an autosomal dominant manner, with high heritability, approximately 30 to 60%. Familial cases are linked to mutations in one of many different genes. Currently, more than 50 disease-modifying genes have been identified, among the most common are C9orf72 (Chromosome 9 72), SOD1 (superoxide dismutase 1), FUS (FUS RNA binding protein) and TARDBP (TAR DNA binding protein), which account for 40%, 20%, 1-5% and 2-5% of familial ALS cases, respectively. SOD1 was the first gene linked to the disease (Obrador *et al.*, 2020; Masrori & Van Damme, 2020).

Sporadic ALS has no clear genetic link, and the main cause triggering its onset is unknown. However, like other neurodegenerative diseases, it is associated with various risk factors, including age (age-related dysfunctions), lifestyle, head trauma, intense physical activity, BMI, smoking, viral infections, prolonged exposure to air pollution, environmental factors such as exposure to toxic substances, agricultural chemicals (pesticides and herbicides), lead, heavy metals, radiation, electromagnetic fields, and electric shocks. Risk factors related to eating habits have also been identified.

The consumption of certain foods and nutrients such as processed red meat, sodium, zinc, and glutamic acid is associated with a high risk, while the consumption of other foods such as coffee, tea, wholemeal bread, raw vegetables, and citrus fruits is associated with a lower risk (Longinetti & Fang, 2019; Obrador *et al.*, 2020). It is also related to EO, mitochondrial dysfunction, excitotoxicity, neuroinflammation, and apoptosis, among others. This category is the most common in patients, accounting for 90% of cases (Cenini *et al.*, 2020; Mathis *et al.*, 2019).

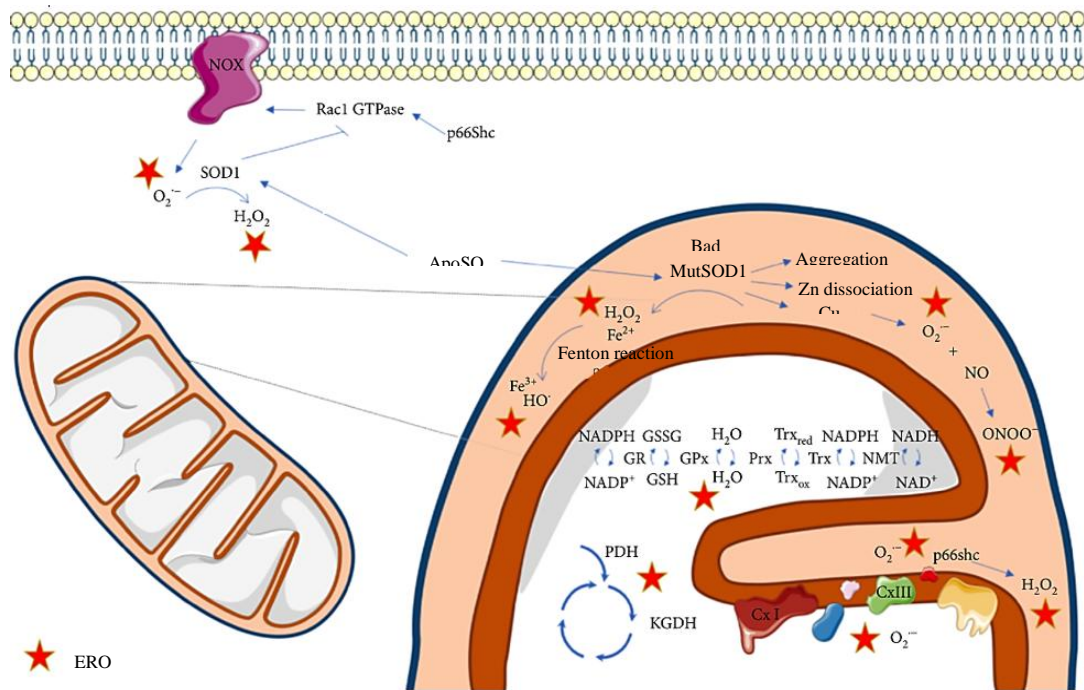
Given that mutations and environmental risk factors do not fully describe the pathogenesis of this disease, a gene-time-environment model has emerged to explain the development of ALS (Cunha-Oliveira *et al.*, 2020; Goutman *et al.*, 2022), although the pathological mechanism leading to the disease is not yet fully understood. A large number of studies have shown that OST is one of the best-known causes of ALS pathogenesis, due to the excessive production of ROS, which causes motor neuron loss and mitochondrial dysfunction, as well as oxidative damage to proteins, lipids, and DNA in the CNS and tissues.

It is difficult to determine whether oxidative damage is the primary cause or a secondary consequence. This is supported by the increase in LO in the muscles involved in the initial phase of the disease, which leads to the 'death' of nerve fibres and culminates in the loss of motor neurons, contributing to the neurodegeneration of ALS (Smith *et al.*, 2019; Cunha-Oliveira *et al.*, 2020).

The mechanism of OS production in ALS cases results from mutations in the SOD1 gene, which encodes SOD, responsible for catalysing the elimination of excess $O_2^{\bullet-}$ by converting it into H_2O_2 and O_2 through the following dismutation reactions: Cu- and Zn-containing SOD1 binds to SOD (Cu^{2+}/Zn^{2+} -SOD), which is found in the cytosol and mitochondrial intermembrane space; and manganese superoxide dismutase (MnSOD or SOD2), which resides in the mitochondrial matrix. In peroxisomes, CAT and GPX reduce H_2O_2 to H_2O and O_2 . H_2O_2 and O_2 are not as toxic to cells; however, H_2O_2 in higher concentrations affects protein folding and generates other ROS, increasing oxidative damage. Therefore, Cu^{2+}/Zn^{2+} -SOD dismutation is directly associated with OS and inflammation (Park & Yang, 2021; Sienes *et al.*, 2022).

Figure 19 shows the proposed mechanism of the effect of mutations in the SOD1 gene (mutSOD1), which is the main focus of research in relation to ALS, as it causes serious alterations in the respiration and metabolic activities of cells. MutSOD1 causes a detrimental effect by moving into the space between the mitochondrial membranes, where it tends to accumulate due to the decreased stability of monomers/dimers. It can also cause high oxidative damage by releasing Zn from the enzyme or by exposing itself to toxic copper at its active site, which facilitates increased production of $O_2^{\bullet-}$ (1).

This FR reacts rapidly with NO to form $ONOO^-$ (2), resulting in the nitration of tyrosine in cellular proteins (3). In addition, mutSOD1 can act as a peroxidase by using H_2O_2 as a substrate, or the H_2O_2 produced in the dismutation reaction can generate $\bullet OH$ through the Fenton reaction (4). Furthermore, mutSOD1 can act as a peroxidase by using H_2O_2 as a substrate, or the H_2O_2 produced in the dismutation reaction can generate $\bullet OH$ radicals through the Fenton reaction (7). MutSOD1 accounts for approximately 20% of ALS cases. (Cunha-Oliveira *et al.*, 2020; Teleanu *et al.*, 2022).

Box 21

Figure 19

Association of SOD1 mutations with oxidative stress in amyotrophic lateral sclerosis
Cunha-Oliveira et al. (2020).

2.4. Cardiovascular diseases

CVDs are one of the most significant public health problems worldwide, with 65% of global mortality concentrated in Mexico ([Mendoza-Herrera et al., 2019](#)). They are considered the leading causes of death, accounting for 30% of cases, and their incidence is increasing ([Sarre-Álvarez et al., 2018](#); [Dávila, 2020](#)). Eighty-five per cent of deaths are due to strokes and myocardial infarctions ([Moon et al., 2023](#)). The incidence of CVD is usually higher in men than in women; however, women have a higher mortality rate and a worse prognosis after acute cardiovascular events ([Gao et al., 2019](#)). They are closely related to age, mainly contributing to morbidity and mortality in the elderly, but they also affect people between the ages of 30 and 70, which is referred to as premature death ([Mendoza-Herrera et al., 2019](#); [Steven et al., 2019](#); [Townsend et al., 2022](#)).

CVDs are a set of disorders that encompass all cardiovascular conditions caused mainly by atherosclerosis and affecting the heart and blood vessels. They are studied as a group because they share many similar characteristics regarding their cause, physiology, prognosis, and treatment ([Veloza et al., 2019](#); [Elizondo et al., 2020](#)). They can be classified into high blood pressure, coronary heart disease, cerebrovascular disease, heart failure (HF), atrial fibrillation, atherosclerosis, congenital heart disease, and cardiomyopathies ([Koliaki et al., 2019](#); [Mensah et al., 2019](#)). Among the most common CVDs are:

- Atherosclerosis refers to the thickening and hardening of the arteries, mainly medium-sized ones; It is considered the leading cause of cardiovascular death. Its main mechanisms are the activation of pro-inflammatory signalling pathways, the expression of cytokines/chemokines, and increased EO. Its prevalence is approximately 50% in people aged 30 years ([Sarre-Álvarez et al., 2018](#); [Dávila, 2020](#)).
- Hypertension is a condition in which the pressure of blood against the artery walls is too high. It is a common disease that affects the arteries of the body. Its prevalence is 30-45% in adults and increases with advanced age, with more than 60% of people over 60 suffering from it ([Senoner & Dichtl, 2019](#)).
- Cerebrovascular disease is the third leading cause of death. It is associated with strokes and transient ischaemic attacks, and its incidence increases after the age of 60 ([Cruz et al., 2020](#)).

- Coronary heart disease is the result of reduced myocardial perfusion causing angina (chest pain, painful sensation during breathing and exhalation) due to ischaemia and can lead to myocardial infarction and/or HF. It is common in people over the age of 50 and the risk increases with age; accounting for between one-third and one-half of CVD cases (López *et al.*, 2022).
- HF is a condition in which the heart can no longer effectively pump O₂-rich blood to the rest of the body. It affects around 1-2% of the adult population aged 51-69, with an annual mortality rate of 24.5%. Increased ROS generation is implicated in its pathogenesis (Maldonado, 2018).
- Atrial fibrillation represents arrhythmia, is clinically associated with HF, promotes embolisms and impairs quality of life. It has a prevalence of 1.5-2% in the general population, mainly affecting people aged 75-85, with the risk increasing with age. It is estimated to affect 6% of adults over 60 and 8% of those over 80 (Reyes *et al.*, 2018).

The way in which CVD manifests itself can range from asymptomatic, as in the case of silent ischaemia, coronary artery disease without symptoms, among others, to classic presentations such as anginal chest pain characteristic of a myocardial infarction or sudden symptoms of an acute cardiovascular accident that manifests itself with focal neurological deficits. The specific symptoms depend on the affected area of the brain. However, there are commonly reported symptoms that raise concern for a diagnosis of stroke, such as sudden weakness in the limbs, difficulty speaking, and drooping of the facial muscles (López *et al.*, 2022).

The specific symptoms of some diseases are as follows:

- Strokes present with ataxia, nystagmus, sudden numbness or weakness of the face, arms, or legs, particularly on one side of the body; sudden confusion or difficulty walking, speaking, or understanding speech; and sudden visual loss in one or both eyes. Other mild symptoms include dizziness or loss of balance or coordination, headache, fainting, nausea, or vomiting (Han *et al.*, 2019; López *et al.*, 2022).
- Heart attack, including neck, jaw, or back pain, feeling weak, light-headed, or faint, chest, arm, or shoulder pain, and difficulty breathing (Han *et al.*, 2019).
- Coronary artery disease usually manifests as angina, respiratory disorders, weakness in the arms and legs, pain in the shoulders, neck, and/or jaw, and may also be associated with nausea, vomiting, palpitations, excessive sweating, fainting, or even sudden death (Da Silva *et al.*, 2019).

There are also negative emotional symptoms such as anxiety, depression, stress, sadness, and anger, which act independently in the onset and worsening of CVDs, such as stroke and acute myocardial infarction (García *et al.*, 2018). The diagnosis of CVD is made through a detailed evaluation of the clinical history and a thorough physical examination, focusing particularly on the cardiovascular system. A history consistent with obesity, angina, reduced exercise capacity, difficulty breathing when lying down and/or during the night, fainting, and claudication are key signs to consider (López *et al.*, 2022). CVD has a multifactorial origin, and there are different risk factors that determine predisposition to the disease, which are divided into two main groups: non-modifiable and modifiable. Non-modifiable risk factors are those that cannot be changed, such as age, gender, race, and family history. On the other hand, modifiable factors are those that can be altered through lifestyle changes or drug therapy, for example, high blood pressure (representing 13% of cases), smoking (9%), hypercholesterolemia (8%), diabetes (6%), sedentary lifestyle (6%), overweight and obesity (5%) (Veloza *et al.*, 2019; Elizondo *et al.*, 2020; Moon *et al.*, 2023). Secondary risk factors account for 17% of cases and are due to lifestyle factors such as poor diet, physical inactivity, muscle weakness, fatigue, alcohol consumption, sex hormones, oral contraceptive use, and air pollution. On the other hand, emotional disorders such as anxiety, depression, stress, and aggression (mainly hostility and anger) can also increase the risk of cardiac events, especially when not properly managed (Núñez & Castillo, 2019; Hernández-Martínez *et al.*, 2020; Troncoso-Pantoja *et al.*, 2020). Smoking is considered the most influential risk factor in the onset of the main causes of morbidity and mortality from CVD, as it causes a negative regulation in the vasodilation capacity of the oestrogen-dependent endothelial wall, thus generating atherosclerotic diseases due to the impact of tobacco smoke on the cardiovascular system.

It also contributes to the chronic process of arteriosclerosis because nicotine induces physiological alterations and raises blood pressure, causing hypertension (Fernández & Figueroa, 2018; Gao *et al.*, 2019). It has been established that approximately 30% of CVD-related deaths are attributed to smoking, and its damage is not only to the smoker but also to those around them. (Gao *et al.*, 2019). It has been established that approximately 30% of CVD-related deaths are attributed to smoking, and the damage is not only to the smoker but also to anyone exposed to second-hand smoke (Fernández & Figueroa, 2018). Hypercholesterolemia is a significant risk factor in CVD. High levels of low-density lipoproteins (LDL or 'bad cholesterol') in the blood begin to accumulate on the arterial walls, forming plaque and thus initiating what is known as atherosclerosis (Sarre-Álvarez *et al.*, 2018; Elizondo *et al.*, 2020). Age is another well-known risk factor, as its prevalence increases due to the accumulation of oxidative damage (Dávila, 2020).

Air pollution is one of the most important risk factors, with fine particles, such as those from diesel vehicle exhaust emissions, being of particular interest due to the high proportion of ultrafine particles in these emissions, which have the capacity to induce harmful effects on the cardiovascular system, both acutely and chronically. ozone gas is one of the most studied risk factors (Al-Kindi *et al.*, 2020). Air pollution is associated with various CVDs such as cerebrovascular disease, HF, peripheral arterial disease, atherosclerosis, coronary heart disease, arrhythmia and cardiac arrest, accounting for 40-60% of mortality (Miller & Newby, 2020). Similarly, domestic air pollution, such as the use of kerosene or solid fuel for cooking and/or heating, affects health by contributing to CVD (Troncoso-Pantoja *et al.*, 2020).

There is evidence to suggest that the presence of CVD risk factors may influence differently according to gender. For example, the main risk factors affecting men are age, hypertension, total cholesterol, and LDL cholesterol. On the other hand, the factors that have an effect on women are smoking, diabetes, triglycerides, and high-density lipoprotein (HDL) cholesterol levels (Gao *et al.*, 2019).

CVDs involve a variety of pathophysiological mechanisms. It has been suggested that OS plays a fundamental role in regulating cytokine production and secretion, establishing a link between ERO and inflammation, as well as endothelial activation and dysfunction (Incalza *et al.*, 2018; Steven *et al.*, 2019). Likewise, several studies have indicated that the heart's ability to tolerate LOA decreases with age due to a reduction in antioxidant enzyme levels, thus contributing to the development of alterations in the cardiovascular system (Liguori *et al.*, 2018). As shown in Figure 20, LOX and inflammation are the main drivers of endothelial dysfunction, which is defined as a decrease in NO production and availability driven by various oxidative enzyme systems such as NADPH oxidase, xanthine oxidase, cyclooxygenases, lipoxygenases, myeloperoxidase, cytochrome P450 monooxygenases, uncoupled NOS, and peroxidases (1) (Higashi, 2022). Nitric oxide synthases (NOS) are the main enzymes responsible for NO synthesis.

They have the ability to produce high levels of $O_2^{\bullet-}$, leading to vascular OS and endothelial dysfunction (2) (Incalza *et al.*, 2018; Senoner & Dichtl, 2019). Three types of NOS have been identified: type I or neuronal NOS (NOS1 or nNOS), type II or inducible (NOS2 or iNOS) and type III or endothelial NOS (NOS3 or eNOS). The NOS1 and NOS3 isoforms are expressed in the heart, particularly in striated muscle and endothelial cells, while the NOS2 isoform is not constitutively expressed in the healthy heart, but is expressed in pathological conditions such as inflammation (Dubois-Deruy *et al.*, 2020). eNOS uncoupling, i.e., the generation of ROS through eNOS as part of endothelial activation (3) (Senoner & Dichtl, 2019), is a mediator of endothelial dysfunction, which can be measured by acetylcholine-dependent or flow-mediated dilation, making it an important, measurable, and early predictor of cardiovascular events. For this reason, it is considered a hallmark of CVD (Steven *et al.*, 2019).

$O_2^{\bullet-}$ reacts with NO and leads to the formation of ONOO⁻, which decreases the bioavailability of NO and induces vasoconstriction, causing blood pressure to rise. In turn, this promotes protein nitration and contributes to endothelial cell dysfunction and death (Incalza *et al.*, 2018). It participates in the progression of atherosclerosis by inhibiting vasorelaxation, decreasing the beneficial effects of NO on platelet aggregation and vascular smooth muscle cell proliferation, and oxidising DNA and lipids (4) (Senoner & Dichtl, 2019). Furthermore, ageing increases OS in resistant arteries by increasing ONOO⁻ production (Dubois-Deruy *et al.*, 2020). Vascular endothelial dysfunction is the beginning of the development of atherosclerosis and, as it progresses, the vascular endothelium itself is damaged, making it the main risk factor for stroke, myocardial infarction, and HF (Higashi, 2022).

NADPH oxidases (NOX) are a family of membrane-bound enzyme complexes whose main function is the production of ROS, through their activation by AngII and the catalysis of the reduction of O_2 to $O_2^{\bullet-}$ NADPH or NADH as an e- donor. NOX-mediated ROS release, also known as oxidative burst, promotes the elimination of invading microorganisms in macrophages and neutrophils (*Incalza et al., 2018; Jahandideh & Wu, 2020*). Seven members of the NOX family are identified in neutrophils, designated NOX 1-5 and dual oxidase (DUOX) 1-2, each with specific catalytic subunits. The NOX1, 2, 4, and 5 isoforms are particularly expressed in the cardiovascular system and are regulated by AngII, which increases blood pressure. NOX2 is activated during AngII-induced cardiovascular stress, being constitutively active but increasing under conditions of hypoxia, ischaemia or pressure overload. NOX enzymes are the main source of $O_2^{\bullet-}$ in blood vessels. At the cardiac level, NOX-dependent $O_2^{\bullet-}$ production increases in the left ventricle of guinea pigs after three weeks of aortic ligation, leading to the activation of four extracellular signal-regulated kinase 1/2 (Erk1/2), JNK and p38 MAPK signalling pathways. It has been reported that excess ROS derived from NOX2 activates apoptosis via ASK-1/p38MAPK and the proapoptotic CAMKII pathway after myocardial infarction or AngII stimulation (5) (*Jahandideh & Wu, 2020*).

ERO overproduction occurs during mitochondrial dysfunction, causing irreversible damage to mitochondria, which contributes significantly to the development of CVD. Mitochondria are a primary target of ROS, especially mtDNA, which is highly susceptible to oxidative damage due to its low repair capacity and proximity to the ETC. The presence of OH in mitochondria leads to a significant decrease in mtDNA, as well as a significant decrease in the transcripts of mtDNA-encoded genes for respiratory complexes I, III, and IV. These alterations in the mitochondrial respiratory chain are associated with an increase in OER and the generation of ROS, triggering the activation of various protein kinases and transcription factors involved in hypertrophic signalling (6). (*Dubois-Deruy et al., 2020*).

Box 22

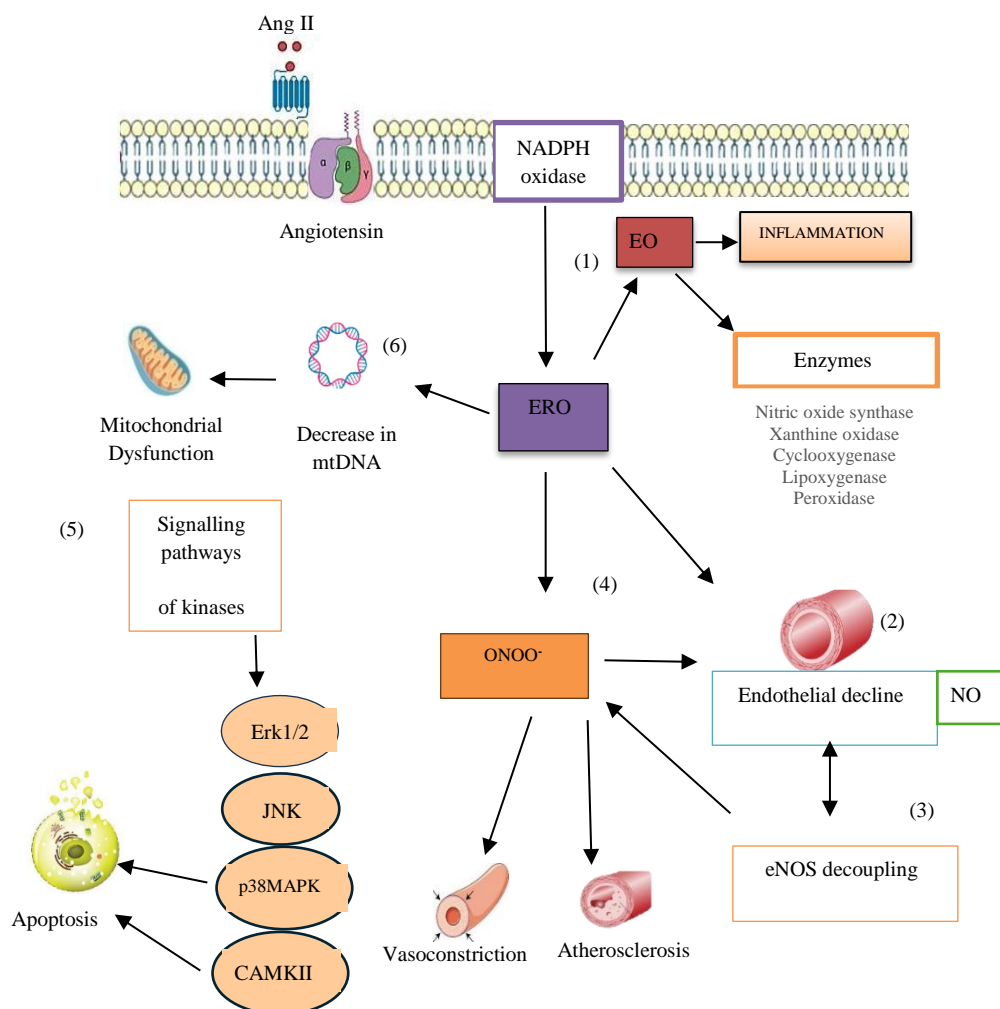


Figure 20

Oxidative stress in cardiovascular diseases

Own Elaboration

2.5. Liver Diseases

Liver disease is a major public health problem worldwide, ranking as the fourth leading cause of death. It occurs in people aged 35 to 55 and is more prevalent in men (Cedeño *et al.*, 2019).

The term ‘liver disease’ covers a range of conditions, all of which affect the liver or cause abnormalities that prevent it from functioning properly. The liver and its cells change dramatically when a normal liver becomes fatty or cirrhotic (Cedeño *et al.*, 2019).

According to Barba (2019), liver diseases can be classified into two categories based on the damage:

1. Cellular necrosis: refers to cell death in the liver and is often associated with inflammation. It is classified by its duration as acute, such as viral hepatitis, toxic hepatitis, and alcoholic hepatitis; and chronic, such as chronic active hepatitis, autoimmune hepatitis, and cirrhosis (Del Valle *et al.*, 2017).
2. Cholestasis: characterised by an alteration in bile secretion and transport in which direct bilirubin increases as a result of the blockage or suppression of bile flow, totally or partially preventing bile from reaching the duodenum (Sticova *et al.*, 2018; Barba, 2019). This is subdivided according to the time of evolution: acute (on average, its evolution is less than 6 months) and chronic (when the period of acquisition is greater than 6 months); in turn, they are subdivided by their anatomical location and type of lesion: intrahepatic, which are those resulting from hepatocellular alterations of the bile canaliculi or microscopic ducts that may be due to tumours, primary biliary cirrhosis, and sclerosing cholangitis. Acute intrahepatic diseases include viral hepatitis (A, B, C, and E), autoimmune hepatitis, toxic hepatitis, and obstetric cholestasis. Chronic intrahepatic diseases include viral hepatitis (B, C, and D), autoimmune hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. and extrahepatic diseases, which refer to those that affect the macroscopic bile ducts outside the liver and may be due to tumours or lithiasis, such as bile duct disease, choledocholithiasis, pancreatitis, and vesicular cancer, among others (Barba, 2019; Onofrio & Hirschfield, 2020).

Among the most common pathologies of liver disease are non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD), with a prevalence of 40-60%, and viruses that cause chronic hepatitis, such as hepatitis B and C, with a prevalence of 25-30% (Cheemerla & Balakrishnan, 2021). Similarly, there are other pathologies with a high mortality rate, such as cirrhosis, hepatocellular carcinoma, and fulminant hepatitis (Barba, 2019).

NAFLD is the leading chronic liver disease and the most common worldwide. It is associated with metabolic syndrome and is now referred to as metabolic dysfunction-associated fatty liver disease (MAFLD) (Burgos-Santamaría *et al.*, 2020; Guerra-Ruiz *et al.*, 2021). It affects approximately 25% of the adult population, and its high prevalence is due to the rapid increase in sedentary behaviours, low levels of physical activity, and excessive calorie consumption (Ore & Akinloye, 2019; Eslam *et al.*, 2020; Mantovani *et al.*, 2020; Loomba *et al.*, 2021).

MAFLD is a chronic, multisystemic inflammatory disease that progresses silently (Eslam *et al.*, 2020). It is mainly characterised by the storage of excess macrovesicular fat, resulting from imbalances in the homeostatic mechanisms that regulate fat synthesis versus utilisation in the liver, affecting more than 5% of hepatocytes (Arroyave-Ospina *et al.*, 2021). It is identified by fatty changes in the liver ranging from simple steatosis (the presence of abnormal fat accumulation in the liver) to non-alcoholic steatohepatitis (where, in addition to fat, there is inflammation), with the potential to progress to advanced fibrosis, liver failure, cirrhosis, hepatocellular carcinoma, the need for liver transplantation, and liver-related morbidity and mortality (Masarone *et al.*, 2018; Castera *et al.*, 2019; Burgos-Santamaría *et al.*, 2020; Mantovani *et al.*, 2020; Guerra-Ruiz *et al.*, 2021). MAFLD is associated with metabolic syndrome, which is distinguished as a clinical condition that includes a set of abnormalities in lipid and glucose metabolism such as obesity, insulin resistance, high blood pressure, diabetes, hyperinsulinemia, and plasma dyslipidaemia, characterised by high triglyceride concentrations and low HDL cholesterol concentrations (Vasconcelos-de Dios *et al.*, 2022).

AHD is a progressive clinical-pathological entity caused by excessive and chronic alcohol consumption (Martinez-Castillo *et al.*, 2023). It includes a broad spectrum of diseases, starting with fatty liver, where fat accumulation participates as a bystander in an inflammatory process that affects fat-laden hepatocytes, beginning with resident and non-resident liver cells that infiltrate immune cells, thus triggering damage (Mitra *et al.*, 2020). This then has more serious consequences such as fibrosis, alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma (Ramadori *et al.*, 2017; Ezhilarasan, 2018). Alcohol is one of the most common causes of liver disease and is attributed to 50% of mortality from cirrhosis (Mitra *et al.*, 2020).

The progression from one entity to another depends on continued alcohol consumption and the complex interaction of numerous factors, such as genetic, biological, immunological, psychological, social, and environmental factors. During ALD, steatosis is present in approximately 90% of alcohol consumers, and 35% of them progress to steatohepatitis. When excessive alcohol consumption continues, liver fibrosis develops, which can progress to cirrhosis in about 20% of cases, and between 1-2% of these develop hepatocellular carcinoma (Del Valle *et al.*, 2017; Martinez-Castillo *et al.*, 2023). ALD is the third leading cause of morbidity and mortality worldwide (Ezhilarasan, 2018), with the highest prevalence in people under 45 years of age (Cheemerla & Balakrishnan, 2021).

Viral hepatitis is a disease caused by different viruses that replicate in hepatocytes and commonly result in liver damage, mainly through inflammation and hepatocellular necrosis (Mateos *et al.*, 2020). There is a wide variety of viruses that can cause this condition, among the most common are hepatotropic viruses, which are a heterogeneous group of viruses that show tropism or preference for liver cells to replicate, causing infections, inflammation and hepatic necrosis. They are named with letters of the alphabet, such as hepatitis A, B, C, D, and E, and are one of the most frequent causes of death in children and young adults. They are spread through contact with the blood, saliva, semen, or other bodily fluids of an infected person (Rojas-Peláez *et al.*, 2021).

Hepatitis B and C are one of the main causes of acute and chronic infection, inflammation, and liver damage such as fibrosis, cirrhosis, and hepatocellular carcinoma. Their high incidence and severity have made them the ninth leading cause of death worldwide (Rojas-Peláez *et al.*, 2021; Pol, 2022). Although both viruses cause the same damage, they are completely different. Hepatitis B is considered the most common and the one that causes the highest morbidity due to its chronic infection (Mateos *et al.*, 2020).

The hepatitis B virus (HBV) is an enveloped double-stranded DNA virus consisting of an outer lipoprotein portion and a central portion or nucleocapsid containing DNA. It specifically infects hepatocytes and replicates through an RNA intermediary, causing serious liver disease (Herrscher *et al.*, 2020; Tsukuda & Watashi, 2020). It belongs to the Hepadnaviridae family, a group of pararetroviruses that replicate through reverse transcription (Hu *et al.*, 2019). Tsukuda & Watashi, 2020). It belongs to the Hepadnaviridae family, a group of pararetroviruses that replicate by reverse transcription (Hu *et al.*, 2019), is found in several different forms in the blood (Herrscher *et al.*, 2020) and can be transmitted perinatally from mother to child or horizontally through contact with contaminated fluids, either parenterally, through wounds, blood transfusions, reuse of needles or syringes, or sexually, with a risk greater than 90% during childhood (Hu *et al.*, 2019; Castro-Aroyave *et al.*, 2023). Hepatitis B that manifests for the first time is classified as acute hepatitis and fulminant hepatitis. Chronic hepatitis B, on the other hand, is the necroinflammatory activity of the liver caused by persistent infection with this virus. In terms of its natural progression, in 2% of patients, acute infection progresses to fulminant liver failure, 5-10% of these cases become chronic, and 15-40% of these progress to cirrhosis and hepatocellular carcinoma, leading to death (Rojas-Peláez *et al.*, 2021).

The hepatitis C virus (HCV) is a hepatotropic, single-stranded positive-sense RNA virus belonging to the Flaviviridae family that has no persistent genomic form, so it needs to replicate constantly to persist, allowing antivirals to attack it efficiently (Hu *et al.*, 2019; Khatun & Ray, 2019). It is mainly transmitted among men, people with immune deficiencies, and alcohol, drug, or tobacco users (Rojas-Peláez *et al.*, 2021). It is a systemic disease with multiple extrahepatic manifestations and a prevalence of approximately 1.6%. It is considered one of the main risk factors for liver-related pathogenesis (Khatun & Ray, 2019; Vignolo *et al.*, 2020). It causes acute asymptomatic hepatitis in 80% of cases, appears 5-45 days after infection, and has the peculiarity of being the only chronic viral infection that can be cured, but if left untreated, it can lead to hepatocellular carcinoma (Pol, 2022).

In terms of its natural progression, approximately 85% of infected individuals develop a chronic infection that leads to liver inflammation, which often triggers liver fibrosis. Fibrosis is the result of the wound healing response and constitutes a constant process of regeneration of damaged tissue, maintaining a balance between the formation and dissolution of fibrous tissue (Khatun & Ray, 2019).

Autoimmune hepatitis (AIH) is an inflammatory disease of the liver that is chronic, progressive, uncommon, and whose aetiology is not fully understood. Its origin is multifactorial, influenced by genetic, immunological, and environmental mechanisms (Díaz-Ramírez, 2020; Rojas-Díaz *et al.*, 2021). It is characterised by an abnormal immune response directed at hepatocytes or bile ducts, causing immunological alterations such as the presence of antibodies, high serum globulin levels, elevated transaminases and typical histological lesions. Its medical significance lies in its frequent progression to severe liver damage such as fibrosis, cirrhosis, liver failure and, in some cases, death (Díaz-Ramírez, 2020; Vera-Mesias *et al.*, 2021; Olivás *et al.*, 2022). AIH has a global distribution and can affect patients of both genders and all ages. It is predominant in women of any age and occurs at an earlier age in men. It is estimated to be responsible for 56.6% of liver diseases (Rojas-Díaz *et al.*, 2021; Olivás *et al.*, 2022).

Liver cirrhosis is the final stage of liver disease, resulting in the alteration of the liver's architecture, which leads to the formation of generalised nodules, vascular reorganisation, neoangiogenesis (formation of new blood vessels) and the deposition of an extracellular matrix (Fortea *et al.*, 2020; Sharma & Nagalli, 2023). It is characterised by the formation of scar tissue, which is formed as a result of continuous injury and chronic inflammation of the liver, usually caused by the accumulation of toxins in the blood. (Sharma & Nagalli, 2023).

It is characterised by the formation of scar tissue, which results from continuous injury and chronic inflammation of the liver, usually caused by liver disease, and a decrease in normal liver function. As liver cirrhosis progresses, scar tissue gradually replaces healthy liver tissue, thus affecting the structure and function of the liver (Alvarado-Villavicencio *et al.*, 2023).

Cirrhosis is one of the leading causes of mortality and morbidity worldwide. In Mexico, it is the fourth leading cause of mortality, having a considerable impact on public health in our country. It is characterised by a higher risk of hospital readmission, with a mortality rate of 13% at 90 days. Alcohol accounts for 30-50% of cirrhosis-related deaths worldwide (Cedeño *et al.*, 2019; Cheemerla & Balakrishnan, 2021). It has a higher prevalence in patients between the ages of 60 and 80 and affects men more than women (Guevara *et al.*, 2021).

Hepatocellular carcinoma is the most common type of liver cancer, accounting for 75-85% of cases, and its prevalence is rapidly increasing worldwide (McGlynn *et al.*, 2021). It arises from hepatocytes, which are the main parenchymal cells of the liver (Chidambaranathan-Reghupaty *et al.*, 2021). It generally develops in the context of aggressive chronic liver disease, and its progression is induced by advanced fibrosis, mainly cirrhosis and hepatitis (Craig *et al.*, 2020).

It is considered the fifth leading cause of cancer death worldwide, and in men it is the fourth most common cancer and the second leading cause of death, meaning that men are at greater risk of developing liver cancer than women (Chidambaranathan-Reghupaty *et al.*, 2021). The average age of onset in men is between 60 and 64 years, while in women it is between 65 and 69 years (McGlynn *et al.*, 2021). The 2-year survival rate is less than 50%, and the 5-year survival rate is only 10% (Ogunwobi *et al.*, 2019).

The symptoms of liver disease can vary, but are often characterised by fatigue, weakness, asthenia (persistent fatigue), jaundice (yellowing of the skin or eyes due to excessive production or insufficient elimination of bilirubin), swelling of the abdomen and legs, easy bruising, and changes in the colour of stools and urine (Sharma & Arora, 2020; Jorquera *et al.*, 2022).

The specific symptoms of each liver disease are as follows:

- In MAFLD, most patients are asymptomatic and the disease may remain silent until it has progressed to cirrhosis. However, some patients experience symptoms such as pain and fatigue in the upper right quadrant, nausea, and jaundice (Guerra-Ruiz *et al.*, 2021; Loomba *et al.*, 2021).

- In AHE, there is a wide spectrum of diseases that can range from a completely asymptomatic disease (such as fatty liver) to a severe and advanced stage that includes complications of cirrhosis, jaundice, ascites, sarcopenia, asthenia, variceal bleeding, hepatojugular reflux, hepatic encephalopathy, and hepatocellular carcinoma (Sharma & Arora, 2020; Martinez-Castillo et al., 2023).
- In viral hepatitis, the disease may initially present with gastrointestinal symptoms such as diarrhoea, nausea, vomiting, and abdominal pain. followed by symptoms of acute hepatitis such as jaundice, acholia (very light-coloured stools due to the absence of bilirubin pigments), lethargy, fever, respiratory symptoms, hyporexia (loss of appetite in older adults), weight loss and/or anorexia (Jorquera et al., 2022; Sharma & Nagalli, 2023).
- In autoimmune hepatitis, the onset can be insidious, with most patients being asymptomatic or presenting mild forms of the disease, with general symptoms such as nausea, fatigue, weakness, abdominal pain, and joint pain (Rojas-Diaz et al., 2021; Olivas et al., 2022). Severe acute hepatitis is often accompanied by jaundice, choloria (very dark urine due to the presence of bilirubin), fever, and anorexia (Vera-Mesias et al., 2021). Thirty per cent of patients have cirrhosis at the time of diagnosis (Olivas et al., 2022).
- Liver cirrhosis can lead to various complications and symptoms such as jaundice, ascites (fluid accumulation in the abdomen), leg oedema, hepatosplenomegaly (enlargement of the liver beyond its normal size), weakness, fatigue, nausea, loss of appetite, weight loss, hepatorenal syndrome, hepatic encephalopathy (impaired brain function), and abnormal bleeding due to coagulation disorders (Guevara et al., 2021; Alvarado-Villavicencio et al., 2023).
- In hepatocellular carcinoma, patients may remain asymptomatic, present with insidious onset or slow progression of symptoms, however, in advanced stages they present symptoms such as pain in the upper right abdominal quadrant, discomfort, anorexia, vomiting, early satiety, abdominal distension, weight loss, obstructive jaundice, fever, watery diarrhoea, lethargy, and bone pain due to metastasis (Ogunwobi et al., 2019; Laube et al., 2021).

The spectrum of aetiologies of liver disease is broad, including genetics, sex, age, ethnicity, and lifestyles such as changes in diet, obesity or dyslipidaemia, diabetes, alcohol consumption habits, and viruses. The most common causes are alcohol consumption, hepatitis C virus infection, and MAFLD (Cedeño et al., 2019; Sharma & Nagalli, 2023).

Genetics is a risk factor for liver disease, with polymorphism in the PNPLA3, NCAN, LYPLAL1, GCKR, and PPP1R3B genes affecting lipid metabolism, cytokine regulation, fibrosis mediators, EO, and infectious factors. However, it is only heritable in 20-34% of Hispanic families (Morales-Romero et al., 2023). Likewise, there is a risk in patients with genetic predisposition, after exposure to antigens and certain factors that affect the presentation of autoantigens, the activation of immunocytes, and the proliferation of effector cells. Genetic variants and polymorphisms can increase or decrease the risk of disease (Rojas-Diaz et al., 2021). Likewise, having obese parents increases the risk of developing these diseases (Morales-Romero et al., 2023).

Sex and age are other risk factors for these diseases. With regard to sex, a higher incidence is reported in men than in women; however, the relative risk is higher in women, and the age of onset varies according to geographical location, with the average age being around 60 years, with a tendency to affect the young and middle-aged population (Mitra et al., 2020; Montalvo-Javé et al., 2021).

Ethnic factors play an important role in the development of some liver diseases. Apparently, this ethnic difference lies in the distribution of fat, where visceral fat is fundamental in the development of steatosis through the release of FFA directly into the portal circulation. Likewise, radical differences in hepatic steatosis are a reflection of metabolic responses to obesity and insulin resistance (Morales-Romero et al., 2023). It has been identified that the Latin American population tends to suffer more from non-alcoholic fatty liver disease. All these factors are reflected in liver conditions that culminate in liver failure, cirrhosis, and hepatocellular carcinoma (Montalvo-Javé et al., 2021).

Changes in diet are one of the risk factors that have a major impact on liver disease, including inadequate nutrition characterised by high-calorie diets, excess saturated fats, and ultra-processed foods, which are the main triggers for MAFLD (Morales-Romero *et al.*, 2023). In Mexico, more than 50% of the population consumes high amounts of fats such as fried foods, pork, and cold cuts (Morales-Romero *et al.*, 2023), leading to a higher prevalence of diseases such as metabolic syndrome, obesity, and diabetes, which cause fatty liver disease. As these diseases increase, they can become the leading cause of hepatocellular carcinoma worldwide (McGlynn *et al.*, 2021). Insulin resistance and diabetes are considered risk factors for liver disease, as they are considered a common comorbidity and critical cellular abnormality underlying MAFLD (Mitra *et al.*, 2020). Similarly, poisoning with aflatoxins and metals such as arsenic can activate a synergistic effect with underlying chronic inflammatory liver conditions such as fibrosis and cirrhosis (McGlynn *et al.*, 2021; Montalvo-Javé *et al.*, 2021).

Excessive alcohol consumption is harmful to health and is a risk factor. High consumption leads to a wide range of diseases such as hepatic steatosis, hepatitis, cirrhosis, and can cause hepatocellular carcinoma (Ramadori *et al.*, 2017). Alcohol-attributable mortality is more common in the young and middle-aged population between 15 and 49 years of age, with a higher incidence in men than in women; however, the risk is higher in women (Mitra *et al.*, 2020). Pure ethanol does not directly cause inflammation or liver damage; however, toxic by-products of alcohol catabolism, such as the accumulation of acetaldehyde and RL, can influence EO, apoptotic cell death, necrosis, and necroptosis. Alcohol catabolism also affects lipid metabolism, leading to hepatic steatosis and inhibition of FA oxidation (Ogunwobi *et al.*, 2019).

HBV, with a prevalence of approximately 15.2%, and HCV, with a prevalence of 11.8%, are the most important risk factors for certain liver diseases such as cirrhosis and hepatocellular carcinoma (Fortea *et al.*, 2020). Patients with HCV-induced cirrhosis are at particularly high risk of developing hepatocellular carcinoma, with an incidence ranging from 0.5-10% (Kulik & El-Serag, 2019). On the other hand, the pathogenesis of HBV-induced hepatocellular carcinoma involves several mechanisms, including HBV DNA integration into the host's genetic machinery, DNA methylation, and ROS (Ogunwobi *et al.*, 2019).

The liver is more vulnerable to oxidative conditions than other organs (Sadasivam *et al.*, 2022), ROS play an important role in the pathogenesis of various liver diseases, causing LOX in liver cells; likewise, excessive fat accumulation in liver cells leads to increased LOX. One of the main mechanisms contributing to hepatic steatosis is lipid peroxidation (Yang *et al.*, 2018).

As shown in Figure 21, MAFLD is a multifactorial disease that begins with fatty liver, and its pathogenesis is primarily defined by insulin resistance, an increase in the fat load in hepatocytes leading to steatosis and liver injury (Chen *et al.*, 2020). Fat accumulation in the liver occurs as a result of an imbalance between the rate of triglyceride entry and removal; excess free fatty acids (FFAs) induce lipid accumulation, leading to a general deterioration in lipid metabolism and causing steatosis. Similarly, FFA cause lipotoxicity by increasing the levels of toxic lipid species (Ore & Akinloye, 2019; Chen *et al.*, 2020; Arroyave-Ospina *et al.*, 2021). Fat accumulation sensitises the liver to induce inflammation and cell death through a second pathogenic attack (viral hepatitis A, B, C) that promotes ONS, which is considered the primary contributor to liver injury and disease progression leading to fibrosis.

On the other hand, excess FFA increases mitochondrial β -oxidation as an adaptive mechanism, producing ROS that damage hepatocytes, causing lipid peroxidation and contributing to inflammation and fibrosis (Ore & Akinloye, 2019; Sadasivam *et al.*, 2022). MAFLD is also related to mitochondrial dysfunction, which manifests itself through changes in respiratory complex activity and FFA oxidation, with CTE activity gradually decreasing, as well as ATP production during disease progression. In addition, ROS generated in mitochondria can modify mitochondrial DNA by increasing OS and causing deletions and mutations (1) (Masarone *et al.*, 2018; Arroyave-Ospina *et al.*, 2021).

Alcohol is a small polar organic molecule that can diffuse through cell membranes, reach the bloodstream, and be distributed throughout all tissues. However, only a small portion of ingested alcohol is absorbed and metabolised in the liver through oxidative activity (Ramadori *et al.*, 2017). Alcohol metabolism is directly associated with the production of ROS, which results in the appearance of OST and mitochondrial damage.

This involves two main pathways: in the first, alcohol dehydrogenase (ADH) converts alcohol into acetaldehyde, and then acetaldehyde dehydrogenase (ALDH) converts acetaldehyde into acetate. Unlike acetate, which is stable, acetaldehyde is highly reactive and forms adducts with DNA, promoting tissue damage, ODS, and inflammation. Likewise, during alcohol metabolism, the enzymes ADH and ALDH reduce NAD^+ to NADH, and as a result of O_2 consumption, ROS production increases (Li *et al.*, 2015; Conde de la Rosa *et al.*, 2022). The second pathway for alcohol oxidation is the microsomal ethanol oxidation system (MEOS), which involves the cytochrome P450 enzyme CYP2E1. Its high activity results in increased intracellular OST and lipid peroxidation.

The MEOS pathway is mainly activated in people who consume alcohol chronically (2) (Li *et al.*, 2015; Sadasivam *et al.*, 2022). Chronic hepatitis infections also play an important role in EO, because viruses enter the cell by endocytosis and act as an intracellular parasite, using the host cell's synthetic processes for replication, causing persistent inflammation in the liver and OS damage, affecting the physiological state of the ER and mitochondria (Conde de la Rosa *et al.*, 2022).

Variations in ROS generation have been reported among hepatitis variants. An excess of iron deposits in the liver was discovered in patients infected with HCV, and this has been attributed to FR generation. Therefore, HBV and HCV infections are characterised by elevated ROS levels (3) (Ezhilarasan, 2018).

Patients with liver disease initially develop fatty liver, then show more serious consequences such as fibrosis, mainly mediated by EO, which can lead to cirrhosis and even hepatocellular carcinoma. Liver fibrosis is a dynamic molecular, tissue and cellular process that drives the progression of liver disease to cirrhosis (Li *et al.*, 2015; Ezhilarasan, 2018). Extensive ERO formation and steatohepatitis induce the release of inflammatory cytokines that cause apoptosis and necrosis of hepatocytes.

The development of fibrosis mainly determines quality of life and prognosis correlated with liver function, being a critical risk factor for the development of hepatocellular carcinoma (4) (Conde de la Rosa *et al.*, 2022). Hepatocellular carcinoma is a cancer related to inflammation and mild or excessive iron deposition induced through Fenton reactions, with OS acting as a critical factor promoting carcinogenesis (5). (Li *et al.*, 2015; Conde de la Rosa *et al.*, 2022).

Box 23

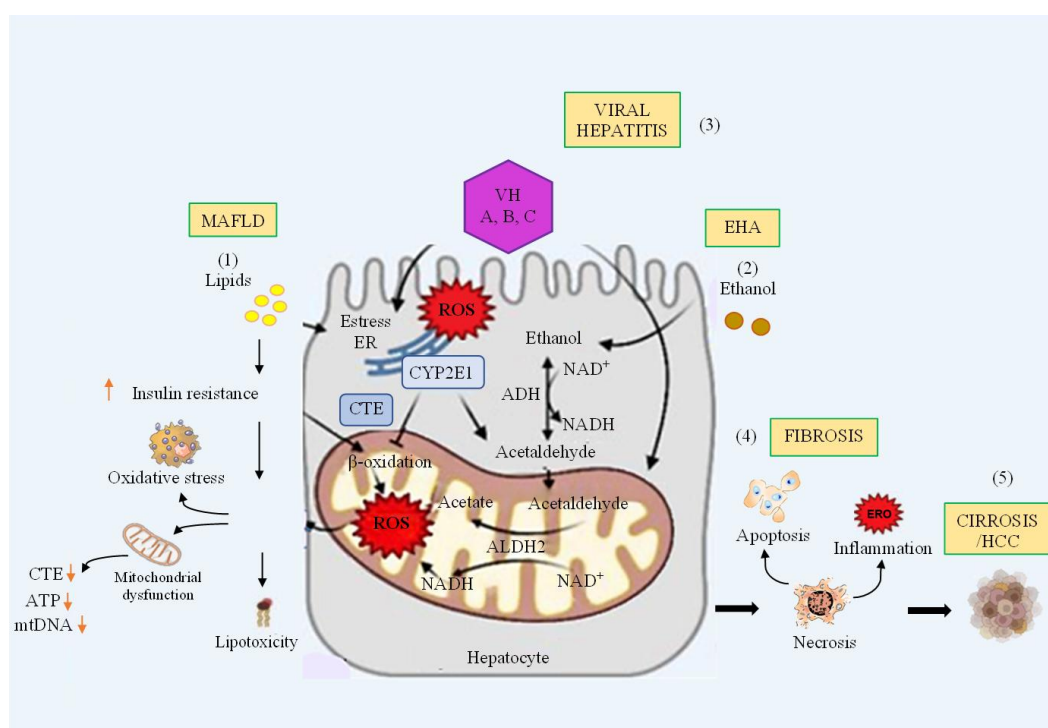


Figure 21

Mechanism of oxidative stress in liver diseases. Taken and edited from

Conde de la Rosa *et al.* (2022).

2.6. Diabetes

Diabetes mellitus (DM) is one of the most significant health problems in the world. It is the second leading cause of morbidity in Mexico and worldwide, accounting for 85-90% of cases (Ramírez *et al.*, 2019; Flores *et al.*, 2020). Due to its high prevalence, it is considered a pandemic (Uyaguari-Matute *et al.*, 2021). It is a chronic, non-communicable, hereditary disease related to nutrition, consumption of processed foods, obesity, sedentary lifestyle, stress, and socioeconomic status (Beltrán *et al.*, 2018; Poblete-Aro *et al.*, 2018; Valenzuela *et al.*, 2018). It can occur at any age but generally manifests in adult patients, mainly in middle-aged and elderly people between 40 and 79 years of age. It can reduce life expectancy and quality of life by up to 10 years, is more prevalent in women, and its main causes of death are CVD and cancer (Einarson *et al.*, 2018; Poblete-Aro *et al.*, 2018, Figueredo *et al.*, 2020). Patients with DM have a 10% risk of coronary heart disease, 53% risk of myocardial infarction, 58% risk of stroke, and a 112% higher risk of HF (Einarson *et al.*, 2018).

[DM is a disease characterised by high blood glucose levels. It is a complex metabolic process involving carbohydrates, lipids, and proteins that occurs when the body becomes resistant to insulin or there is a deficiency in insulin secretion by the β cells of the pancreas or defects in insulin receptors, depending on the type of diabetes involved (Magkos *et al.*, 2020; Piñate *et al.*, 2020). Insulin deficiency can be absolute or relative. It is absolute when insulin secretion is lower than normal and relative when it does not meet the increased demand for insulin in situations where the action of the hormone decreases (Montier *et al.*, 2015).

Insulin sensitivity can be affected by various factors such as glucose and lipid overload, OI, inflammation, adipokines (cell signalling molecules secreted by adipose tissue), autophagy (the process by which the cell breaks down and destroys old, damaged or abnormal proteins and other substances in its cytoplasm) and disordered insulin secretion (Xu *et al.*, 2018). DM is accompanied by metabolic disorders including hyperglycaemia, hyperinsulinaemia and hypertriglyceridaemia, with hyperglycaemia being its biochemical marker (Montier *et al.*, 2015). It is classified into type 1 diabetes mellitus (DM1), type 2 diabetes mellitus (DM2) and gestational diabetes mellitus (GDM) according to the factors that cause it, such as genetic, environmental and pharmacological factors, but greater emphasis is placed on the first two types (Flores *et al.*, 2020; Barría *et al.*, 2022).

DM1 is an autoimmune disease characterised by an absolute insulin deficiency caused by the destruction of pancreatic β cells (Katsarou *et al.*, 2017; Xu *et al.*, 2018). Sugar cannot reach the body's cells to be used as energy, so people with DM must use insulin injections to control their blood glucose levels (Barría *et al.*, 2022). DM1 is less common than DM2, accounting for 5-10% of cases. It generally occurs in people under the age of 30, which is why it is known as juvenile diabetes or early-onset diabetes. However, it can also occur at any age (Beltrán *et al.*, 2018).

DM2 is the most common type in which the pancreas produces insulin. It is characterised by various pathophysiological mechanisms, among which the following stand out: inadequate insulin secretion by pancreatic β cells, altered response of peripheral tissues to the action of insulin (insulin resistance), excessive production of glucose in the blood (hyperglycaemia) leading to alterations in carbohydrate, protein, and lipid metabolism (Vázquez *et al.*, 2019; Barría *et al.*, 2022). It is also associated with reduced glucose absorption in the brain, affecting the feeling of satiety provided by dietary carbohydrates (Magkos *et al.*, 2020; Barría *et al.*, 2022).

It is recognised as a chronic, slowly progressing disease that evolves over long periods of time, has a high genetic component, is associated with obesity and a sedentary lifestyle, and can manifest at any age (Valenzuela *et al.*, 2018; Guamán-Montero *et al.*, 2021). It is classified as early-onset T2D (<40 years) and late-onset T2D. The former is characterised by a more rapid deterioration of β -cell function compared to late-onset T2D and appears to carry a higher risk of complications. Its prevalence is higher in adolescent women than in men (Magliano *et al.*, 2020). However, T2DM is more common in people over 40 years of age, accounting for 90-95% of adults with diabetes, but cases in children are increasing (Henning, 2018; Xu *et al.*, 2018). It is considered one of the most psychologically demanding chronic diseases, as patients experience mood disorders such as anxiety and depression (Piñate *et al.*, 2020). It also has a significant psychosocial impact associated with the need to constantly adapt to new lifestyles and possible complications that may arise. It is a disease that requires continuous medical monitoring and patient education for self-care (Valenzuela *et al.*, 2018).

GDM is a condition in which women who did not previously have diabetes have high blood sugar levels during pregnancy. It is detected in the second or third trimester and usually shows few signs or symptoms (Barquilla, 2017). It has been shown that up to 16% of pregnant women are affected by GDM, with pregnant women with a family history of diabetes and certain ethnic backgrounds being more likely to develop the condition (Dwivedi & Pandey, 2020). Table 3 shows differences between DM1 and DM2.

Box 24

Table 3

Types of Diabetes

Type 1 diabetes mellitus	Type 2 diabetes mellitus
Requires external insulin administration	Occasionally requires insulin administration, but not as a general rule
Does not require administration of oral antidiabetic drugs	Requires administration of oral antidiabetic drugs if there is no response to the diet and exercise plan.
Requires dietary control. The insulin dose must be adjusted to the amount of food planned to be eaten.	Closely related to obesity and a sedentary lifestyle. Your diet should be planned.
Requires physical activity to avoid complications from diabetes	Physical activity is part of the treatment and is recommended as a healthy lifestyle choice.
Blood sugar levels should be monitored daily.	Blood sugar levels should be monitored regularly.
Blood pressure should be monitored.	Blood pressure should be monitored.

Beltrán et al., (2018)

DM can occur in three forms: symptomatic, asymptomatic, and ketosis (a metabolic state in which the body uses fats and ketones instead of glucose as its main source of energy) or ketoacidosis (a serious metabolic state that occurs when there is an excessive accumulation of ketone bodies in the blood) (Carvajal *et al.*, 2020).

Generally, there are no symptoms in DM; there is a long asymptomatic period during which micro- and macrovascular complications develop (Barquilla, 2017; Katsarou *et al.*, 2017), but it can also present general symptoms of varying intensity such as polyuria (abnormal production of large amounts of urine), polydipsia (excessive thirst), polyphagia (overeating or increased appetite), asthenia (lack of strength or fatigue characterised by apathy, physical fatigue or lack of initiative), numbness or tingling in the feet or hands, weight loss, blurred vision and sores that do not heal (Barquilla, 2017; Medina-Chávez *et al.*, 2022).

In addition to the general symptoms, men may experience decreased sexual desire, erectile dysfunction, and low muscle strength. Women may also experience symptoms such as urinary tract infections, fungal infections, and dry, itchy skin (Dwivedi & Pandey, 2020; Flores *et al.*, 2020). If left untreated, DM can cause acute complications such as ketosis or ketoacidosis (Carvajal *et al.*, 2020; Figueredo *et al.*, 2020).

Symptoms may vary depending on the type of DM. Symptoms of DM1 include polyphagia, polydipsia, unintentional weight loss, polyuria, blurred vision, and fatigue (Dwivedi & Pandey, 2020). On the other hand, the symptoms of DM2 are polyphagia, polydipsia, polyuria, blurred vision, fatigue, recurrent infections, and sores that take a long time to heal due to high glucose levels. It can also cause morbidity such as depression, sexual dysfunction, and dementia (Valenzuela *et al.*, 2018; Xu *et al.*, 2018). Although the symptoms may be similar to those of DM1, they differ in that they are less intense in DM2 (Flores *et al.*, 2020; Guamán-Montero *et al.*, 2021).

Finally, GDM often does not show clear symptoms, as many can be confused with the usual changes or symptoms of pregnancy, such as fatigue, blurred vision, nausea, polydipsia, polyuria, bladder, vaginal or skin infections, and sugar in the urine (Dwivedi & Pandey, 2020).

In chronic conditions, DM can cause long-term damage, dysfunction, and failure in different organs of the body, especially in the eyes, kidneys, nerves, heart, and blood vessels (Flores *et al.*, 2020). Some of its typical complications are diabetic ketoacidosis, hyperosmolar hyperglycaemic non-ketotic coma, retinopathy (blindness), renal failure, neuropathy, NAFLD, sleep apnoea, polycystic ovary syndrome, dyslipidaemia, diabetic foot disorder, which can lead to serious leg infections and eventually amputation, and CVD such as arteriosclerosis, coronary heart disease, cerebrovascular disease, peripheral vascular disease, and cognitive impairment (Figueredo *et al.*, 2020; Beltrán *et al.*, 2018).

DM is associated with modifiable and non-modifiable risk factors. Non-modifiable factors include genetics, sex, age, ethnicity, and family history, while modifiable factors include lifestyle choices such as obesity, sedentary behaviour, alcohol consumption, and smoking; eating habits such as malnutrition; and environmental factors that interact with each other, contributing to its prevalence (Poblete-Aro *et al.*, 2018; Medina-Chávez *et al.*, 2022).

Non-modifiable risk factors:

- Globally, the incidence and prevalence of DM vary considerably according to ethnicity and geographical region. Several studies have found that people from certain ethnic groups are more likely to develop the disease than people from other ethnic groups (Galicía-García *et al.*, 2020).
- Other important risk factors are genetics and family history. It has been found that people whose parents have DM have up to a 40% chance of developing the same condition. Certain genes, such as PPARG and KCNJ11, are linked to DM. The PPARG gene is responsible for encoding PPAR- γ . This receptor improves sensitivity to insulin action or secretion by regulating genes related to glucose and lipid metabolism, such as glucose transporter-2 (GLUT-2) and liver-type glucokinase (LGK), which are responsible for detecting fluctuations in blood glucose levels (Montier *et al.*, 2015; Khan *et al.*, 2019). Likewise, women with a history of GDM, as well as their children, have a higher risk of developing DM (Uyaguari-Matute *et al.*, 2021; Medina-Chávez *et al.*, 2022).
- Gender is a factor that influences DM, and although the imbalance in prevalence according to gender is not yet understood, it is believed to be influenced by a combination of biological and environmental factors. Although it is diagnosed more in men, women have more cases of obesity, which is one of the main causes of DM (Carvajal *et al.*, 2020).
- Ageing is associated with an increased likelihood of developing DM. The prevalence of this disease is more than double in older people than in young individuals. This is mainly attributed to decreased insulin sensitivity with age, as well as possible alterations in β cells resulting from insufficient insulin production (Khan *et al.*, 2019).

Modifiable risk factors:

- Several studies have confirmed that obesity is the most important risk factor for DM. It is associated with metabolic abnormalities that cause insulin resistance and β -cell dysfunction. In addition, there is an inverse linear relationship between BMI and age (Carvajal *et al.*, 2020; Galicía-García *et al.*, 2020). A normal BMI should be $<25 \text{ kg/m}^2$, and obesity is considered to be a BMI of $\geq 30 \text{ kg/m}^2$ (Barquilla, 2017).
- A sedentary lifestyle is one of the main causes of developing DM. Watching television is one of the main sedentary activities, as are playing board games, sewing, reading, writing, and driving a car. This is because the metabolic rate is lower. The explanation for this can be seen in BMI: as people tend to spend more time without physical activity, their BMI increases (Khan *et al.*, 2019; Guamán-Montero *et al.*, 2021).

- Smoking is another risk factor; people who are chronic smokers have a higher risk of developing this disease compared to non-smokers. One study found that people who smoke 20 cigarettes a day have a 61% higher risk of developing DM, while people who consume fewer than 20 cigarettes have only a 29% higher risk. It has been discovered that smoking aggravates glucose tolerance and causes a reduction in insulin sensitivity due to nicotine (Khan *et al.*, 2019; Medina-Chávez *et al.*, 2022).
- Another risk factor is alcohol, which is determined by a threshold value, generally 63 g/day. Consumption above this value increases the likelihood of developing DM, while consumption below this value reduces the risk (Khan *et al.*, 2019). There is no cure for DM, but with treatment including medication and insulin injections and lifestyle changes such as diet, weight control and exercise, it is possible to live a long and healthy life (Katsarou *et al.*, 2017; Ramírez *et al.*, 2019). Physical activity has benefits that delay the onset of DM. The contraction of skeletal muscle cells induces an increase in blood flow to the muscle, which improves both plasma glucose absorption by up to 40% and insulin sensitivity, reduces intra-abdominal fat, which is a risk factor that promotes insulin resistance, and improves or even reduces inflammation and ROS (Galicía-García *et al.*, 2020; Uyaguari-Matute *et al.*, 2021).

The formation of ROS is inherent to aerobic metabolism, through which energy is obtained from different molecules in cells. Glucose is the main molecule that is oxidised to provide energy and is the most abundant in cells and in the body for metabolic purposes. ROS are obtained through various oxidative reactions of glycolysis and the tricarboxylic acid cycle. When there is an increase in the concentration of ROS, whether endogenous or exogenous, or when there is a reduction in antioxidant defences, OST is generated (Calderón *et al.*, 2013; Arana *et al.*, 2017).

OER plays a fundamental role in the pathophysiology of the chronic inflammatory process that characterises DM (Arana *et al.*, 2017), hyperglycaemia, insulin resistance and excess fatty acids increase OER, alter the signalling of protein kinase C (PKC) signalling, which acts as a biochemical trigger for redox signalling, and increase the end products of advanced glycation, causing vascular inflammation, vasoconstriction, thrombosis, and atherogenesis (Henning, 2018; Aggarwal *et al.*, 2022). Hyperglycaemia is primarily responsible for altering the body's redox state, increasing ROS production and reducing antioxidant defence, so that this imbalance increases OER and endothelial dysfunction, causing oxidative cell damage and affecting different tissues and organs in diabetic patients, contributing to the development of chronic complications such as retinopathy, nephropathy, and neuropathy (Storino *et al.*, 2014; Montier *et al.*, 2015). In hyperglycaemia, O₂ radicals are greatly increased and antioxidant defences are decreased. Oxidative reactions are present, especially lipid peroxidation and the attack of •OH radicals on DNA, structurally altering proteins (Montier *et al.*, 2015; Arana *et al.*, 2017). Therefore, the pathological effects of hyperglycaemia result from the overproduction of O₂•– in the mitochondrial ETC, thus producing ROS (Fig. 22) (Katsarou *et al.*, 2017).

Various mechanisms have been proposed to explain how hyperglycaemia and the metabolic state of DM can generate EO, among which are the generation of ROS in the TET, this being the main one; the auto-oxidation of glucose, the sorbitol pathway, protein glycation, advanced glycation end products (AGEs), the activation of the polyol pathway, excessive expenditure of reduced cofactors, among others (Cruz *et al.*, 2011; Storino *et al.*, 2014; Galicía-García *et al.*, 2020).

In auto-oxidation, glucose is capable of auto-oxidising, which occurs very abundantly under conditions of higher concentration in the cell. In this condition, the formation of an enediol takes place first, an oxidation that occurs in the α -hydroxyaldehyde radical of glucose (Cruz *et al.*, 2011). In the presence of transition metals such as Fe²⁺ and Fe³⁺, enediol reacts with O₂ and a protein to produce an oxidised product called 1,4-dideoxyglycosone-protein, which results in a glycated protein capable of generating a chain oxidation that will lead to AGEs. From this compound, acetaldehydes are produced by oxidation, which continue to generate various oxidised products that further damage the protein and generate various chain oxidation reactions, ending with protein-protein bonds that cause further structural and functional damage (Storino *et al.*, 2014; Hernández-García *et al.*, 2017). The oxidation of these intermediates can produce the partial oxidation of O₂ with the consequent formation of O₂•–, which is transformed into H₂O₂ by the activity of the SOD enzyme and can be transformed into •OH by transition metals, all of which contribute to the oxidation of lipids and proteins, nucleic acids and carbohydrates.

Not only can the auto-oxidation of glucose contribute to EO, but an excess of glucose in cells can also generate pro-oxidant compounds due to the excess of glycolysis itself (Fig. 22) (Calderón *et al.*, 2013).

The increase in glucose concentration in the cell also leads to an increase in a pathway that produces sorbitol from the reduction of glucose (polyol pathway), and the accumulation of sorbitol causes increases in intracellular osmolarity with consequent cell damage. This reduction of glucose to sorbitol is achieved by the oxidation of $\text{NADPH} + \text{H}^+$, a reaction carried out by an aldol reductase, which uses up antioxidant reducing capacity and generates the partial reduction of O_2 in the reaction, producing H_2O_2 . Sorbitol accumulation can reach high concentrations and, once a certain limit is reached, a pathway is activated that can convert sorbitol into fructose, through an oxidative reaction catalysed by sorbitol dehydrogenase, which forms high concentrations of $\text{NADH} + \text{H}^+$, activating the enzyme NADH oxidase, which causes the loss of the e^- of $\text{NADH} + \text{H}^+$ and produces $\text{O}_2^{\bullet-}$, which causes the reducing power of both $\text{NADPH} + \text{H}^+$ and $\text{NADH} + \text{H}^+$ to be depleted, producing H_2O_2 and $\text{O}_2^{\bullet-}$, leading to a more oxidative state, lower reducing power and less antioxidant protection (Calderón *et al.*, 2013; Hernández *et al.*, 2017). Likewise, the abnormal production of $\text{O}_2^{\bullet-}$ radicals alters NO metabolism, as they react with each other to form OONO^- . Therefore, NADPH is an important factor in protecting against damage caused by ROS (Fig. 22). (Hernández *et al.*, 2017).

Box 25

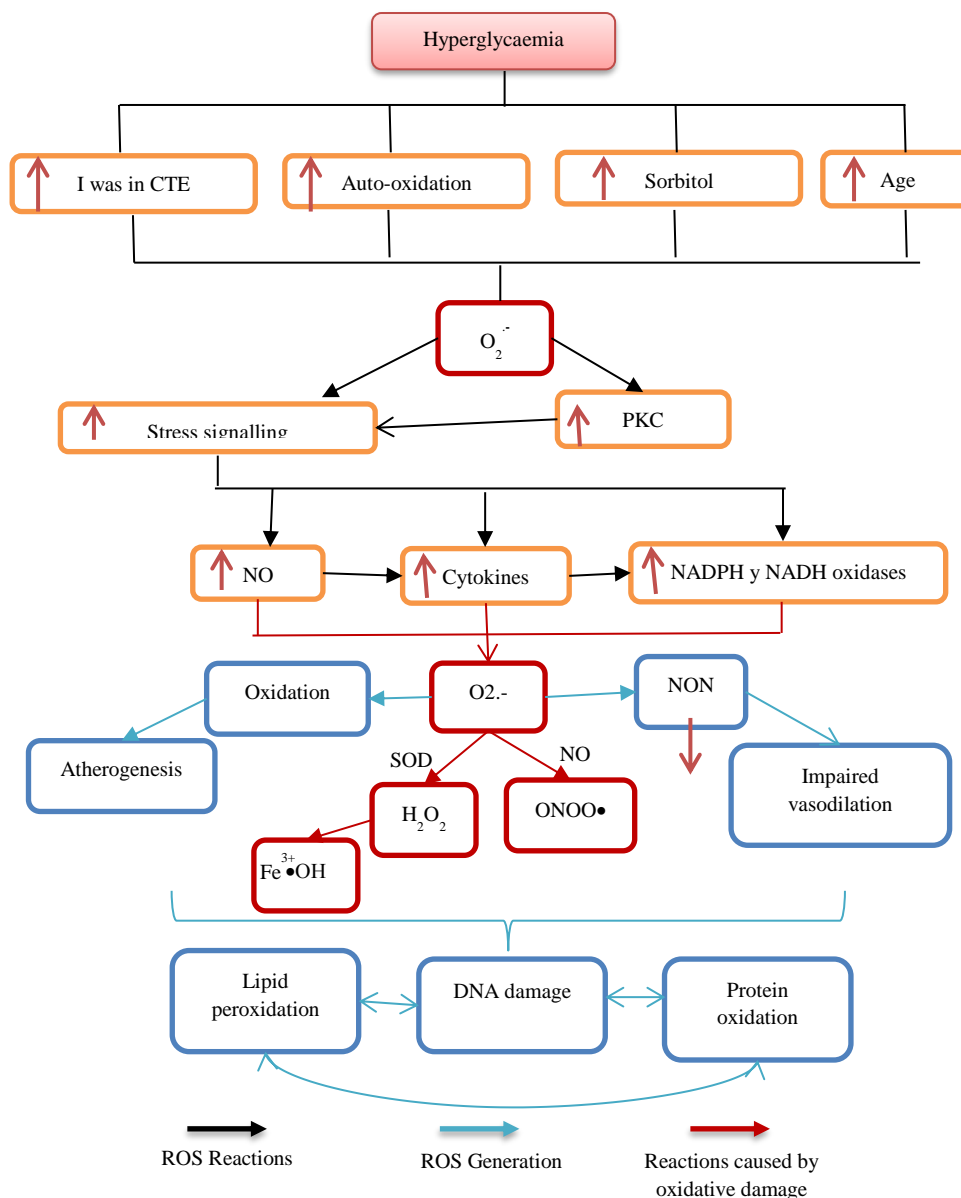


Figure 22

Diabète et stress oxydatif.

Calderón *et al.* (2013)

2.7. Cancer

Cancer is a disease that is present worldwide. According to the WHO (2021), it is considered the leading cause of death in the world, with one in six deaths attributed to this disease, and the incidence and mortality rates continue to increase. In Mexico, it is the second or third leading cause of death.

Cancer is a disorder that occurs when normal cells transform into tumour cells through a multi-stage process that usually consists of the progression from a lesion to a malignant tumour (Blackadar, 2016). Malignant tumours are the leading cause of mortality worldwide, representing a major economic and social challenge for the health system (Reynoso-Noverón & Torres-Domínguez, 2017). It results from genetic or epigenetic alterations and is characterised by the abnormal and widespread growth of cells,

They multiply rapidly and uncontrollably due to the alteration of cell division and death mechanisms, which leads to the development of a group called neoplasia or tumour, forming abnormal masses in any part of the body that can spread to other organs and destroy them, thus altering their functioning, a process known as metastasis (Blackadar, 2016; Villafuerte *et al.*, 2019; Rivas & Armisén, 2022). The spread of metastasis is the leading cause of death from the disease (WHO, 2021).

According to the National Cancer Institute (2019), there are more than 100 types of cancer, which are named after the organs or tissues where they form. The most common types of cancer are breast, lung, colorectal, prostate, skin, and gastric. The main neoplasms causing mortality in the female population are breast cancer (15.3%), cervical cancer (10.4%), liver and biliary tract cancer (8.0%), and stomach cancer (7.0%); and in men, prostate (16.7%), trachea, bronchi, and lung (11.3%), stomach (8.1%), and liver and biliary tract (7.9%) (Reynoso-Noverón & Torres-Domínguez, 2017).

Symptoms at the time of diagnosis are few and limited to specific cancer sites, however, there are others that are shared; general symptoms of cancer include changes in normal body processes, abdominal pain, changes in bowel habits, back pain, fatigue and weight loss, and may also include unexplained bleeding or the development of a lump (Koo *et al.*, 2020).

The origins or causes of cancer are multifactorial. There are modifiable and non-modifiable factors. Non-modifiable factors include biological factors such as sex, race or ethnicity, age, and genetics. Modifiable factors are related to environmental factors and lifestyles such as smoking, alcoholism, exposure to ionising and ultraviolet radiation, radiation from sources emitting alpha, gamma, beta, and X-rays, use of tanning beds, unhealthy eating habits, obesity, sedentary lifestyle, and stress. Therefore, these factors may be preventable (Fernández *et al.*, 2016; Saini *et al.*, 2020; López-Plaza *et al.*, 2022).

Lung cancer is one of the most common neoplasms and is the leading cause of cancer death worldwide (Rivas & Armisén, 2022). It originates when cells begin to reproduce uncontrollably, forming a tumour. It usually begins in the cells surrounding the bronchi and, less frequently, in the bronchioles and/or alveoli. They then spread to other parts of the body, where they begin to grow and form new tumours that replace normal tissue (Camacho-Beiza *et al.*, 2022).

Unlike other tumours, this type of cancer is the most aggressive and deadly, affecting mainly people between 50 and 65 years of age on average, with less than 15% of cases occurring in people under 30 (Nazario *et al.*, 2021; Cordova *et al.*, 2022). It is more prevalent in men, although the incidence of this type of cancer in women has increased in the last decade (Cordova *et al.*, 2022). In Mexico, it is the second leading cause of death in men and the fourth in women (Camacho-Beiza *et al.*, 2022).

This disease is divided into two main types: non-small cell cancer and small cell cancer. The first type of cancer grows and spreads more slowly than the small cell variant, is diagnosed more frequently and accounts for 85% of all lung cancer cases. Its early stages have few specific symptoms, which means that 70% of cases are not diagnosed until the disease is already advanced, making treatment more difficult and less successful, which leads to low survival rates. Small cell lung cancer is more aggressive, metastasises at an earlier stage of the disease, and accounts for approximately 15% of all lung cancers worldwide (Camacho-Beiza *et al.*, 2022; Valencia *et al.*, 2022).

Lung cancer may not produce noticeable symptoms in the early stages, and many people are not diagnosed with the disease until it has advanced. In the early stages, 80% of patients present with general symptoms such as asthenia, hyporexia, and weight loss. In advanced stages, they present with cough, dyspnoea, dysphonia, weakness, haemoptysis, and chest pain (Escalera *et al.*, 2021; Cordova *et al.*, 2022). The discomfort experienced by patients with metastatic disease is mainly determined by the specific sites affected, such as bone, brain, liver, and adrenal glands (Escalera *et al.*, 2021).

The main risk factor is tobacco; smoking is closely related to squamous cell carcinoma and small cell cancer. Tobacco smoke contains 7,000 toxic substances, 60 of which are known carcinogens. Nicotine itself could directly intervene in the pathogenesis of lung cancer (Nazario *et al.*, 2021; Arroyo-Hernández *et al.*, 2022). There are also other risk factors such as environmental pollution, wood smoke, exposure to inorganic materials, ionising radiation such as radiotherapy, viral infections and genetics (Saini *et al.*, 2020; Arroyo-Hernández *et al.*, 2022; Valencia *et al.*, 2022). These factors usually depend on the dose and duration of exposure and act synergistically when combined with smoking (Arroyo-Hernández *et al.*, 2022).

Breast cancer is the most common malignant neoplasm in women, according to the WHO (2021), accounting for 16% of female cancers worldwide, in both developed and emerging countries. In Mexico, it is the second leading cause of death in women and the leading cause of cancer, mainly affecting women between the ages of 40 and 50 (Palmero *et al.*, 2021), with more than 75% of cases diagnosed after menopause (Osorio *et al.*, 2020).

Breast cancer is an oncological process in which healthy cells in the mammary gland, commonly in the inner lining of the milk ducts or in the lobules that supply milk to the ducts, which after puberty respond to periodic oestrogenic influences from the ovary, degenerate and become tumourous. It is a clonal disease, one type of which proliferates to form a tumour, which subsequently invades surrounding tissues and metastasises to different areas of the body (Sharma *et al.*, 2010; Osorio *et al.*, 2020; Goff & Danforth, 2021).

The aetiopathogenesis of this disease is known to be caused by the interaction of genetic, environmental and lifestyle factors. It is classified as sporadic, which occurs in patients with no family history and accounts for 70-80% of cases; familial, which occurs in patients with a clear history and is not attributed to the alteration of a single gene, but to the mutation of various genes such as BRCA1, BRCA2 and obesity, accounting for 15-20% of cases; and hereditary, which is passed down from first-degree relatives such as mothers, sisters/brothers and children who have been diagnosed with breast or ovarian cancer before the age of 50.

It is derived from the mutation of a single BRCA1 or BRCA2 gene or the p53 genome, which cause uncontrolled cell division, inhibition of apoptosis and metastasis to distant organs. If a person has had breast cancer at an early age, it could be a sign that their family carries a hereditary cancer gene (Fernández *et al.*, 2016; Peña *et al.*, 2017; Goff & Danforth, 2021). The likelihood of developing this cancer increases with age, but it tends to be more aggressive when it occurs in young women, as diagnosis is delayed because mammography is less effective in the dense breasts of young women (Fernández *et al.*, 2016).

Early breast cancer does not usually cause symptoms, but when the disease is more advanced, it presents symptoms such as swelling or a lump in the breast or armpit, which women should check through self-examination, sharp pain in any part of the breast that persists after menstruation, changes in the colour or appearance of the skin of the breast (scaling or pitted skin), with special attention to the appearance of orange peel skin, dimples or indentations in the skin, inverted (retracted) nipple, nipple discharge, noting the appearance (clear, milky or bloody) of the discharge; in the advanced (metastatic) stage of the disease, the lymph nodes in the armpits are present with other symptoms such as bone pain (bone metastases), difficulty breathing (lung metastases), loss of appetite and unintentional weight loss (liver metastases), headaches, neurological pain or weakness (Sharma *et al.*, 2010; Palermo *et al.*, 2021; Osorio, 2020).

Like most oncological pathologies, breast cancer has a multifactorial origin, including non-modifiable and modifiable factors. The former include menarche and genetic factors such as age, race, family history (genetic) and personal history of benign breast diseases, while the latter are related to the environment or lifestyle factors such as diet, tobacco and alcohol consumption, physical activity, overweight or obesity, exposure to radiation and viral infections (Peña *et al.*, 2017; Palmero *et al.*, 2021). Risk factors experienced by women, such as late onset of sexual activity, first childbirth, menopause, increased exposure to non-oestrogenic mutagens and oestrogen genotoxicity, increase and are strongly associated with the development of this disease. Likewise, a diet high in animal fats, alcohol consumption, low physical activity, and obesity are factors that also increase the risk of developing it (Peña *et al.*, 2017; Kashyap *et al.*, 2022).

Prostate cancer is the most common cancer among men. In Mexico, it has increased in the last two decades and is currently the leading cause of cancer death in men. It has a higher prevalence in adults over 65 years of age, and its incidence increases significantly with age (Núñez-Liza *et al.*, 2017; Islas *et al.*, 2021).

Prostate cancer is the abnormal growth of cells in the prostate gland that has the ability to invade other organs. More than 95% of cases are adenocarcinomas, i.e., cancers that begin in the cells that produce and release mucus and other fluids (Núñez-Liza *et al.*, 2017; Ángeles-Garay *et al.*, 2019).

This type of cancer often has no early symptoms, and the signs of prostate cancer are often first detected by a doctor during a routine check-up. However, some men experience changes in urinary or sexual function, such as difficulty starting to urinate or retaining urine, weak or interrupted urine flow, urinary urgency (sudden and strong urge to urinate), nocturia (need to urinate at night), pollakiuria (need to urinate many times during the day or night), erectile dysfunction, painful ejaculation, blood in the urine or semen, frequent pain or stiffness in the lower back, hips, or upper thighs, etc. (Núñez-Liza *et al.*, 2017; Ángeles-Garay *et al.*, 2019).

Risk factors associated with prostate cancer include age, family history, ethnicity, obesity, environmental factors, and lifestyle (Islas *et al.*, 2021; Sekhoacha *et al.*, 2022). In terms of age, it is rare for prostate cancer to affect men under the age of 40, but the likelihood of developing it increases rapidly after the age of 50, with a higher prevalence detected in men over the age of 65. Black men are also more likely to develop the disease than white men (Jinez-Sorroza *et al.*, 2017; Sekhoacha *et al.*, 2022).

Most prostate cancers occur in men with no family history of the disease. However, there is a likelihood of developing it due to hereditary or genetic factors. If the father or brother has the disease, the risk of developing it doubles, and among these, the risk is higher when the brother has it. The risk also increases when several relatives are affected, and even more so if those relatives were young when the cancer was detected. Genetic mutations, particularly in the BRCA2 gene, can also increase the risk (Jinez-Sorroza *et al.*, 2017; Islas *et al.*, 2021).

Obesity is another important factor, believed to double the risk due to the consumption of calories contained in foods rich in carbohydrates, while the abuse of red meat and saturated fats increases the risk up to 3.5 times (Jinez-Sorroza *et al.*, 2017; Ángeles-Garay *et al.*, 2019).

On the other hand, environmental factors and lifestyles such as exposure to pollutants and chemicals, as well as alcohol and tobacco consumption, are believed to increase the risk of developing this disease; however, further studies are needed to verify this (Ángeles-Garay *et al.*, 2019).

The risk of cancer can be reduced by avoiding tobacco and alcohol consumption, maintaining a healthy body weight, following a healthy diet that includes fruits, vegetables, cereals, and legumes, reducing red meat consumption, engaging in regular physical activity, avoiding ultraviolet radiation or protecting oneself from sunlight, and minimising occupational exposure to ionising radiation and outdoor and indoor air pollution (Saini *et al.*, 2020; López-Plaza *et al.*, 2022; Rivas & Armisén, 2022). Currently, 30-50% of cancer cases can be prevented by reducing risk factors and implementing preventive strategies (WHO, 2021). In every cell, external and internal factors can cause DNA damage, and its repair process or mechanism must be maintained or function constantly to prevent structural damage. The cell can follow three paths: first, the normal process of senescence; second, apoptosis or programmed cell death; third, changes that lead to cancer or carcinogenesis (Núñez-Troconis, 2017).

As is well known, the generation of ROS is part of normal cell metabolism and they function as mediators in physiological processes and cancer. However, when there is an imbalance between its generation and neutralisation, it can lead to ROS, affecting several signalling pathways associated with cell proliferation and contributing to the transformation of cancer cells. In addition, the presence of ROS and cancer cells generates more ROS than normal cells, altering the expression of the p53 suppressor gene, which is a key factor in apoptosis. Therefore, ROS causes changes in gene expression, cell proliferation, and apoptosis, playing an important role in tumour initiation and progression (Granado, 2010; Alonso *et al.*, 2021).

The involvement of ROS in tumour formation suggests that various aspects related to the control of RLs influence tumour development, including inflammation, transformation, survival, proliferation, invasion, angiogenesis, and metastasis. RLs can act directly or indirectly on DNA, causing genetic and/or epigenetic alterations, cell signalling, and oxidative damage to proteins and lipids that drive the initiation of carcinogenesis and/or cell death (Núñez-Troconis, 2017; Alonso *et al.*, 2021).

Carcinogenesis is defined as the ability of a compound to trigger a complex process involving the transformation of a normal cell into a tumour cell. It mainly occurs in three stages of intervention: initiation (1), promotion (2) and progression (3), as shown in Figure 23 (Núñez-Troconis, 2017).

Initiation is a relatively rapid but reversible phase that involves the exposure of cells to a carcinogenic agent, as well as its distribution and transport to organs and tissues where its metabolic activation, detoxification and the interaction of ROS with cellular DNA can occur, causing oxidative damage that can be crucial in the initiation of the cancerous process (Granado, 2010). The initiation of carcinogenesis involves a non-lethal mutation in the DNA of a cell, resulting in an initiated cell that performs at least one cycle of DNA synthesis to repair the damage.

If the damaged cell is dividing, it may be able to temporarily interrupt its cell cycle, repair the damage and continue dividing, but if the DNA damage is too great, the cell will initiate a programmed suicide mechanism called apoptosis to eliminate genetically altered cells (Núñez-Troconis, 2017; Xu *et al.*, 2019). Apoptosis, or programmed cell death, is a mechanism of ‘cell suicide’ that occurs through intrinsic and extrinsic signalling pathways.

The process can be divided into an activation phase, in which the cell receives the stimulus that will lead to death, and the execution phase, in which most of the morphological and biochemical changes that cause the cell to lose contact with neighbouring cells occur. When these repair or elimination mechanisms do not work, the initiated cells proliferate and the carcinogenesis process advances to the promotion phase (1) (Granado, 2010; Xu *et al.*, 2019).

Promotion is a relatively long phase compared to the initiation phase, in which the damaged cell persists, replicates, and can give rise to a group of preneoplastic cells. Likewise, in this phase, angiogenesis processes occur, consisting of the formation of new blood vessels necessary to ensure access to nutrients and gas exchange in tumours (Granado, 2010; Alonso *et al.*, 2021). O₂ and H₂O₂ have been observed to function as signalling molecules to mediate angiogenesis; therefore, OS plays a fundamental role in both the promotion and progression of cancer (2) (Alonso *et al.*, 2021).

Progression is the final and irreversible phase of carcinogenesis, characterised by uncontrolled growth of tumour cells that gradually transform from premalignant to neoplastic cells and increase their invasive capacity, allowing them to invade new target tissues (metastasis) (Granado, 2010).

Metastasis involves the spread of cancer cells from the primary tumour to surrounding tissues and distant organs. ROS have been shown to promote this transition, specifically O₂ and H₂O₂, which participate in the invasion and metastasis of cancer cells (3). (Alonso *et al.*, 2021).

Box 26

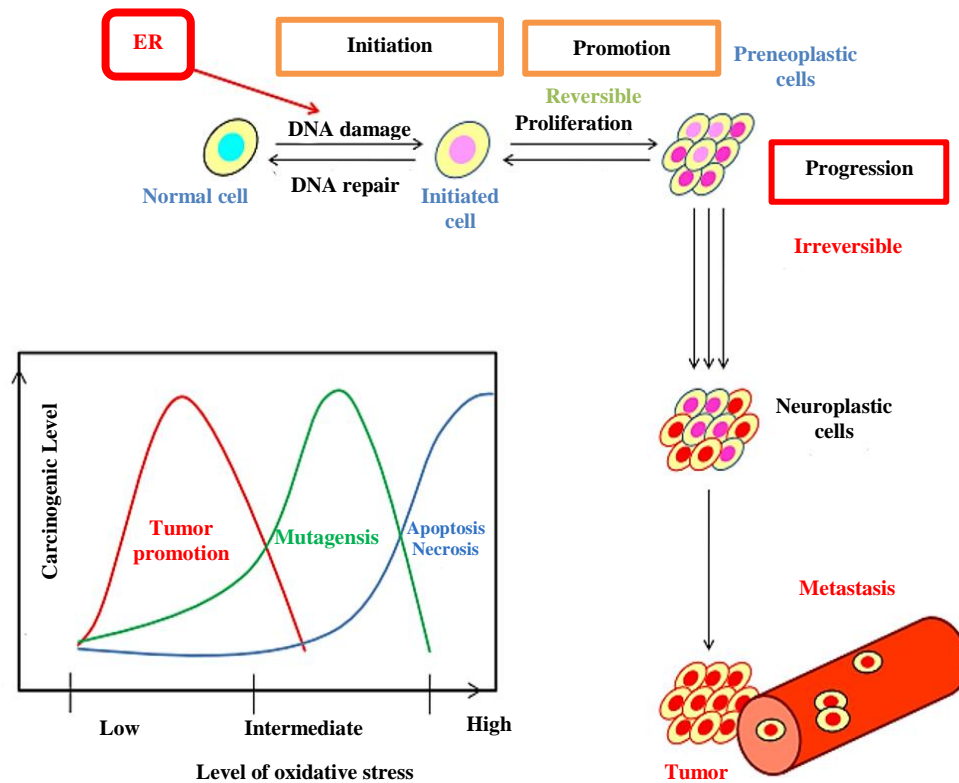


Figure 23

Cancer and oxidative stress

Granado (2010).

2.8. Physical activity

Physical activity is defined as any bodily movement produced by the contraction of skeletal muscles that results in energy consumption (Mahecha, 2019; Cotignola *et al.*, 2023). It is a fundamental tool for health and physical performance (Clemente-Suárez *et al.*, 2023). These activities can be part of everyday life, exercise that includes pre-established, deliberate and repetitive activity, or moderate-intensity activity such as walking, cycling or playing a sport (Simioni *et al.*, 2018).

The term ‘physical activity’ should not be confused with ‘exercise’, which is a subcategory of physical activity characterised by being planned, structured, constant and designed to improve or maintain one or more aspects of physical condition (Mahecha, 2019; Cotignola *et al.*, 2023). Physical activity can be beneficial or harmful to health depending on the intensity of the exercise, duration, physical condition, and nutritional status of the individual (Simioni *et al.*, 2018).

There are different types of physical activity, including regular, endurance, prolonged endurance, anaerobic, intense, and strenuous physical activity (Powers *et al.*, 2020).

Regular physical activity is associated with the prevention and treatment of chronic diseases and has important effects on mental and cognitive health and sleep quality, among other benefits (Mahecha, 2019). It is characterised by the positive regulation of the enzymatic antioxidant system and the control of oxidative damage (Clemente-Suárez *et al.*, 2023). It is recommended that all adults engage in this activity for at least 30 minutes per day and children and adolescents for at least 60 minutes per day (Mahecha, 2019).

Resistance physical activity is defined as cardiovascular exercise such as running, cycling, skiing, or swimming performed over a prolonged period of time. It has a profound impact on EO, intestinal permeability, muscle damage, systemic inflammation, and immune responses (Mach & Fuster-Botella, 2017). This activity consists of performing dynamic or static contractions against resistance, such as lifting weights using resistance machines or elastic bands.

These resistance exercises increase muscle myoglobin content by 75-80%, which promotes O₂ storage, increases the number and size of mitochondria, and increases oxidative enzymes, resulting in more intense functioning of the oxidative system (Rubio del Peral & Gracia Josa, 2018; Chasi, 2022).

Prolonged resistance physical activity is defined as the ability of humans to exert themselves for a prolonged period of time while maintaining a high work capacity. Its value is based on the ability to exert oneself for very long periods of time, maintaining minimal inevitable losses of intensity, but at the same time, practising prolonged exertion of varying intensities over not very long periods of time (Chasi, 2022).

Anaerobic physical activity is defined as intense physical activity of very short duration, fuelled by energy sources within the contracting muscles independently of the use of inhaled O₂ as an energy source (Patel *et al.*, 2017; Chasi, 2022). This process produces less ATP than aerobic activity and leads to the accumulation of lactic acid. Exercises typically considered anaerobic involve fast-twitch muscles, such as sprinting, high-intensity interval training, weightlifting, etc. (Patel *et al.*, 2017).

Intense physical activity is that which requires a great deal of effort and causes rapid breathing and a substantial increase in heart rate, for example, competitive sports and games, intense shovelling, digging trenches or moving heavy loads (>20 kg). This type of activity can cause heart attacks in patients with high cholesterol, hypertension, diabetes, obesity, and smokers, especially if these individuals are sedentary and suddenly engage in intense activity without being in appropriate physical condition. Likewise, maintaining physically intense work activity for years increases the risk of arrhythmia, especially atrial fibrillation (Bravo, 2012). O₂ consumption during vigorous exercise generates ROS production and thus cellular and muscular damage, which causes oxidative stress (OS) that extends to various important biomolecules such as lipids, proteins, and DNA (Enriquez-del-Castillo *et al.*, 2019).

Strenuous physical activity consists of at least 30 minutes of intense, near-limit muscle contractile activity. This increases FR production in the muscle because it causes a 10- to 20-fold increase in O₂ consumption, which inevitably produces ROS. Therefore, the generation of these species depends on the intensity and duration of the exercise, as different types of exercise differ in their energy requirements, level of O₂ consumption and mechanical stress imposed on tissues (Thirupathi *et al.*, 2021).

Regular physical activity is established as an important health factor because it has positive effects on various tissues, organs, and systems (García-Giménez *et al.*, 2024), including the reduction, prevention, and treatment of multiple diseases such as obesity, CVD, stroke, DM, cancer, metabolic disorders, and AD; improves glucose tolerance and bone mineral density, reduces inflammation, improves mitochondrial biogenesis and protein synthesis in skeletal muscle, prevents health problems and their associated risk factors, promotes weight loss, and improves brain, immune and lung function (Thirupathi *et al.*, 2021; Cotignola *et al.*, 2023; García-Giménez *et al.*, 2024).

There is also an increase in the production of enzymatic antioxidants in the blood, which prevents ONS, reduces lipid peroxidation levels and various pathological disorders, and slows down the ageing process (Enriquez-del-Castillo *et al.*, 2019; Godoy, 2023). There is also a transient increase in ROS that has positive effects on physiological signalling pathways, regulates muscle contractile activity, stimulates muscle regeneration and improves vasodilation during exercise, all of which are essential for adaptation to training (Clemente-Suárez *et al.*, 2023). Moderate, scheduled physical activity has often been reported to be therapeutic in both adulthood and ageing. It is therefore advisable to integrate physical activity into daily life and make it a fundamental component of maintaining a healthy lifestyle, reducing sedentary behaviour and chronic diseases (Simioni *et al.*, 2018).

Intense physical activity can trigger biochemical signalling pathways that contribute to fatigue, stagnation, reduced performance, limited vasodilation and blood flow, and metabolic disturbances (Godoy, 2023). Exhaustive and extreme amounts of exercise have been linked to adverse effects that lead to muscle and joint injuries and even disease (Godoy, 2023; García-Giménez *et al.*, 2024). In addition, there is inflammation in the body and oxidative damage in numerous tissues, including blood, heart, brain, adipose tissue, liver, and skeletal muscles, because a greater amount of ROS is generated due to the high metabolic requirements necessary to carry it out, which is no longer adequate and experiences OST (Mach & Fuster-Botella, 2017; Thirupathi *et al.*, 2021; Godoy, 2023).

Muscle contractions are predicted to stimulate ROS production in active muscle fibres, making skeletal muscle a major source during exercise (Powers *et al.*, 2020). It also increases protein oxidation, lipid peroxidation and profound metabolic changes (Thirupathi *et al.*, 2021).

Progressive training allows cells to more easily detoxify greater amounts of ROS, thereby increasing their antioxidant defences. On the other hand, excessive physical activity is harmful to untrained individuals, causing ROS, inflammation, muscle fatigue, and weakening their antioxidant defences (Fig. 24). (Simioni *et al.*, 2018).

Box 27

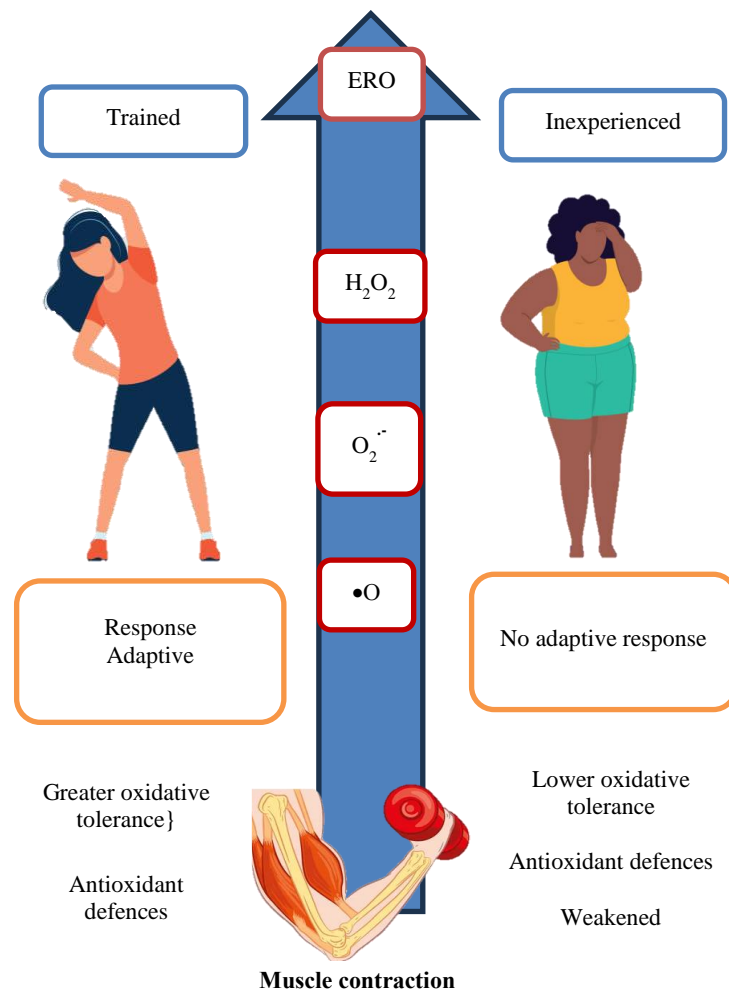


Figure 24

Response to ERO in trained and untrained individuals.

Clemente-Suárez et al. (2023).

As mentioned, ROS are produced during repeated muscle contraction due to prolonged, high-intensity, anaerobic physical activities. The main source of ERO production during physical activity is skeletal muscle, but there are other possible sources in muscle fibres such as mitochondria, NADPH oxidase (NOX/DUOX) enzymes, especially NOX2 and NOX4, xanthine oxidase (XO) and phospholipase A2 (PLA2), located at four sites within the mitochondrial fibres, sarcolemma, sarcoplasmic reticulum and T-tubules (Powers *et al.*, 2020; Clemente-Suárez *et al.*, 2023).

PLA2 is an enzyme that cleaves membrane phospholipids to release arachidonic acid, which functions as a substrate for various ROS-generating enzyme systems from the ETC; PLA2 can also activate NADPH oxidases (Poblete-Aro *et al.*, 2018; Powers *et al.*, 2020).

Skeletal muscle expresses two isoforms of NADPH oxidase (NOX2 and NOX4). NOX2 is found within the sarcolemma and T-tubule, while NOX4 is found in the sarcoplasmic reticulum and mitochondria. Therefore, NOX2 is the main source of NADPH oxidase-mediated ROS generation in contracting muscle, while NOX4 produces ROS in muscle fibres (Powers *et al.*, 2020). Consequently, NOX enzymes are considered the main contributor to contraction-induced ROS production.

They are responsible for producing $O_2^{\bullet-}$ as the main molecule in the ROS cascade, which is subsequently dismutated to H_2O_2 and finally reacts with Fe^{2+} to produce $\bullet OH$ (Fig. 25). (Carvajal, C., 2019; García-Giménez *et al.*, 2024).

Box 28

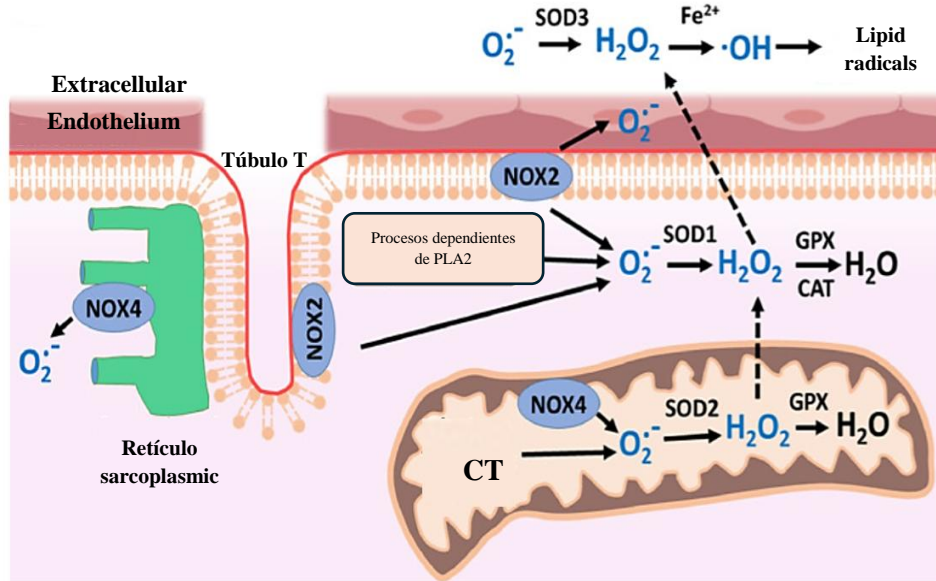


Figure 25

Generation of oxidative stress during physical activity

Powers et al. (2020).

Chapter 3 Antioxidants

An antioxidant is a molecule stable enough to donate an e⁻ to an RL, thereby reducing its ability to cause damage and stopping the chain reaction, with the aim of preventing, delaying, inhibiting and eliminating the oxidative damage caused by these physiological oxidants, protecting molecules such as lipids, proteins and DNA and cellular organs (Gulcin, 2020; Khadim & Al-Fartusie, 2020; Pérez-Gálvez *et al.*, 2020; Comino-Sanz *et al.*, 2021). When an antioxidant donates its e⁻, it becomes an RL, but it does not have the ability to be reactive (Castillo-Velarde, 2019).

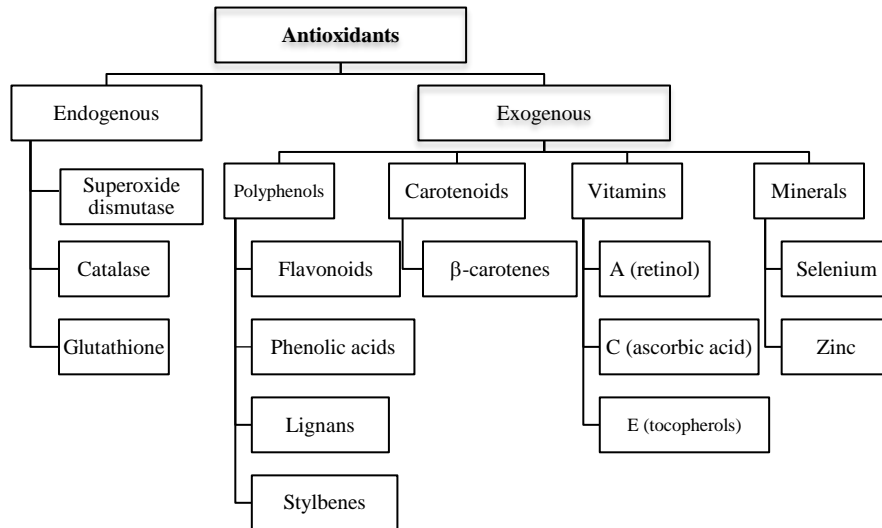
The main function of antioxidants is to maintain redox homeostasis by counteracting the effects of ROS, converting RLs into non-radicals or less reactive species, reducing their reactivity or preventing the conversion of inactive radicals into more harmful species (Navarro-González *et al.*, 2017; Adwas *et al.*, 2019; Higgins *et al.*, 2020; Meitha *et al.*, 2020). They also reduce the risk of ECD by slowing the progression of many chronic diseases caused by ROS, as well as LPO (Gulcin, 2020; Parcheta *et al.*, 2021). Conversely, low levels of antioxidants or their inhibition cause ROS and can damage or kill cells (Khadim & Al-Fartusie, 2020).

Some authors classify antioxidants as enzymatic and non-enzymatic. Enzymatic antioxidants include SOD, CAT, and GPx, while non-enzymatic antioxidants are low molecular weight compounds such as vitamins, mainly C and E, carotenoids, flavonoids, and minerals (Adwas *et al.*, 2019; Comino-Sanz *et al.*, 2021; Averill-Bates, 2023). Other authors, such as Ifeanyi (2018), Higgins *et al.* (2020), and Balendra & Singh (2021), classify antioxidants as endogenous and exogenous. Endogenous antioxidants are produced by the body and include SOD, CAT and GSH.

They are considered very powerful antioxidants for repairing damage caused by ROS, as they initiate cell regeneration, work in membrane domains and act intracellularly to impact gene expression (Higgins *et al.*, 2020; Balendra & Singh, 2021). On the other hand, exogenous antioxidants are acquired through diet because the body cannot manufacture some micronutrients, including vitamins C and E, polyphenols, flavonoids, carotenoids, and minerals such as Se, Zn, and Mn.

Their main sources are fruits and vegetables, and they can also be found in legumes, nuts, eggs, meat, fish, tea, wine, coffee, and fruit juices (Fig. 26) (Navarro-González *et al.*, 2017; Ifeanyi, 2018; Meitha *et al.*, 2020). Their main function is to repair damage caused by ROS at the extracellular level, which is achieved by transferring an e⁻ to reduce them; stimulate cell regeneration and sequester transition metals through a chelation process. They also play a key role in reinforcing and replenishing endogenous antioxidants to eliminate excess O₂ metabolites (Higgins *et al.*, 2020; Meitha *et al.*, 2020; Balendra & Singh, 2021).

Antioxidant defence is a universal mechanism present within cells (Ali *et al.*, 2020), and its oxidative capacity varies depending on the type of RL. Endogenous antioxidants are the first line of defence against RLs. They are more complex and allow for a more controlled localised effect, while exogenous antioxidants act as a second line of defence, offering greater protection, eliminating non-specific RLs and helping to reinforce the defence of endogenous antioxidants by strengthening them and restoring optimal balance by neutralising ROS (Ighodaro & Akinloye, 2018; Adwas *et al.*, 2019; Higgins *et al.*, 2020). However, it has been shown that high doses of antioxidants can cause toxicity due to their antioxidant activities. (Ali *et al.*, 2020).

Box 29**Figure 26**

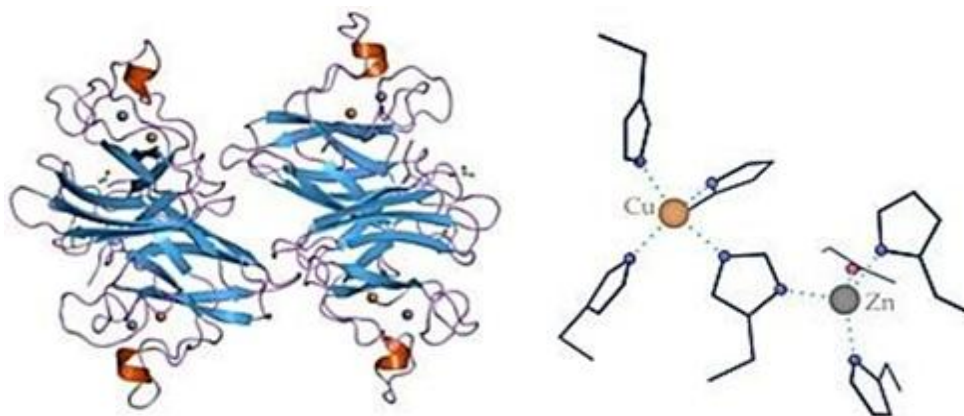
Classification of antioxidants

*Own Work.***3.1. Endogenous antioxidants**

The human body has a series of endogenous enzymes that are considered part of the defence mechanisms against ROS because they are responsible for neutralising the ROS that are formed. They constitute the active O₂ elimination system, reducing and eliminating reactive species such as O₂^{•-}, H₂O₂ and •OH (Zheng *et al.*, 2023). Among the most important endogenous enzymes are SOD, CAT, GPx and glutathione reductase (GRx). These enzymes constitute the first line of antioxidant defence, playing a fundamental role in the protective mechanisms of the body's biological system (Ighodaro & Akinloye, 2018; Sutrisno *et al.*, 2022). There are three defence mechanisms in the body against ROS and RNS. The first line of defence, which involves enzymes such as SOD and CAT, is to prevent these reactive species from reacting with compounds that are essential for cells. The second is assisted by GPx and uric acid, which causes the termination of FR chain reactions, and the third involves the repair and/or elimination of damage caused by the interaction of ROS and RNS with biomolecules (Parcheta *et al.*, 2021).

3.1.1. Superoxide dismutase

SODs are a group of enzymes that contain metals such as Cu, Mn, Zn, and other metal ions, which is why they are called 'metalloenzymes' (Fig. 27). They are found in eukaryotic cells and some prokaryotic cells (Younus, 2018).

Box 30**Figure 27**

Structure of superoxide dismutase and its active site

Puig (2023)

SOD activity can have a dual and opposite meaning. Firstly, it functions as an antioxidant enzyme when its activity is coordinated with CAT, GPx or Peroxiredoxin (Prx) enzymes (Balendra & Singh, 2021; Rosa *et al.*, 2021), which constitute a very important antioxidant defence against OS in the body, preventing damage to cells, DNA and lipids. It also regulates signal transduction in the body, lipid metabolism and inflammation (Islam *et al.*, 2021; Sutrisno *et al.*, 2022).

They are characterised as a key cellular antioxidant because they are responsible for the elimination of $O_2^{\bullet-}$ (Wang *et al.*, 2018; Balendra & Singh, 2021), its main function is to catalyse the dismutation of the $O_2^{\bullet-}$ radical into O_2 and H_2O_2 (Eq. 28), reducing the probability of $\bullet OH$ formation and the level of O_2 that damages cells in excessive concentrations (Hong *et al.*, 2018; Younus, 2018; Zinellu & Mangoni, 2021). They are also the only enzymes that can prevent the formation of ONOO⁻ by eliminating $O_2^{\bullet-}$. However, the accumulation of ONOO⁻ resulting from inefficient elimination of $O_2^{\bullet-}$ in the mitochondria can significantly affect mitochondrial function (Wang *et al.*, 2018); Secondly, SOD can accumulate in excess, resulting in overproduction of ROS and cellular toxicity (Rosa *et al.*, 2021).



SOD acts as an antioxidant enzyme that eliminates ROS through redox reactions at high speed using transition metal ions present in the active site. However, in the absence of this enzyme, the reaction becomes very slow (Adwas *et al.*, 2019).

SODs are classified into three distinct groups according to their binding metal cofactors and cellular location: copper-zinc SOD (Cu/Zn-SOD or SOD1), which is a cytoplasmic enzyme; manganese SOD (Mn-SOD or SOD2), which is a mitochondrial matrix enzyme, and extracellular SOD (EC-SOD or SOD3) (Table 4) (Hong *et al.*, 2018; Younus, 2018; Singh *et al.*, 2019). The presence of specific SOD isoforms supports the importance of maintaining redox homeostasis between cellular behaviours. Changes in SOD activity in a particular behaviour can lead to the generation of an H_2O_2 concentration gradient and subsequently activate redox-sensitive pathways (Hong *et al.*, 2018).

SOD1 is the main intracellular antioxidant enzyme, distributed in the cytoplasm, nucleus, and cell membrane. Its main function is to regulate basal OS levels by neutralising $O_2^{\bullet-}$ produced in the mitochondria and cytosol (Trist *et al.*, 2021). Its enzymatic activity depends on the presence of Cu and Zn. Zn is only related to the molecular structure of the enzyme and has no catalytic activity; however, it requires catalytic Cu to eliminate $O_2^{\bullet-}$ (Zheng *et al.*, 2023).

SOD2 is an enzyme consisting of a homotetramer containing mitochondrial Mn. It is present in peroxisomes and the mitochondrial matrix, making it an enzyme considered essential for life. Furthermore, Mn is related to the catalytic activity of enzymes (Chang *et al.*, 2020; Islam *et al.*, 2021). It is initially synthesised in the cytoplasm and then transported to the mitochondria via signal peptides that intervene in the disproportionation of O_2 produced by the respiratory enzyme chains. It is found in all mitochondria and cellular fluids, except erythrocytes, and its molecular weight varies according to distribution and source (Zheng *et al.*, 2023). SOD2 is the enzyme responsible for the elimination of $O_2^{\bullet-}$. It is inducible by EO, hyperoxia, environmental pollutants such as cigarette smoke or O_3 , and by inflammatory cytokines (Chang *et al.*, 2020; Janciauskiene, 2020).

SOD3 also binds to Cu and Zn ions and is anchored to the extracellular matrix (Trist *et al.*, 2021). It is a homotetramer consisting of two dimers linked by disulphide bonds in most species and is distributed in the blood, lymph, synovial fluid, and tissues. Its main function is to eliminate ROS produced by metabolism in the body and protect against destruction caused by $O_2^{\bullet-}$ radicals in both the internal and external environments (Zheng *et al.*, 2023).

In addition, it inhibits the activation of vascular NO by eliminating $O_2^{\bullet-}$, thus playing an essential role in vascular maintenance and blood pressure, preventing pathological conditions involving vascular dysfunction (Wang *et al.*, 2018). SOD3 gene polymorphisms have been linked to various diseases such as DM1, heart disease, acute lung injury, and chronic obstructive pulmonary disease (Janciauskiene, 2020).

The main source of SOD enzymes is naturally in the body, however, their levels decrease as the body ages (Younus, 2018), which is why the consumption of other natural sources is encouraged, mainly foods such as cabbage, Brussels sprouts, wheatgrass, barley, and broccoli. Likewise, the consumption of SOD supplements has been suggested (Rosa *et al.*, 2021). While Rosa *et al.* (2021) mention that they are useful in a variety of pathophysiological conditions, Balendra & Singh (2021) mention that it has been discovered that, unfortunately, SOD molecules are deactivated and become bioinactive when they pass through the gastrointestinal tract once they encounter acids and digestive enzymes.

SOD plays a protective role in neurodegeneration, and the properties of these antioxidants are beneficial in various pathophysiological conditions, protecting the immune system, reducing premature tissue ageing, and preventing diseases such as cancer, diabetes, cardiovascular problems, neurodegenerative disorders, and chronic inflammation (Balendra & Singh, 2021; Islam *et al.*, 2021).

Box 31

Table 4

Types and characteristics of SOD

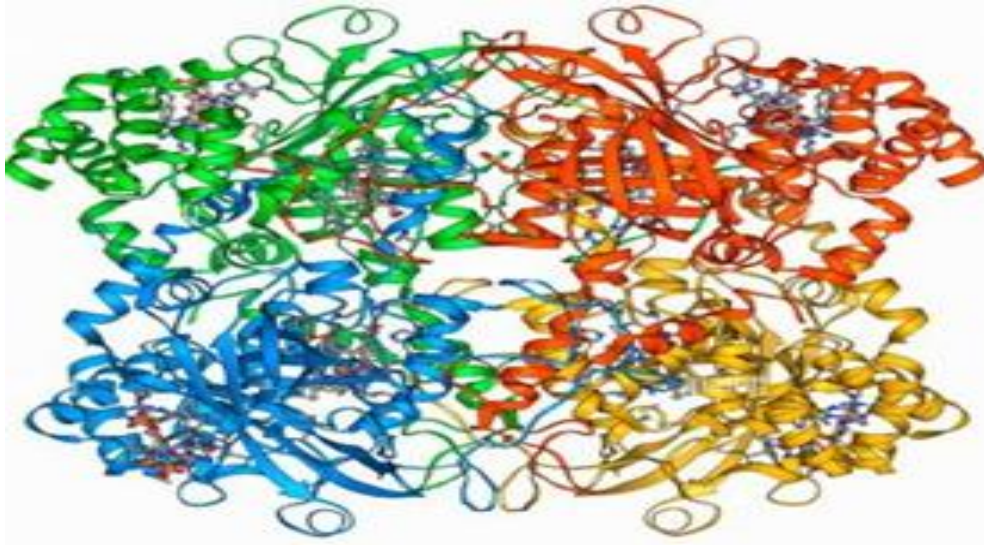
Type	Location	Metal cofactor	Combination
SOD1 (Cu/ZnSOD)	Cytoplasm, mitochondrial membrane space and others (nucleus, lysosomes and peroxisomes)	Cu ²⁺ (catalyst type) Zn ²⁺ (stable form)	The two subunits are mainly held together by hydrophobic and electrostatic interactions; Cu and Zn form coordination bonds with the histidine side chain in the active site.
SOD2 (MnSOD)	Mitochondrial matrix	Mn ³⁺ (catalyst type)	The Mn ion is coordinated with three histidine side chains, one aspartic acid side chain and one H ₂ O molecule or one •OH group (depending on the oxidation state of Mn).
SOD3 (EC-SOD)	Extracellular matrix, cell surface, and extracellular fluid	Cu ²⁺ (catalyst type) Zn ²⁺ (stable form)	The active sites of Mn-SOD and Fe-SOD have the same type of amino acids coordinated with metal ions..

Zheng et al. (2023).

3.1.2. Catalase

CAT is an oxidoreductase enzyme that plays a fundamental role in neutralising ROS. These are a group of metalloenzymes capable of catalysing the decomposition of H₂O₂ (Katiyar & Kumar, 2019), which is generated as a by-product of aerobic respiration, preventing its toxic effects. making it a key antioxidant defence enzyme in organisms (Kaushal *et al.*, 2018; Sandamalika *et al.*, 2021). It is the second most abundant enzymatic antioxidant after SOD (Hadwan, 2018).

Its structure is a tetramer of four polypeptide chains, each more than 500 amino acids in length (Kaushal *et al.*, 2018; Zinellu & Mangoni, 2021) and contains four porphyrin heme (iron) groups as a prosthetic group, which is essential for catalysis, biological activity and e- transfer in other heme-containing proteins (Tehrani & Moosavi-Movahedi, 2018) that allow the enzyme to react with H₂O₂ and NADPH as a cofactor, preventing the auto-oxidation of the enzyme (Fig. 28) (Sandamalika *et al.*, 2021).

Box 32

Figure 28

Structure of catalase

Nandi et al. (2019).

The main function of CAT is to break down H_2O_2 into H_2O and O_2 (Eq. 29), thereby alleviating the OS caused by this substrate (Shin *et al.*, 2018; Milek, 2020; Islam *et al.*, 2021). It is an enzyme that regulates H_2O_2 metabolism and is activated when cellular peroxide concentrations exceed physiological levels. It is considered an extremely efficient enzyme because one catalase molecule is capable of hydrolysing millions of H_2O_2 molecules per second (Ifeanyi, 2018; Kaushal *et al.*, 2018; Katiyar & Kumar, 2019). It can also catalytically eliminate ONOO⁻ (Galasso *et al.*, 2021) and serves as an auxiliary to GPx (Tehrani & Moosavi-Movahedi, 2018).



CAT exerts its effect at various concentrations of H_2O_2 . At high levels, two molecules of H_2O_2 are converted in each cycle known as catalytic activity, in which CAT decomposes H_2O_2 in two steps (Gebicka & Krych-Madej, 2019; Gerrard *et al.*, 2019). CAT is initially oxidised to a hypervalent iron intermediate, known as compound I (Cpd I) (Mahomoodally *et al.*, 2022), which is expressed in photosynthetic tissues and regulated by light (Meitha *et al.*, 2020). Subsequently, Cpd I is reduced back to its resting state by a second H_2O_2 molecule, an external donor of an e⁻ or hydrogen atom, resulting in the formation of compound II (Cpd II) (Eq. 30), which is not effectively reduced to the native enzyme and therefore its accumulation leads to the inactivation of catalase (Gebicka & Krych-Madej, 2019) and is widely expressed in vascular tissue (Meitha *et al.*, 2020).

It can also form another intermediate product known as Compound III (Cpd III), which structurally resembles the oxy forms of myoglobin and haemoglobin (Gebicka & Krych-Madej, 2019) and is found predominantly in seeds (Meitha *et al.*, 2020). On the other hand, at low concentrations of H_2O_2 , the function of CAT is less specific and induces the peroxidase pathway in which various H donors such as alcohols, phenols, hormones, heavy metals, and nitrites act as a second molecule and are oxidised (Ec. 31) (Tehrani & Moosavi-Movahedi, 2018; Katiyar & Kumar, 2019).



CAT has high specificity for H_2O_2 , but low activity against organic peroxide (Meitha *et al.*, 2020). CAT activity is always directly proportional to the dissociation rate of H_2O_2 , i.e., as the concentration of H_2O_2 increases, CAT shows a greater contribution to its degradation (Hadwan, 2018; Shin *et al.*, 2018).

However, it can be affected by various factors such as temperature, pH, substrate concentrations, the presence of inhibitors, and environmental stress in plants, either increasing or decreasing, depending on the intensity and duration of the stress, as well as the specific characteristics of the environment (Meitha *et al.*, 2020; Milek, 2020). On the other hand, during stress, catalytic activity does not occur, CATs can directly dismutate H₂O₂, making them essential for ERO detoxification (Huchzermeyer *et al.*, 2022).

CAT is considered an essential and ubiquitous enzyme, closely regulated in a wide variety of living organisms, with both endogenous and exogenous sources (Sandamalika *et al.*, 2021). Endogenous sources are found in prokaryotic cells, especially in peroxisomes; eukaryotes, hepatocytes, erythrocytes, aerobic and anaerobic organisms (Hadwan, 2018; Shin *et al.*, 2018). It is also found in all organs, with high CAT activity detected in the liver, predominantly in the kidney and adipose tissue, intermediate in the lung and pancreas, and very low in the heart and brain (Ifeanyi, 2018; Gerrard *et al.*, 2019). On the other hand, its exogenous sources come from plants such as cotton, sunflower and pumpkin and from marine organisms (Mahomoodally *et al.*, 2022).

CAT is classified into three categories according to its physical and biochemical properties, structure, and function: monofunctional or typical catalases, catalase-peroxydases or atypical catalases, and pseudocatalases or manganese catalases (Fig. 29) (Grigoras, 2017; Mahomoodally *et al.*, 2022). Although all three categories catalyse the same reaction, their overall structures and active sites, as well as their reaction mechanisms, show significant variations. The CAT gene is located on chromosome 11 and consists of 12 introns (DNA sequences that help to manufacture proteins correctly) and 13 exons (regions of the genome that help to encode proteins) that encode a single protein of 526 amino acids (Galasso *et al.*, 2021).

Box 33

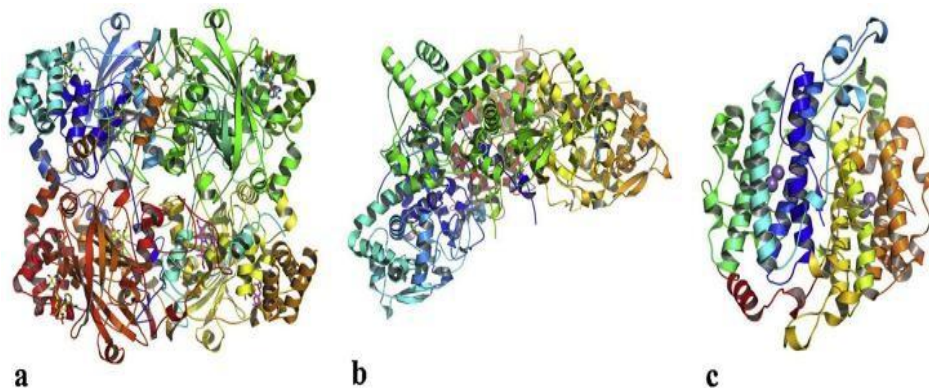


Figure 29

Structures representative of the types of catalases: a) monofunctional or typical catalase, b) catalase-peroxydases or atypical catalases, c) pseudocatalases or manganese catalases.

Grigoras (2017)

Typical catalases are the original class of catalases, contain haem prosthetic groups, and are found ubiquitously in aerobic organisms, mainly humans, animals, plants, and microorganisms (Nandi *et al.*, 2019; Sandamalika *et al.*, 2021). Catalase-peroxydases, unlike typical catalases, are not glycoproteins; they are homodimers present in fungi, bacteria and archaea (Gebicka & Krych-Madej, 2019). They are more sensitive to inactivation by pH and temperature and have a single functionally active channel, making their catalytic activity less efficient than typical catalases, but they have a better affinity for their substrate H₂O₂ (Glorieux & Calderon, 2017).

Manganese catalases are enzymes found exclusively in bacteria, eubacteria and archaea (Glorieux & Calderon, 2017). They are composed of six subunits containing a manganese core instead of a ferric core, which is why they are also known as non-haem catalases (Galasso *et al.*, 2021). They are characterised by the use of two manganese ions in the active site and can form oligomeric structures. They do not share significant similarities with either typical catalases or catalase-peroxydases (Glorieux & Calderon, 2017), as they exhibit lower specific activities (Grigoras, 2017). For example, they catalyse a two-step reaction like typical catalases, however, no reactive intermediate is formed (Galasso *et al.*, 2021).

As mentioned above, CAT plays an important role in regulating the cellular level of H_2O_2 , and its catabolism protects cells from oxidative attack (Nandi *et al.*, 2019). It has therefore been recognised as an important biomarker of OS (Mahomoodally *et al.*, 2022). Its deficiency or malfunction is associated with various diseases such as diabetes, CVD, hypertension, anaemia, AD, atherosclerosis, neurological and inflammatory diseases, carcinogenesis, metabolic syndrome, and ageing (Hadwan, 2018; Nandi *et al.*, 2019).

3.1.3. Glutathione

GSH is a low molecular weight tripeptide consisting of three amino acids, γ -glutamyl-cysteinyl-glycine (Fig. 30) (Flohé, 2022), found in abundance in all cellular compartments such as the nucleus, mitochondria, cytoplasm, cytosol, chloroplasts, and ER. (Huchzermeyer *et al.*, 2022).

Box 34

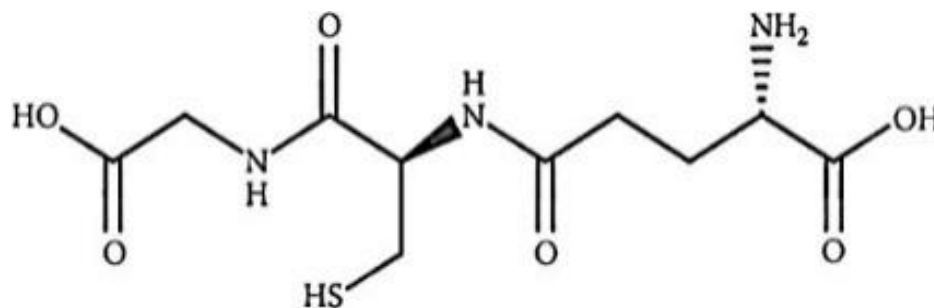


Figure 30
Structure of glutathione

Flohé (2022).

GSH is found in high concentrations and performs a variety of important functions such as cell differentiation, cell development and division, senescence and programmed cell death, xenobiotic detoxification, metabolite formation, regulation of enzyme activity, and protein and nucleotide synthesis (Huchzermeyer *et al.*, 2022). As an antioxidant, it has the ability to help maintain cellular redox homeostasis, reduce ROS and RNS during enzymatic and non-enzymatic reactions, form DNA precursor deoxyribonucleotides, transport and store certain amino acids. In addition, it is characterised by regenerating other oxidised antioxidants such as vitamins C and E, participating in the recovery of peroxidised lipids and maintaining the sulphhydryl fractions of proteins in reduced form (Janciauskiene, 2020). The GSH system includes glutathione S-transferase (GST), glutathione reductase (GR), and glutathione peroxidase (GPx) (Fig. 31). GSTs are another class of enzymatic antioxidants that participate in the breakdown of lipid peroxides, while GPx shows high activity with H_2O_2 and organic hydroperoxides, which aids in the cellular detoxification mechanism (Adwas *et al.*, 2019). When GSH oxidises, it forms glutathione disulphides (GSSG), which can be reduced back to GSH with the help of GR using NADPH (Flohé, 2022).

Box 35

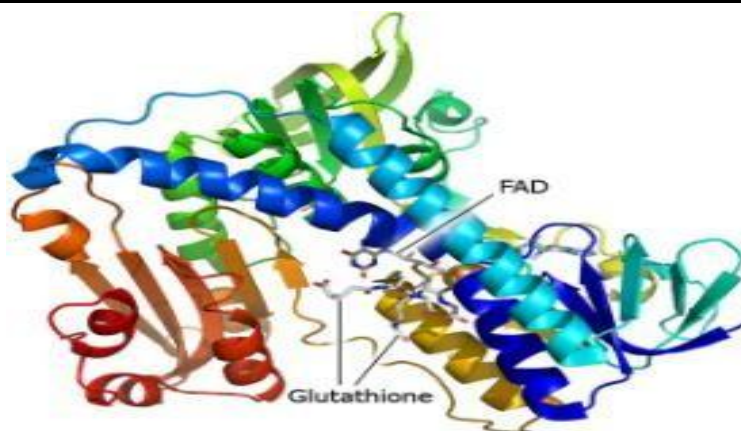
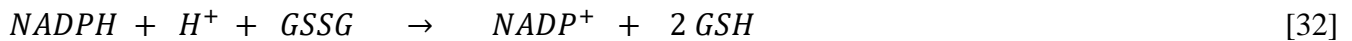


Figure 31
Structure of glutathione reductase

Authoritative neurology information (2024)

GR is a flavoprotein containing two molecules of flavin adenine dinucleotide (FAD) as a prosthetic group that is reducible by NADPH (Fig. 31). It is a ubiquitous, thermostable enzyme present in all organisms containing GSH, eukaryotic and prokaryotic cells, and is an almost universal enzyme. Its main function is to catalyse the reduction of GSSG to GSH in an NADPH-dependent reaction (Eq. 32), allowing the cell to maintain adequate levels of cellular GSH (Adwas *et al.*, 2019). GSH, through the action of GR, will be used by GPx to reduce H₂O₂ and lipoperoxides (L-OOH) (López-Quesada, 2018).



GR has different isoforms present in the cytosol of cells, both in prokaryotic and eukaryotic organisms, so they have differences in their structure, which depends on the organism in which they are found. The GR subunits in humans are linked by a Cys disulphide bond (López-Quesada, 2018). GPx are a family of enzymes that prevent the formation of FR from hydroperoxide, making them antioxidant enzymes (Flohé *et al.*, 2022).

They have a tetrameric structure with one Se atom per unit, making them the first Se-dependent protein, whose main function is to transfer H⁺ to ROS (Quisirumbay-Gaibor & Vélchez, 2019). Initially, it was believed that their function was to protect the haemoglobin in red blood cells from oxidative denaturation by reducing H₂O₂ with GSH (Flohé *et al.*, 2022). It is currently used as a powerful antioxidant because they are isoenzymes that catalyse the destruction of H₂O₂ generated during cellular oxidative metabolism and convert lipid peroxides into harmless molecules before they can form FR or attack cell membranes (Quisirumbay-Gaibor & Vélchez, 2019; Sutrisno *et al.*, 2022).

GPx is a very important family of enzymes produced in the cytosol. Its main biochemical function is to catalyse the reduction of H₂O₂ to H₂O and lipid hydroperoxides by converting GSH to GSSG, thus protecting the body against oxidative damage, inactivation and damage to biological molecules, cross-linking, fragmentation and peroxidation (Al-Madboly *et al.*, 2020; Huchzermeyer *et al.*, 2022; Zhao *et al.*, 2022). It also participates in the physiological adjustment of peroxide concentrations in intracellular and extracellular behaviours and can act as repair enzymes and scavengers (Janciauskiene, 2020).

The GPx family consists of eight isoenzymes (GPx1-8), of which five members (GPx1-4 and GPx6) are selenocysteine (SeCys)-containing proteins and three members (GPx5, GPx7 and GPx8) are Cys-containing proteins (Chang *et al.*, 2020; Zinellu & Mangoni, 2021). These isoenzymes are encoded by different genes and differ in their molecular structure, subcellular localisation, substrate specificity, enzymatic characteristics and biological function (Zhao *et al.*, 2022).

GPx1 is the most abundant GPx, is ubiquitously expressed in many tissues and is mainly distributed in the cytosol and mitochondria of erythrocytes, liver, lungs and kidneys. It uses GSH as a substrate to catalyse the reduction of H₂O₂, lipid peroxides and ONOO⁻, which contributes to decreasing intracellular ROS (Gerrard *et al.*, 2019; Zhao *et al.*, 2022). The GPx1 gene is located on chromosome 3 and consists of two exons (Brigelius-Flohé & Flohé, 2020).

GPx2 is an intestinal enzyme, found mainly in the gastrointestinal tract and observed in many endothelial cells, especially in malignant tissues and pluripotent stem cells. It is the enzyme responsible for protecting against the toxicity of dietary lipid hydroperoxides (Gerrard *et al.*, 2019; Ramblado, 2022).

The GPx2 gene is located on chromosome 14 and contains one intron (Brigelius-Flohé & Flohé, 2020). GPx3 is a selenoprotein and the only extracellular enzyme, found especially in plasma (Ramblado, 2022), characterised by sharing functional similarities with GPx1 (Brigelius-Flohé & Flohé, 2020), as its main function is to catalyse the detoxification of hydroperoxides, including H₂O₂ and soluble lipid hydroperoxides, using GSH, which it can use as substrates.

In addition, GPx3 acts as a tumour suppressor and pro-survival protein (Chang *et al.*, 2020). The GPx3 gene is located on chromosome 5 and is composed of five exons (Brigelius-Flohé & Flohé, 2020).

GPx4 is a Se-dependent enzyme found in the cytoplasm, nucleus, and mitochondria. It is characterised by being the only antioxidant enzyme capable of repairing lipid peroxides, which is why it has a high preference for lipid hydroperoxides to protect cells from LPO and cell membranes from oxidative damage (Li *et al.*, 2018; Ramblado, 2022; Zhao *et al.*, 2022). It also contributes to the resolution of inflammation by eliminating ROS (Li *et al.*, 2018).

The GPx4 gene is located on chromosome 19 and consists of seven exons. It is expressed in three different forms, each with its own transcription and translation start sites (Brigelius-Flohé & Flohé, 2020).

The catalytic efficiency of GPx is remarkable regardless of its Sec or Cys content (Brigelius-Flohé & Flohé, 2020). A decrease in its activity is associated with an increase in H₂O₂ movement, which leads to the activation of inflammatory pathways and direct tissue damage. Furthermore, a deficiency of Se over very long periods or its absence decreases its action against peroxides, leading to deterioration of the membrane cytoskeleton and morphological alterations, which is why it is considered a risk factor for diseases such as cancer, liver cirrhosis, and muscular dystrophy (Al-Madbolly *et al.*, 2020).

GSH can act directly as an antioxidant to protect cells against ROS and pro-oxidants. It also acts as a cofactor for various antioxidant and detoxifying enzymes, including GPx, GST, and glyoxalase, which depend on GSH to carry out their activities of neutralising ROS and detoxifying harmful compounds. It also belongs to the defence system that protects the body against OS (Averill-Bates, 2023). Overexpression of GRx provides protection against damage caused by ROS, which highlights its importance in antioxidant defence and the response to OES in a variety of living organisms (López-Quesada, 2018). However, GRx deficiency is characterised by haemolysis due to the increased sensitivity of erythrocyte membranes to H₂O₂, which contributes to OES and plays a key role in the pathogenesis of various diseases (Adwas *et al.*, 2019).

The GPx/GRx system has been shown to be related to other antioxidant systems, such as the SOD and CAT systems. Although the two systems do not function in parallel, CAT acts in the presence of high concentrations of H₂O₂, while GPx acts at low concentrations (Galasso *et al.*, 2021). This collaboration between different antioxidant enzymes allows for a more complete defence against ROS by eliminating different ROS under various environmental conditions (López-Quesada, 2018).

3.2. Exogenous antioxidants

3.2.1. Polyphenols

The most common antioxidants in our diet are polyphenols (Abbas *et al.*, 2017). A phenol is an •OH group bound to one or more aromatic rings. When a phenyl group has more than one •OH, it is called a polyphenol (Ayala-Mata *et al.*, 2019) and is chemically represented as C₆H₅OH (Fig. 32) (Swallah *et al.*, 2020).

Box 36

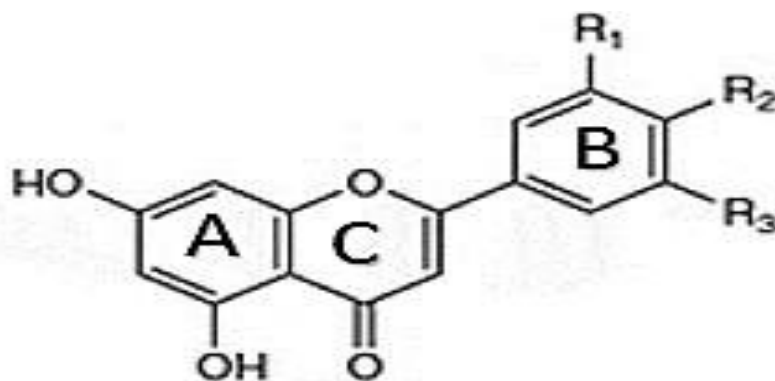


Figure 32

Structure of flavonoid polyphenol

Abbas *et al.* (2017).

Polyphenols are the most numerous and widely distributed group of bioactive molecules in plant-based foods that form part of the human diet, although they are not considered nutrients (Abbas *et al.*, 2017). They are characterised as secondary metabolites of plants derived from the shikimate pathway (a crucial target for the development of antimicrobial agents and herbicides) and phenylpropanoids (Lizárraga-Velázquez *et al.*, 2018; Hano & Tungmunnithum, 2020; Almeida *et al.*, 2023).

They have diverse structures and functions, their main function being their antioxidant activity due to their ability to capture ROS and RNS, which confers health-promoting properties by preventing diseases associated with OE such as ECD (Stagos, 2019; Swallah *et al.*, 2020), are metabolised and absorbed mainly in the small intestine, colon and liver, although rapid absorption in the gastric mucosa may also occur (Kumar & Goel, 2019; Abd El-Hack *et al.*, 2023). Due to the diversity of their structures, polyphenols are considered to be very efficient antioxidants, even more so than others (Belščak-Cvitanović *et al.*, 2018).

There are more than 8,000 different polyphenols as main components of foods such as fruits, vegetables, cereals and derivatives (Magrone *et al.*, 2019), their structural diversity implies the existence of a wide variety of molecules belonging to this group, ranging from simple structures to complex compounds, which can be classified in different ways: by their source of origin, natural distribution, biological function and chemical structure (Belščak-Cvitanović *et al.*, 2018).

Polyphenols can be divided structurally into two main classes: flavonoids, which include flavones, flavonones, flavonols, isoflavones, and phenolic acids such as hydroxybenzoic and hydroxycinnamic acids (Ayala-Mata *et al.*, 2019). However, the basic classification of polyphenols includes five main classes: flavonoids, phenolic acids, lignans, stilbenes and others, which are in turn divided into subclasses (Fig. 33) (Belščak-Cvitanović *et al.*, 2018).

Other authors classify them into two large groups, including other compounds: flavonoids, which include flavonols, flavones, isoflavones, flavonones, dihydroflavonols, anthocyanins, and chalcones; and non-flavonoids, which include phenolic acids, stilbenes, saponins, anthocyanidins, tannins and various compounds such as lignans and coumarins (Stagos, 2019; Abd El-Hack *et al.*, 2023).

They can also be classified according to their degree of solubility: H₂O-soluble compounds such as phenolic acids, flavonoids, phenylpropanoids, and quinones; and H₂O-insoluble compounds such as condensed tannins, lignins, and hydroxycinnamic acids, which are bound to the cell wall of plant cells (Valencia-Avilés *et al.*, 2017).

This classification is important because of the nutritional composition or constituents, as their solubility and digestibility are crucial for their effective use in the gastrointestinal tract and in various physiological functions. When polyphenols are insoluble, they cannot be digested and are totally or partially excreted in the faeces, while soluble compounds are absorbed through the intestines into the bloodstream as metabolites (Swallah *et al.*, 2020).

Finally, there is a classification according to the number of phenolic rings and the structural elements linked to the basic units, the main groups of phenolic compounds being flavonoids, phenolic acids, hydrolysable tannins, condensed tannins, stilbenes and lignans (Valencia-Avilés *et al.*, 2017).

Box 37

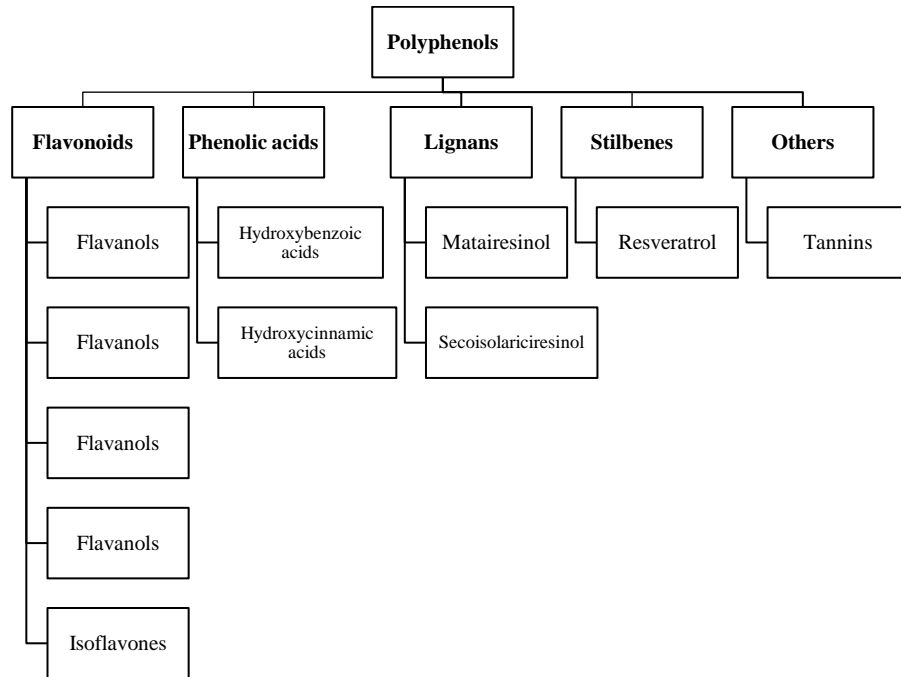


Figure 33

Classification de base des polyphénols

Source: Own Creation

Flavonoids are the most abundant class of polyphenols. They are low molecular weight compounds necessary for plant development and are formed by two benzene rings attached to three carbon atoms of the ring that form an oxygenated heterocycle (C6-C3-C6) known as rings A, B and C, respectively (Fig. 32) (Abbas *et al.*, 2017) and are derived from essential aromatic amino acids, phenylalanine and tyrosine, which are discussed in the chapter on flavonoids (Valencia-Avilés *et al.*, 2017). Phenolic acids are types of aromatic compound acids that have a carboxylic acid group and a benzene ring (Olszowy, 2019). They are mainly divided into two subgroups: hydroxybenzoic acid and hydroxycinnamic acid, which have main chains of C6-C1 and C6-C3, respectively (Fig. 34). (Hano & Tungmannithum, 2020). They have a phenol residue and a resonance-stabilised structure that causes H atom donation to result in antioxidant properties through the elimination of RL. Their potential depends on the number and position of the –OH in a particular phenolic compound (Kumar & Goel, 2019). They are found ubiquitously, mainly in the peel, seeds and skins of fruits and vegetable leaves (Abbas *et al.*, 2017; Kumar & Goel, 2019).

Box 38

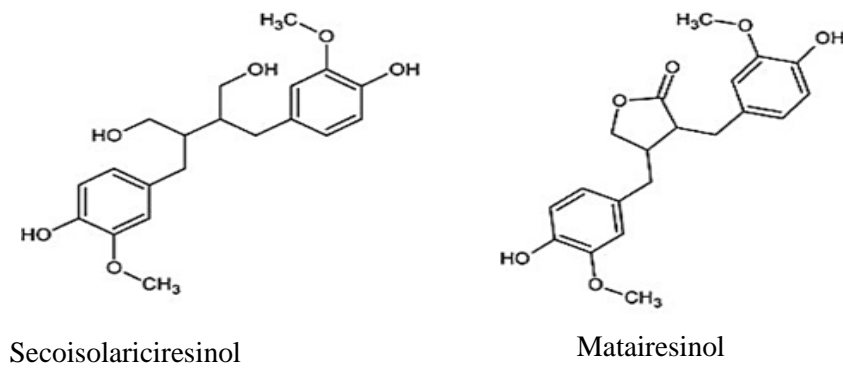


Figure 34

Chemical structure of the main phenolic acids.

-Velázquez *et al.* (2018).

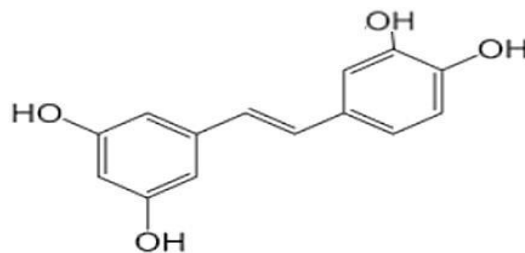
Lignans belong to the group of diphenolic compounds derived from the combination of two C6C3 phenylpropanoid units. Among the main lignan compounds are secoisolariciresinol, lariciresinol, matairesinol, pinoresinol, medioresinol, and syringaresinol (Durazzo *et al.*, 2018). They differ in the type of bond between the two units and the changes that occur after dimerisation (Hano & Tungmannithum, 2020). The lignans commonly found in foods are secoisolariciresinol and matairesinol (Fig. 35) (Castro, 2019).

Box 39**Figure 35**

Chemical structure of the main lignans

Durazzo et al. (2018).

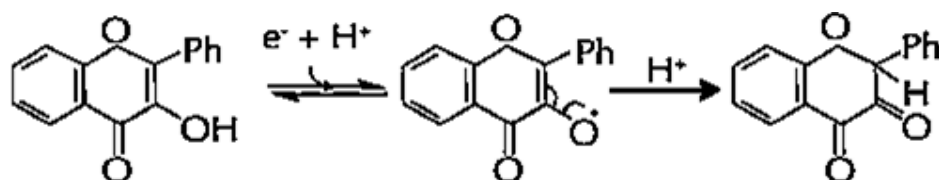
Stylbenes can occur in a wide variety of forms in the plant kingdom. Their molecular skeleton consists of two phenolic rings per C₆C₂C₆ ethane unit (Fig. 36). They can be classified into two groups: monomeric and oligomeric stilbenes, which in turn can be divided into subgroups. Their high structural diversity is a determining factor in their absorption rate and metabolism (El Khawand *et al.*, 2018; Magrone *et al.*, 2019). The most studied stilbene has been resveratrol, which has various biological activities, including antioxidant, anti-inflammatory and antiproliferative effects (El Khawand *et al.*, 2018).

Box 40**Figure 36**

Chemical structure of stilbene

Ayala-Mata et al. (2019).

As mentioned above, the main function of polyphenols is their antioxidant activity, which is carried out through four chemical pathways: transfer of e⁻ coupled to H⁺, transfer of e⁻ and transfer of H⁺, sequential transfer of e⁻ with loss of H⁺, and formation of adducts (Olszowy, 2019). Antioxidant activity is related to their redox property, where they trap and dissipate free radicals. Part of the phenol acts as a reducing agent, which transfers an H⁺ atom from an aromatic –OH to an RL, resulting in the formation of a phenoxyl radical that is less harmful to cells (Fig. 37). In addition, it has the ability to chelate the ¹O₂ radical and metal ions, mainly Fe and Cu, which in their free state tend to combine with FR through Fenton and Haber-Weiss reactions, which inhibit the formation of FR such as O₂•⁻. They also have the ability to inhibit LDL (Soledad, 2017; Ordoñez-Gómez *et al.*, 2018; Luo *et al.*, 2022).

Box 41**Figure 37**

Antioxidant mechanism of action of polyphenols

Ayala-Mata et al. (2019).

According to Olszowy (2019), the antioxidant capacity of phenolic compounds depends on the number of -OH groups in the ring structure and their position; the greater the number of -OH groups and the position of the para position, the better their antioxidant properties.

In addition to antioxidant defence, polyphenols play a protective role against various environmental attacks such as ultraviolet radiation and temperature (Magrone *et al.*, 2019). They also help regulate growth, antimicrobial activity, pH, metabolism, and induction of the dormancy period (Olszowy, 2019). Similarly, some polyphenols such as tannins and lignins are responsible for the aroma and colour of fruits, vegetables, seeds and nuts (Hano & Tungmunnithum, 2020).

Humans acquire polyphenols through their diet. Flavonoids are generally the most abundant class of polyphenols found in food, while phenolic acids are the second most abundant component (Castro, 2019). The main sources are fruits, vegetables, and beverages derived from certain plants, containing various types of polyphenols. Among the fruits and vegetables are apples, oranges, tangerines, cherries, pears, grape extracts, lemons, tomatoes, onions, broccoli, kale, among others (Lizárraga-Velázquez *et al.*, 2018); and beverages such as tea, coffee, red wine, and fruit juices such as pomegranate juice. They can also be found in some nuts, legumes, cereals, chocolate, mint, and cinnamon (Table 5) (Magrone *et al.*, 2019; Rudrapal *et al.*, 2022).

Box 42

Table 6

Polyphenol content of major food sources.

Flavonoids	Flavanols	Apples, cherries, grapes, pears, nectarines, blueberries, blackberries, raspberries, cereals, legumes, cocoa powder, dark chocolate, red wine, black/green tea, beer.	Kay <i>et al.</i> , 2017; Belščak-Cvitanović <i>et al.</i> , 2018; Luo <i>et al.</i> , 2022
	Flavanones	Dried mint, oregano, citrus fruits, oranges, tangerines, limes, lemons, grapefruit juice, orange juice.	Barreca <i>et al.</i> , 2017; Castro, 2019; Swallah <i>et al.</i> , 2020
	Flavones	Celery seed, dried mint, oregano, carrots, celery, whole wheat flour, olives, parsley, thyme.	Kay <i>et al.</i> , 2017; Belščak-Cvitanović <i>et al.</i> , 2018; Swallah <i>et al.</i> , 2020
	Flavonols	Apples, plums, spinach, blueberries, red onions, saffron, oregano, peppers, tomatoes, lettuce, broccoli, tea, red wine.	Kay <i>et al.</i> , 2017; Belščak-Cvitanović <i>et al.</i> , 2018; Castro, 2019
	Isoflavones	Grape seeds and skins, soybeans, soy flour, soy milk or yoghurt, alfalfa.	Kay <i>et al.</i> , 2017; Castro, 2019; Swallah <i>et al.</i> , 2020
	Anthocyanins	Blueberries, blackberries, cherries, red grapes, strawberries, raspberries, red apples, plums, black olives, red wine.	Kay <i>et al.</i> , 2017; Castro, 2019; Rudrapal <i>et al.</i> , 2022
Phenolic acids	Hydroxybenzoic acids	Clove, pomegranate juice, raspberry, mango, blackberry, blueberry, strawberry.	Belščak-Cvitanović <i>et al.</i> , 2018; Swallah <i>et al.</i> , 2020
	Hydroxycinnamic acids	Apple, blueberry, cherry, pear, orange, lemon, melon, mint, dried rosemary, oregano, thyme, spinach, lettuce.	Belščak-Cvitanović <i>et al.</i> , 2018; Castro, 2019; Swallah <i>et al.</i> , 2020
Lignans	Matairesinol	Sesame seeds, linseed, sunflower seeds, raisins	Castro, 2019
	Secoisolaricire-sinol	Pumpkin, potato, kiwi, linseed, flax seeds, peanuts	Castro, 2019; Swallah <i>et al.</i> , 2020
Stylbenes	Resveratrol	Red wine, blueberry, grape, redcurrant, strawberry, peanut, pistachio.	Kay <i>et al.</i> , 2017; Castro, 2019; Ayala-Mata <i>et al.</i> , 2019
Others	Tannins	Grape seeds and skins, blackberries, apples, plums, olives, walnuts, lentils, wine, tea, coffee, cocoa, chocolate	Belščak-Cvitanović <i>et al.</i> , 2018

The polyphenol content of various dietary sources varies depending on the source itself (Table 6) and its bioavailability is affected by factors such as chemical structure, genotype, species, cultivation techniques, use of fertilisers, environmental conditions, changes in sun exposure, degree of ripeness, soil composition, geographical location and storage conditions (Valencia-Avilés *et al.*, 2017; Abd El-Hack *et al.*, 2023). Likewise, processing techniques can alter their content; on the one hand, boiling and steaming foods can concentrate them, while frying them decreases them (Stagos, 2019; Abd El-Hack *et al.*, 2023).

Box 43**Table 6**

Polyphenol content of major food sources

Food (g)	Polyphenol content (mg/100)
Grape	893
Lemon	843
Kiwi	791
Lima	751
Raspberry	670
Blueberry	327
Pink guava	247
Cutter	199
Sour cherry	156
Pomegranate	147
Pear	125
Green apple.	118
Yellow apple.	100
Pineapple	94
Sweet cherry	79

Swallah et al. (2020)

The average consumption of polyphenols varies between countries and populations, generally related to sociodemographic factors and lifestyles. The average intake is between 25 mg and 1 g per day, which is 10 times higher than vitamin C and 100 times higher than vitamin E. In Mexico, the average consumption is reported to be approximately 684 mg/day (Castro, 2019).

Polyphenols are characterised by their beneficial effects as cardioprotective, neuroprotective, anticancer, antidiabetic, anti-lipid peroxidation, anti-allergic, antiatherogenic, antitumour, anti-inflammatory, detoxifying, antimicrobial, and vasodilator agents (Ordoñez-Gómez *et al.*, 2018), thereby helping to prevent inflammatory, cardiovascular, neurodegenerative and chronic diseases such as diabetes, cancer and asthma (Chaaban *et al.*, 2017).

Conversely, if their intake is high or between 1 and 5% of the total daily diet, they can reach toxic concentrations and cause adverse health effects such as antinutritional effects due to their ability as chelating agents, interfering with iron absorption and causing anaemia (Valencia-Avilés *et al.*, 2017).

3.2.2. Flavonoids

Flavonoids are an essential and diverse class of secondary plant metabolites present in leaves, flowers, roots, and fruits in varying concentrations (Mathesius, 2018; Chagas *et al.*, 2022). They are the largest and most abundant group of natural polyphenolic compounds, derived from the aromatic amino acids phenylalanine and tyrosine. They are characterised by their low molecular weight, necessary for plant development, and act as chemical signals with effects on certain enzymes linked to plant physiology and metabolism (Valencia-Avilés *et al.*, 2017).

Their basic chemical structure consists of a 15-carbon skeleton (C6-C3-C6) comprising two aromatic rings called rings A and B, connected by a nearby pyran ring containing O₂ called ring C (Fig. 38) (Magrone *et al.*, 2019; Nakayama *et al.*, 2019; Rudrapal *et al.*, 2022). Ring B is usually attached to position 2 of ring C, but it can also be attached to position 3 or 4 (Ronsisvalle *et al.*, 2020).

Box 44

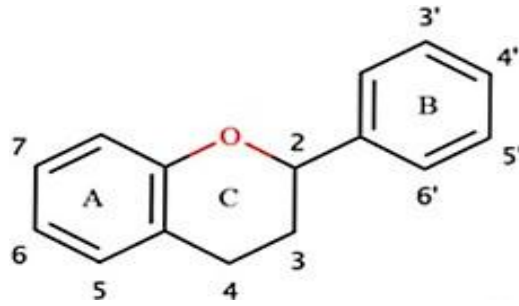


Figure 38

Basic chemical structure of flavonoids

Ronsisvalle et al. (2020).

Flavonoids are mainly found in the plant kingdom in vegetables, fruits, herbs and cereals, but they can also be found in dairy products and some beverages (Khan *et al.*, 2020; Rudrapal *et al.*, 2022), and fruits that contain them include red grapes, apples, lychees, pears, and blueberries (Al-Dashti *et al.*, 2018); citrus fruits such as oranges, limes, mandarins, and lemons (Testai & Calderone, 2017; Khan *et al.*, 2020); vegetables such as onions, parsley and celery (Dos Santos *et al.*, 2020), as well as beverages such as tea, red wine, cider and beer (Panche *et al.*, 2016) and other foods such as cocoa, walnuts, hops and oregano (Luo *et al.*, 2022).

The structural diversity of flavonoids leads to a wide variety of biological effects due to the different substitutions of carbon atoms (Zaragoza *et al.*, 2020). They are recognized as beneficial to the human body for their positive effects as antioxidants, anti-inflammatories, anti-apoptotics, antithrombotics, vasorelaxants, anticoagulants, antivirals, cardioprotective, antimutagenic, anticarcinogenic, antimicrobial, neuroprotective, chemoprotective, antiobesity, and antidiabetic (Akhlaghi *et al.*, 2018; Luo *et al.*, 2022) effects for the treatment and prevention of various chronic and neurological diseases (Wen *et al.*, 2017).

Flavonoids are characterized by their diverse biological functions, the main one being their antioxidant activity. They are capable of eliminating ROS, which depends largely on their structure, act as reducing agents in various reactions, activate enzymes that are antioxidant in nature, and can reduce the concentration of substances that play an active role in the production of ROS (Khan *et al.*, 2020; Muchtaridi *et al.*, 2024).

They can also exert inhibitory effects on some pro-oxidants such as NADPH oxidase, oxidants such as $O_2^{\bullet-}$ and H_2O_2 , and angiotensin-converting enzyme and endothelin 1. They can induce smooth muscle relaxation (vasodilation) through the prostacyclin pathway, independently of $\bullet NO$ formation (Al-Dashti *et al.*, 2018), can interact with $1O_2$ to reduce the risk of membrane lipid peroxidation, has the ability to chelate trace metals, and plays an important role in non-enzymatic protection against OS (Panche *et al.*, 2016; Huchzermeyer *et al.*, 2022; Muchtaridi *et al.*, 2024).

The antioxidant activity of flavonoids depends largely on their bioavailability (Zaragoza *et al.*, 2020), which is influenced by the arrangement of functional groups according to their structure, both the configuration and the total number of $-OH$. The configuration of the $-OH$ of ring B is the most important determinant for the elimination of ROS, so any modification of their structure, such as alkylation or glycosylation, leads to an increase or decrease in their antioxidant activity (Chaaban *et al.*, 2017; He *et al.*, 2017). Likewise, the physicochemical environment of their storage, such as light, oxygen, pH, temperature, and darkness, causes variations. Flavonoids exposed to light or oxygen undergo structural degradation. However, flavonoids in raw foods are stable to light because they are protected by the food matrix, while processed foods undergo photodegradation (Chaaban *et al.*, 2017).

Flavonoids act primarily as buffers, capturing FR with the formation of flavin radicals, which are much less reactive because the unpaired electrons are more delocalised (Fig. 39A). They can also chelate transition metal ions (iron and copper), which prevents the formation of ROS obtained by the Fenton reaction (Fig. 39B). Some flavonoids, such as catechin and quercetin, can directly capture ROS such as $O_2^{\bullet-}$, H_2O_2 and $HOCl$, which can be very harmful to lipids, proteins and DNA (De Luis & Aller, 2008).

Box 45

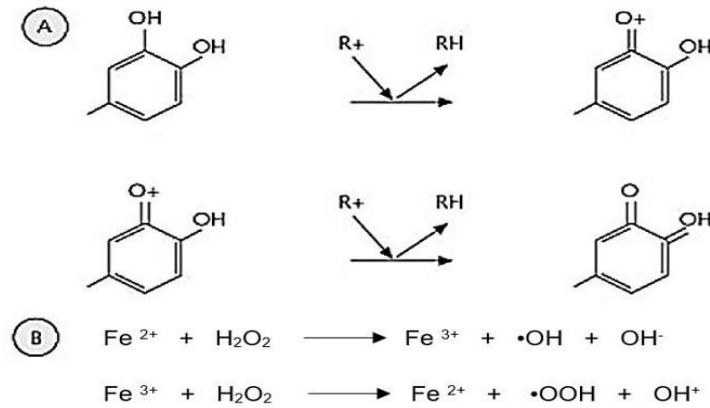


Figure 39

Reaction of flavonoids and free radicals. A) Capture of free radicals with formation of flavin radical; B) Iron chelation by flavonoids

De Luis & Aller (2008).

It is estimated that there are more than 9,000 different flavonoids in the plant kingdom (Yonekura-Sakakibara *et al.*, 2019), which are classified in different ways, according to their structure, including the absence of the C ring, hydroxylation pattern of rings A and B, oxidation state of the central carbon or C ring, structure and position of substitutions, position of the bond between ring B and ring C, the carbon of ring C connected to ring B, and the degree of unsaturation (Zaragozá *et al.*, 2020). According to their structure, they include flavonols, flavones, isoflavones, and anthocyanins (Huchzermeyer *et al.*, 2022), based on the oxidation state of the central carbon in flavanones, flavanols, flavonols, isoflavones, flavones, and anthocyanins (Fig. 40) (He *et al.*, 2017; Testai & Calderone, 2017). Depending on the degree of hydroxylation and the presence of a double bond in the heterocyclic pyron ring, they are classified into 13 classes, the most important being flavonols, flavanols, flavones, isoflavones, anthocyanidins or anthocyanins, and flavanones (Belščak-Cvitanović *et al.*, 2018). Depending on the number and position of hydroxyl groups, as well as functional groups, they can be classified into flavonols, flavones, flavanones, isoflavones, dihydroflavones, anthocyanidins, monomeric flavanols (catechins and leucoanthocyanidins), polymeric flavanols (proanthocyanidins) and, to a lesser extent, chalcones, dihydrochalcones, coumarins, aurones, biflavonoids and neoflavonoids (Akhlaghi *et al.*, 2018).

Other authors classify them differently. Khan *et al.* (2020) classify them as flavonols, flavones, flavanones, flavanols, anthocyanidins, isoflavones and chalcones, while Nakayama *et al.* (2019) divide them into 10 classes, which include flavanones, flavones, isoflavones, dihydroflavonols, flavonols, leucoanthocyanidins, anthocyanidins, flavanols, chalcones, and aurones.

Box 46

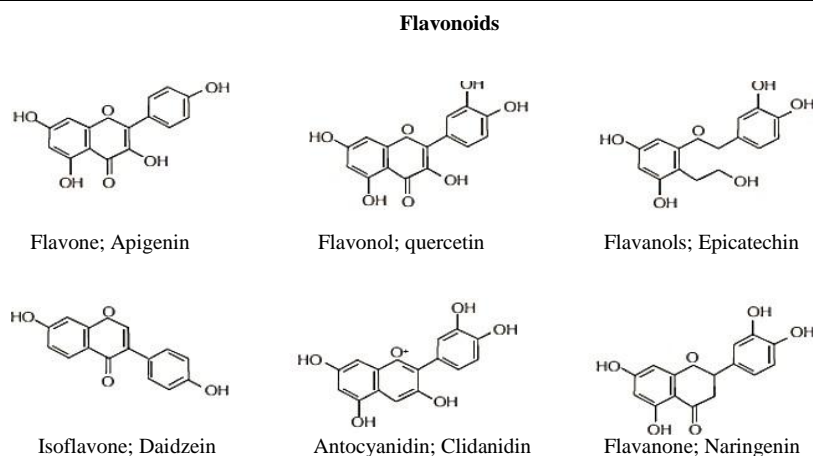


Figure 40

Structure of the main flavonoids.

Ayala-Mata et al. (2019)

Flavones and flavonols are the largest classes of flavonoids, with more than 2,000 known structures. Both groups are very similar, sharing a 2-phenyl-chromo-4-one structure composed of three C6-C3-C6 rings, two benzene rings (A and B) and an oxygen-containing ring with a C2-C3 double bond (C) (Fig. 41) (Dos Santos et al., 2020).

Box 47

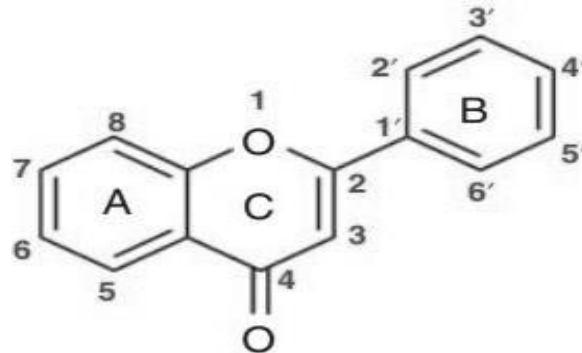


Figure 41

Chemical structure of flavones and flavonols.

Dos Santos et al. (2020).

Flavonols are the largest, most common and representative subgroup of flavonoids. They are a family of natural compounds derived from 2-phenyl-benzo- γ -porane that are distributed throughout the plant kingdom (Barreca et al., 2021). They are characterised by the presence of an oxo group at position 4, an –OH at position 3 of the C ring and a double bond between C2 and C3 in this same ring, which facilitates conjugation between rings A and B and strongly affects the redox properties of these compounds (Fig. 42) (Hano & Tungmunnithum, 2020).

Box 48

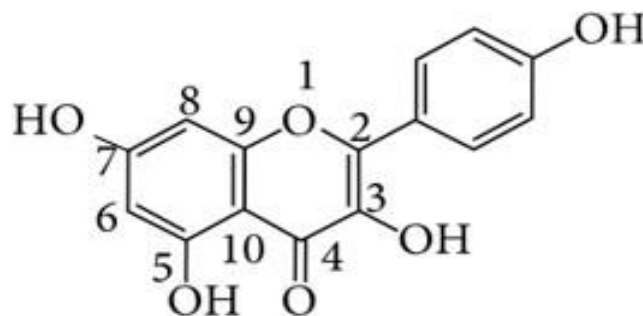


Figure 42

Chemical structure of flavonols.

Chagas et al. (2022)

The most studied flavonols are quercetin, kaempferol, and myricetin (Barreca et al., 2021), characterised by having an –OH at positions C-4, C-5, and C-7, although they differ in the distribution of –OH in ring B (Dos Santos et al., 2020). Flavonols are found in various fruits and vegetables, especially fruit skins, which are rich in this flavonoid because it is activated by light (Abbas et al., 2017). The main sources of quercetin are citrus fruits, apples, blueberries, leafy vegetables, onions and tubers, herbs and spices, tea, cocoa and wine. Kaempferol is found in apples, onions, cabbage, broccoli, tomatoes, strawberries, grapes, and tea, and myricetin is found in blackcurrants, grapes, blueberries, oranges, peppers, grape seeds, garlic, beans, wine, and tea (Abbas et al., 2017). Table 5 lists some foods that contain each subclass of flavonoids.

Flavones are one of the largest groups, characterised by a double bond between positions C-2 and C-3, a ketone group at position 4 and the union of ring B at C-2 (Ronsisvalle et al., 2020). Most of them have an –OH at position 5 of ring A (Fig. 43). (Hano & Tungmunnithum, 2020).

They are characterised by their structural diversity, which allows them to interact with a variety of molecules, establishing their functions in lipid oxidation, DNA and protein binding (Mathesius, 2018). They differ from flavonols by the absence of the –OH group in position 3 (Ronsisvalle *et al.*, 2020), although flavones and flavonols are very similar, in plants neither the oxidation of flavones to flavonols nor the reduction of these to flavones seems to occur (Barreca *et al.*, 2021). They are present in leaves, flowers and fruits mainly as glycosides, the most common being luteolin, found in foods such as carrots, cucumbers, peppers and olives, and apigenin, found in broccoli, celery, parsley, oregano, onions, peppers, corn and rice (Dos Santos *et al.*, 2020; Chagas *et al.*, 2022).

Box 49

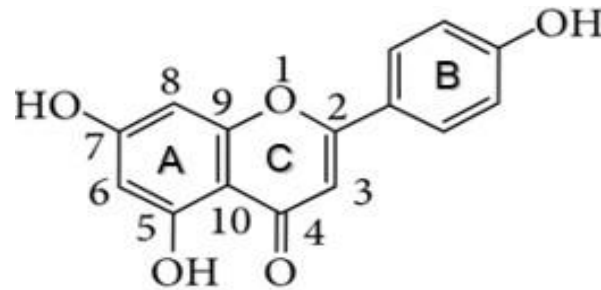


Figure 43

Chemical structure of flavones

Chagas et al. (2022)

Flavonols are characterised by the absence of a double bond between C-2 and C-3 and the absence of a carbonyl group in the C ring (C-4), while they have an –OH group at C-3 or C-4 (Fig. 44). A total of 121 flavonols and their derivatives have been found, distributed across 52 species and 29 families (Luo *et al.*, 2022), ranging from simple monomers known as catechins to oligomers called proanthocyanidins (responsible for the bitterness of cocoa) and from aglycones to glycosides (Al-Dashti *et al.*, 2018; Martins *et al.*, 2020). Their main functions are the elimination of ROS, inhibition of tumour cell growth, regulation of apoptotic and survival pathways, and antidiabetic and cardiovascular effects. Flavonols are abundant in green tea, red wine, cocoa and fruits such as apples, grapes, cherries, raspberries, etc. (Martins *et al.*, 2020).

Box 50

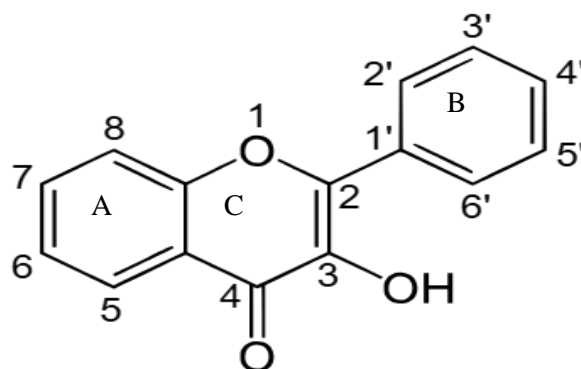


Figure 44

Chemical structure of flavanols

Luo et al. (2022)

Flavanones are isomeric forms of chalcones with 350 aglycones and 100 glycosylated forms identified (Rosa *et al.*, 2019). Their structure is based on the generic structure of flavonoids, a flavon nucleus formed by two aromatic rings (A and B) joined to a completely saturated C ring, lacking a double bond in the C2-C3 position (Fig. 45). (Barreca *et al.*, 2017). Their antioxidant capacity is mainly influenced by the number and spatial arrangement of the –OH groups in their structure. The most common flavanones are naringenin, hesperetin, isosakuranetin, and eriodictyol (Barreca *et al.*, 2017). Their main sources are citrus fruits such as oranges, limes, mandarins, and lemons (Swallah *et al.*, 2020).

Box 51

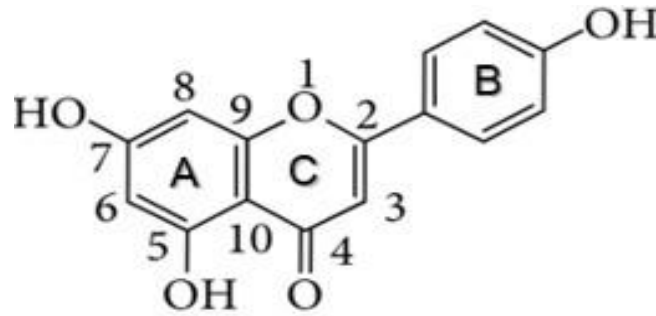


Figure 45

Chemical structure of flavanones.

Chagas et al. (2022)

Isoflavones are flavonoids in which ring B is connected to position 3 of ring C (Fig. 46) (Hano & Tungmunnithum, 2020). They are characterised by having a distinct group of secondary plant metabolites that are produced from the phenylpropanoid pathway (Kim, 2021). This group of flavonoids shows both structural and biological activity similarities to the female hormone oestrogen, which is why they are called phytoestrogens (Smeriglio *et al.*, 2019; Kim, 2021). The most common are genistein, daidzein, formononetin, glucetein, biochanin A, and coumestrol (Křížová *et al.*, 2019; Kim, 2021) and are present in legumes, mainly in soybeans and their derivatives such as flour, protein, tofu, milk, flakes, pasta, and soy sauce (Křížová *et al.*, 2019; Smeriglio *et al.*, 2019).

Box 52

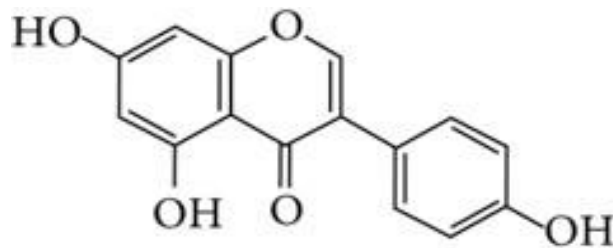


Figure 46

Chemical structure of isoflavones

Chagas et al. (2022)

Anthocyanins, also known as anthocyanidins, are H₂O-soluble pigments belonging to the flavonoid family. They are anthocyanidin glycosides derived from 2-phenylbenzopyrylium, which contains two aromatic rings (A and B) separated by an O⁺ that forms a heterocyclic ring (C) (Fig. 47) (Barragán *et al.*, 2020). Anthocyanins are responsible for the colouring of plants, flowers and fruits, which can vary depending on the methylation or acylation of the –OH groups of rings A and B and the pH (Barragán *et al.*, 2020; Hano & Tungmunnithum, 2020). They can confer the pink, red, orange, blue and violet tones characteristic of various fruits such as strawberries, blackberries, grapes and plums, and vegetables such as aubergines, radishes and red cabbage. On the other hand, proanthocyanins are responsible for the astringent taste of some fruits such as grapes, blueberries, pears, and beverages such as cider, wine, tea, and beer (Kay *et al.*, 2017; Castro, 2019).

Box 53

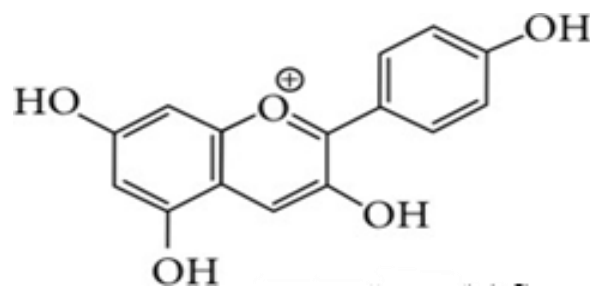


Figure 47

Chemical structure of anthocyanins

Chagas et al. (2022)

Chalcones contain two aromatic rings joined by an unsaturated α , β carbonyl bridge of three carbons (Rosa *et al.*, 2019). They are characterised by the absence of the C ring, which is why they are also called open-chain flavonoids (Fig. 48) (Hano & Tungmunnithum, 2020). The term chalcone comes from the word chalcos, meaning bronze, which is associated with the yellow and orange colours of plant tissues. Most of its properties come from its unique chemical structure; the extended conjugation between the carbonyl group and the double bond gives the molecule reactive properties responsible for biological activities (Pereira *et al.*, 2023). Its main sources are apples and hops (Abbas *et al.*, 2017).

Box 54

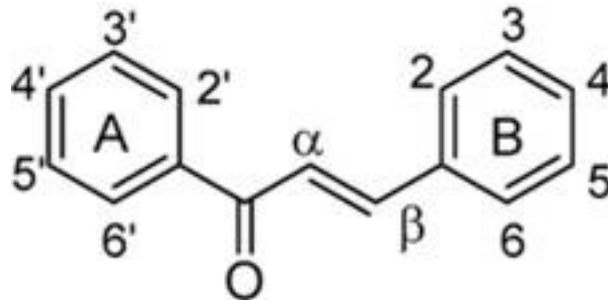


Figure 48

Chemical structure of chalcones

Rosa *et al.* (2019)

The flavonoid content in food can vary due to various factors such as crop management, growing conditions, temperature, ultraviolet radiation, season, contaminants, drought, and salinity stress due to their effect on plant metabolism (Valencia-Avilés *et al.*, 2017; Chagas *et al.*, 2022). Other factors that can influence content include storage, food processing, and cooking techniques (Al-Dashti *et al.*, 2018). For intestinal absorption of flavonoids, they must first be released from plant sources through chewing or by the action of digestive enzymes in the gastrointestinal tract.

After ingestion, absorption depends on their physicochemical properties such as molecular size, lipophilicity, solubility, and pKa values (Khan *et al.*, 2020), and once absorbed, they can influence protein synthesis (Lizárraga-Velázquez *et al.*, 2018).

A daily intake of approximately 100 mg can reduce the risk of morbidity and mortality in the population. Their intake is 10 times higher than vitamin C and 100 times higher than vitamin E or carotenoids (De Luis & Aller, 2008; Khan *et al.*, 2020). The consumption of flavonoids confers benefits in the prevention of ageing, ECD such as PD and AD (Khan *et al.*, 2020), chronic and inflammatory diseases such as CVD, atherosclerosis, thrombosis, cancer, obesity, diabetes, hypertension, asthma, osteoporosis, arthritis and colitis (Wen *et al.*, 2017; Mathesius, 2018; Smeriglio *et al.*, 2019).

3.2.3. Carotenoids

Carotenoids are naturally occurring pigments that cannot be synthesised by humans and must therefore be ingested in food (Eggersdorfer & Wyss, 2018). They are mainly found in most fruits and vegetables, plants, algae, marine animals, fungi and photosynthetic bacteria (Mordi *et al.*, 2020). They are characterised by being highly unsaturated and fat-soluble molecules (Rodríguez-Amaya, 2019) and are notable for their ability to absorb light with colours thanks to the presence of more than seven conjugated double bonds (Nizama, 2019), making them responsible for red, orange, and yellow pigments, which usually indicate different types of carotenoids (Rodríguez-Amaya, 2019; Kabir *et al.*, 2022), and colour intensity is generally related to the amount of carotenoids (Bhatt & Patel, 2020).

Carotenoids are tetraterpenoids formed by eight isoprenoid compounds (Kabir *et al.*, 2022), have a central unit that is a long carbon chain, usually containing 40 carbons, consist of a series of nine conjugated double bonds and four side-chain methyl groups that are primarily responsible for their pigmenting properties (Young & Lowe, 2018; Sandman, 2019). They also contain various cyclic or acyclic terminal groups and have an almost bilateral symmetry around the central double bond (Milani *et al.*, 2016).

They are characterised by being a group that has two different structures, one with O₂ and one without O₂ (Fig. 49). (Bhatt & Patel, 2020), and they present a variety of substitutions, including terminal ring systems linked by conjugated double bond chains containing chromophores such as β-carotene, the presence of •OH in terminal rings such as lutein and zeaxanthin, ketone groups with or without additional •OH groups such as astaxanthin and canthaxanthin, as well as aromatic rings such as sincoxanthin and, rarely, monocyclic carotenoids (Ribeiro *et al.*, 2018).

Box 55

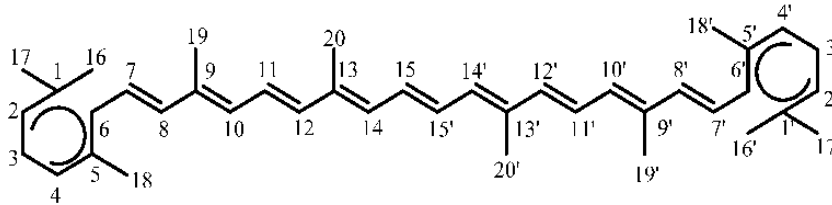


Figure 49

Structure of β-carotene showing the common structural features of carotenoids

Mordi et al. (2018).

Carotenoids are associated with various health benefits and perform different functions in different ways due to their characteristic structure. Their beneficial effects derive mainly from their antioxidant properties, playing an important role against oxidative stress and inflammation (Cicero & Colleti, 2017; Galasso *et al.*, 2017; Eggersdorfer & Wyss, 2018). Their main function is to act as FR scavengers, primarily ¹O₂ and other radicals such as O₂•⁻ and ROO• (Sandman, 2019). This occurs due to the number of conjugated double bonds present in the chemical structure of carotenoids and their ability to delocalise e⁻ along their chain, allowing these radicals to be neutralised and/or eliminated (Nizama, 2019; Mordi *et al.*, 2020).

Carotenoids can eliminate RLs in three steps:

1. E- transfer (oxidation, reduction: CAR + ROO• → CAR• + ROO⁻)
2. Hydrogen extraction (CAR + ROO• → CAR• + ROOH)
3. Addition (CAR + ROO• → ROOCAR) (Milani *et al.*, 2016).

Other functions of carotenoids are to convert ROOH into more stable compounds, prevent the formation of FR by blocking the oxidation reactions of these radicals and inhibit the auto-oxidation chain reaction. They also convert Fe and Cu derivatives into harmless molecules by acting as metal chelators (Galasso *et al.*, 2017), all with the aim of protecting plant cells against oxidation and cell membranes from oxidative damage (Nizama, 2019).

The consumption of carotenoids not only helps in the elimination of FR in the body, but also has positive effects on health, helping in the prevention of CVD by oxidising LDL and decreasing HDL, metabolic diseases, neurodegenerative diseases such as AD, cerebral ischaemia, diabetes, obesity, hypertension (Cicero & Colleti, 2017; Ribeiro *et al.*, 2018) and various types of cancer, mainly breast, prostate, lung and urothelial cancer, by limiting abnormal cell growth and/or improving communication between spaces (Cicero & Colleti, 2017; Eggersdorfer & Wyss, 2018), and also help to reduce neurological disorders and type II diabetes in healthy men and women (Bhatt & Patel, 2020). Due to their multiple beneficial effects, carotenoids are considered effective antioxidants (Young & Lowe, 2018).

Carotenoids work with other biomolecules such as proteins and lipids to enhance their antioxidant activity (Bhatt & Patel, 2020). Their bioavailability and efficacy depend on several factors, including dietary factors such as the presence of fat and fibre in food composition; dose, type and location, chemical changes caused by factors such as storage conditions, variety, ripeness, heat treatment, post-harvest handling, processing (Nizama, 2019), food particle size, interaction between carotenoids or with other compounds, their isomeric form, molecular bonding and subject characteristics such as genetic factors, nutritional status, sex and age.

Therefore, although carotenoids are found in large quantities in food, there is no guarantee that their biological impact will be significant (Ribeiro *et al.*, 2018). Furthermore, modifying the number of conjugated double bonds and adding O₂ functional groups to the backbone of the carotenoid structure alters their reactivity (Young & Lowe, 2018).

Several authors mention that there are between 600 and 750 carotenoids in nature with structural variants (Meléndez *et al.*, 2017; Young & Lowe, 2018). It is estimated that only about 40 of them are present in the human diet, especially in fruits and vegetables (Ribeiro *et al.*, 2018; Pérez-Gálvez *et al.*, 2020), which can be absorbed, metabolised and used in our bodies (Meléndez *et al.*, 2017). In addition, around 20 carotenoids have been identified in human blood and tissues (Milani *et al.*, 2016). The main carotenoids include lycopene, α and β -carotene, astaxanthin, lutein, β -cryptoxanthin and zeaxanthin (Fig. 50) (Meléndez *et al.*, 2017).

Box 56

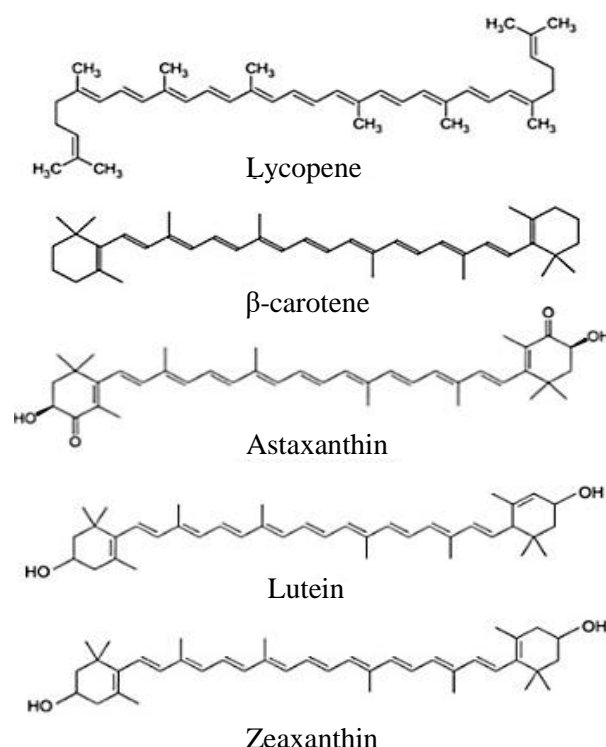


Figure 50

Structures of the main carotenoids.

Kibar et al. (2022)

Carotenoids are mainly classified into carotenes and xanthophylls according to their structure (Mordi *et al.*, 2020). Carotenes are characterised by being non-polar in nature, are composed of hydrogen and carbon, have only one long chain of carbons containing hydroaromatic rings at both ends, and do not contain O₂ in their terminal rings. Examples of carotenes are β -carotene and lycopene (Galasso *et al.*, 2017; Kabir *et al.*, 2022). On the other hand, xanthophylls are distinguished by being more polar in nature, containing hydrogen, carbon and oxygen, specifically their terminal rings have O₂, for example, lutein, astaxanthin and zeaxanthin (Nizama, 2019).

They can also be classified as provitamin A compounds, which include α and β -carotene and β -cryptoxanthin; and non-provitamin A compounds such as lycopene, lutein and zeaxanthin (Cicero & Colleti, 2017). Therefore, carotenoids are divided into xanthophylls, the pigment responsible for giving plants and foods their yellow colour, found in green vegetables; lycopene, a red lipophilic pigment present in ripe tomatoes; carotenes, the pigment responsible for the orange colour, found mainly in carrots; capsanthin, the pigment that gives peppers their bright red colour; and astaxanthin, which gives crustaceans their pink/red colour (Table 7) (Milani *et al.*, 2016).

Box 57**Table 7**

Classification of carotenoids and their main food sources

Carotenoids	Pigment	Main sources	Reference
Xanthophylls	yellow	green vegetables	(Ribeiro <i>et al.</i> , 2018)
Lutein	yellow	corn, mustard, peppers, melon, oranges, kiwis, cucumbers, leafy green vegetables (spinach, cabbage, broccoli, chard, lettuce)	(Dias <i>et al.</i> , 2017; Ribeiro <i>et al.</i> , 2018)
Zeaxanthin	yellow	Pepper, pumpkin, cabbage, tangerine, orange.	(Dias <i>et al.</i> , 2017)
Carotene (α - γ β -)	orange	Carrots, melons, peaches, mangoes, apples, pears, tangerines, red peppers, pumpkins, celery, lettuce, and cereals.	(Dias <i>et al.</i> , 2017; Ribeiro <i>et al.</i> , 2018; Kabir <i>et al.</i> , 2022)
Cryptoxanthin (β -)	orange	orange, tangerine, papaya, nectarine, peach, apple, guava	(Ribeiro <i>et al.</i> , 2018)
Lycopene	red	ripe fruit of the tomato, watermelon, guava, papaya.	(Rodriguez-Amaya, 2019; Kabir <i>et al.</i> , 2022)
Astaxanthin	pink/red	Fish (salmon), crustaceans (crabs, lobsters and prawns)	(Rodriguez-Amaya, 2019; Kabir <i>et al.</i> , 2022)
Little cap	bright red	Pepper, bell pepper	(Ribeiro <i>et al.</i> , 2018)

Source [in italic]

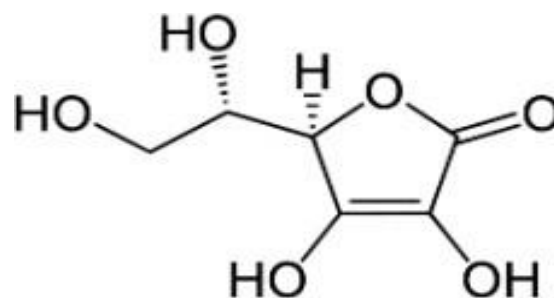
The recommended dose is 6 mg/day (Dias *et al.*, 2017). The amount of carotenoids consumed can affect their bioavailability, as the human intestine has a limited capacity to absorb them, meaning that they can be absorbed more efficiently in small doses (Meléndez *et al.*, 2017).

3.3. Vitamins

Currently, the administration of supplements such as vitamins and minerals can be an alternative adjuvant treatment for various pathologies, with the aim of improving the immune response (Casas *et al.*, 2016). Vitamins are natural or synthetic molecules that are required in small amounts for the human body to perform its vital functions and maintain a healthy metabolism. They are essential nutrients that cannot be synthesised by the body and are found mainly in food, so they must be ingested (Elgailani *et al.*, 2017; Khadim & Al-Fartusie, 2020).

3.3.1. Vitamin C

Ascorbic acid, also known as vitamin C, is the main non-enzymatic antioxidant formed from sugars (Doseděl *et al.*, 2021). It is a weak acid derived from a six-carbon compound similar to glucose that contains two ionising acid groups. Its molecular formula is $C_6H_8O_6$ (Fig. 51), and its IUPAC name is 2-oxo-L-threo-hexone-1,4-lactone-2,3-enediol (Khadim & Al-Fartusie, 2020). It is characterised by being water-soluble and predominantly exists as an ascorbate anion and is present in plasma, glandular and tissue tissues, the brain and, in lower concentrations, in muscle and adipose tissue (Villagrán *et al.*, 2019).

Box 58**Figure 51**

Structure of vitamin C

Khadim & Al-Fartusie (2020).

Ascorbate is the most abundant antioxidant in brain tissue, present mainly in nerve cells, and its presence is very important for maintaining redox balance and proper functioning of the CNS (Każmierczak-Barańska *et al.*, 2020). There are two important biological forms of vitamin C: the reduced form, or ascorbic acid, and the oxidised form, or dehydroascorbic acid. Ascorbic acid is formed after vitamin C donates an e⁻, and is relatively stable and unreactive. It is transported intracellularly via sodium-dependent vitamin C transporters. On the other hand, dehydroascorbic acid is formed after it donates its second e⁻ and is transported by glucose transporters (Castillo-Velarde, 2019; Gegotek & Skrzydlewska, 2022). Once the oxidised form of vitamin C reaches the intracellular space, it undergoes spontaneous reversion to its reduced form through the action of glutathione, making it more stable (Ifeanyi, 2018).

Vitamin C is considered a very important antioxidant because it has three lines of defence: elimination of RL, biosynthesis and activation of antioxidant enzymes, and repair of oxidative damage (Gegotek & Skrzydlewska, 2022). This antioxidant is very effective, as it can easily donate e⁻, protecting fundamental biomolecules such as DNA, lipids, proteins, carbohydrates and nucleic acids from damage caused by ROS (Carr & Maggini, 2017). It is considered the most abundant antioxidant capable of interacting with others to form an antioxidant network (Huchzermeyer *et al.*, 2022). It also plays an important role as a cofactor in enzymatic reactions involved in processes such as antioxidant defence, collagen production, prevention of harmful genetic mutations, and protection of white blood cells, and has beneficial effects on the immune system and inflammation (Travica *et al.*, 2017; Jamshidovich, 2023). It also aids bone development, growth, and connective tissue repair (Foroughbakhch-Pournavab *et al.*, 2020). Its biological efficiency depends on its redox capacity (Van Gorkom *et al.*, 2019).

In its antioxidant action, it protects cellular components against ROS by inhibiting and/or eliminating ROS formed during metabolism, which contributes to the stabilisation of the mitochondrial membrane in biological systems (Każmierczak-Barańska *et al.*, 2020; Njus *et al.*, 2020). Its properties as an FR scavenger are related to its ability to form a stabilised radical, which allows ascorbate to react with more reactive molecules, mainly O₂^{•-} and •OH, but it can also react with H₂O₂, 1O₂, ROO•, •NO, and ONOO- to prevent their interaction with biomolecules important for proper cellular function (Fenech *et al.*, 2019; Njus *et al.*, 2020; Gegotek & Skrzydlewska, 2022).

When ascorbate encounters a •OH, it donates a single e⁻, reducing the •OH to –OH ('quenching' it) and converting itself into a much less reactive ascorbyl radical, which is stabilised by resonance. It can then donate a second e⁻ to quench a second •OH, in which the two hydrogens are lost and replaced by double bonds, resulting in the formation of dehydroascorbic acid. Finally, this decomposes and is excreted or enzymatically reduced back to ascorbic acid. Therefore, one ascorbate molecule is potentially capable of eliminating two FR (Fig. 52) (Deshmukh & Kim, 2019; Gegotek & Skrzydlewska, 2022).

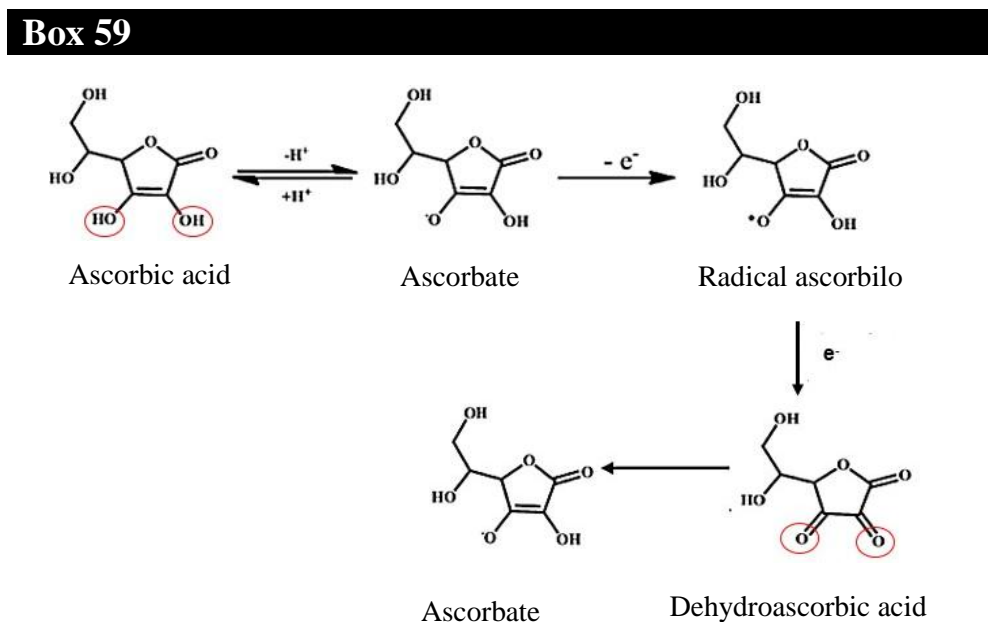


Figure 52

Antioxidant mechanism of action of vitamin C

Deshmukh & Kim (2019).

Vitamin C is the only antioxidant that can protect against peroxidation damage induced by ROS•, thereby inhibiting lipid oxidation (Foroughbakhch-Pournavab *et al.*, 2020) and protecting lung cells from exposure to oxidants and the damage they cause through various pollutants, heavy metals, pesticides, and xenobiotics (Carr & Maggini, 2017), thereby enhancing the immune response (Ifeanyi, 2018).

It also aids in the regeneration of other antioxidants such as vitamin E and GSH (Carr & Maggini, 2017; Travica *et al.*, 2017). Other functions of vitamin C include collagen synthesis reactions, which are essential for its formation and help maintain the integrity of the skin, connective tissue, bones, blood vessel walls, and dentine, making it important in wound healing and facilitating recovery from burns (Sinbad *et al.*, 2019; Khadim & Al-Fartusie, 2020); in the prevention of harmful genetic mutations, it plays an important role in the regulation of DNA and histone methylation, which, when combined, help to shape chromosomes and control gene activity (Carr & Maggini, 2017); it helps reduce elements such as ferric iron to ferrous iron, which promotes its intestinal absorption (Castillo-Velarde, 2019), it is also essential for the synthesis of serotonin, a hormone necessary for the proper functioning of the endocrine, nervous, digestive and immune systems (Sinbad *et al.*, 2019).

As mentioned above, although vitamin C is an essential vitamin for the body, it cannot be synthesised endogenously, so it must be ingested (Khadim & Al-Fartusie, 2020). It can be administered in three different ways: through food, food supplements and synthetic products administered orally or intravenously (Pawlowska *et al.*, 2019).

The main source of this vitamin is food, especially fruits and vegetables. In fruits, it is found in citrus species such as lemon, orange, lime, grapefruit, tangerine, pineapple, blackcurrant, raspberry, and grape (Sinbad *et al.*, 2019; Santos *et al.*, 2022). It is also present in fruits such as papaya, strawberries, kiwis, guavas, mangoes, blackberries, melons, blueberries, tomatoes, green and red peppers (Elgailani *et al.*, 2017; Castillo-Velarde, 2019); and in vegetables such as broccoli, Brussels sprouts, cauliflower, cabbage, spinach, chard, asparagus, and sweet potatoes (Table 8) (Doseděl *et al.*, 2021). Also, in dairy products, eggs, fish, beverages, sauces, and offal such as liver and kidneys (Villagrán *et al.*, 2019) and in fresh aromatic herbs such as coriander, parsley, and spring onion (Doseděl *et al.*, 2021).

Box 60

Table 8

Main sources of vitamin C

Food	Vitamin C content (mg/100g)
Guava	273
Broccoli	158
Red bell pepper	140
Kiwi	90
Papaya	85
Green bell pepper	80
Strawberry	79
Orange	70
Spring onion	58
Red cabbage	57
Orange	50
Mango	45
Lemon	40
Melon	40
Grapefruit	40
Mandarin	25
Cauliflower (cooked)	25
Tomato (raw)	15

Castillo-Velarde (2019); Villagrán et al. (2019).

The vitamin C content in fruits and vegetables varies greatly, depending on several factors, including the type of species, variety, location and type of cultivation, time of harvest (stage of ripeness) or post-harvest conditions, climatic conditions, latitude, genotype, agricultural technology and processing (Fenech *et al.*, 2019; Doseděl *et al.*, 2021).

The change in ascorbate levels during fruit ripening is a characteristic that depends on the species; for example, in tomatoes, grapes, and strawberries, the content increases as the fruit ripens (*Fenech et al., 2019*).

Other important considerations are water solubility, decomposition when stored under aerobic and anaerobic conditions, instability at high temperatures, humid air, light and alkaline pH, and the fact that cooked foods tend to lose up to 90% of their content (*Deshmukh & Kim, 2019; Villagrán et al., 2019*). On the other hand, it is claimed that vitamin C is better absorbed from natural sources than from synthetic ones. However, intake with other substances must be considered, as they can act synergistically with the vitamin, enhancing or decreasing its bioavailability and beneficial health effects (*Pawlowska et al., 2019*). For example, fibre, flavones and tannins are capable of chelating metals that prevent the oxidation of ascorbic acid, promoting its absorption (*Villagrán et al., 2019*).

The bioavailability of vitamin C ingested into the body refers to the proportion that reaches the systemic circulation and is therefore available for physiological metabolic processes (*Pawlowska et al., 2019*).

The recommended daily intake of vitamin C varies slightly from country to country, with an average requirement of 90 mg/day for men and 75 mg/day for women (*Granger & Eck, 2018; Fenech et al., 2019*). Adequate intake helps prevent CVD, mainly coronary heart disease and stroke, certain cancers, neurological disorders and cataracts (*Granger & Eck 2018; Foroughbakhch-Pournavab et al., 2020*). When there is a deficiency, redox balance is disrupted, accelerating ageing and the development of diseases such as diabetes, atherosclerosis, hypertension and hypercholesterolemia, neurodegenerative diseases, scurvy, female infertility and loss of collagen strength throughout the body, due to the progressive deterioration of blood vessels in the heart and brain (*Sinbad et al., 2019; Santos et al., 2022*).

Conversely, when there is an overdose, it limits glucose transport and ATP production, causing an energy crisis and cell death (*Pawlowska et al., 2019*), and may also have pro-oxidant rather than antioxidant effects due to malabsorption and reduction of metal ions such as iron and copper (*Każmierczak-Barańska et al., 2020; Njus et al., 2020*), contributing to pathological and side effects such as kidney stones, digestive system problems, gout, and diarrhoea (*Khadim & Al-Fartusie, 2020*).

3.3.2. Vitamin E (α -tocopherol)

Vitamin E is an essential micronutrient that is among the most active antioxidants (*Montier et al., 2018*). It is a fat-soluble vitamin that acts as an antioxidant in the conversion of fat-soluble radicals to water-soluble radicals in the detoxification chain, protecting the PUFAs of the cell membrane from oxidation (*Ifeanyi, 2018; Lee & Han, 2018; Baltusnikiene et al., 2023*). It is ubiquitous throughout the body and, due to its lipophilic nature, can accumulate in cell membranes and lipoproteins (*Shahidi et al., 2021*).

Vitamin E refers to a group of fat-soluble compounds that are divided into tocopherols and tocotrienols (*Raikos, 2017; Higgins et al., 2020*). They differ in that tocopherols have a saturated side chain and three asymmetric carbons, while tocotrienols have an unsaturated side chain with three double bonds and a single asymmetric carbon (*Gugaliandolo et al., 2017; Kiyose, 2021*). Each category comprises four isomers, which are distinguished as α -, β -, γ -, and δ -tocopherols and α -, β -, γ -, and δ -tocotrienols (Fig. 53) (*Lee & Han, 2018*). These differ in the number and position of methyl groups in the chromanol ring (*Gugaliandolo et al., 2017; Kiyose, 2021*).

Box 61

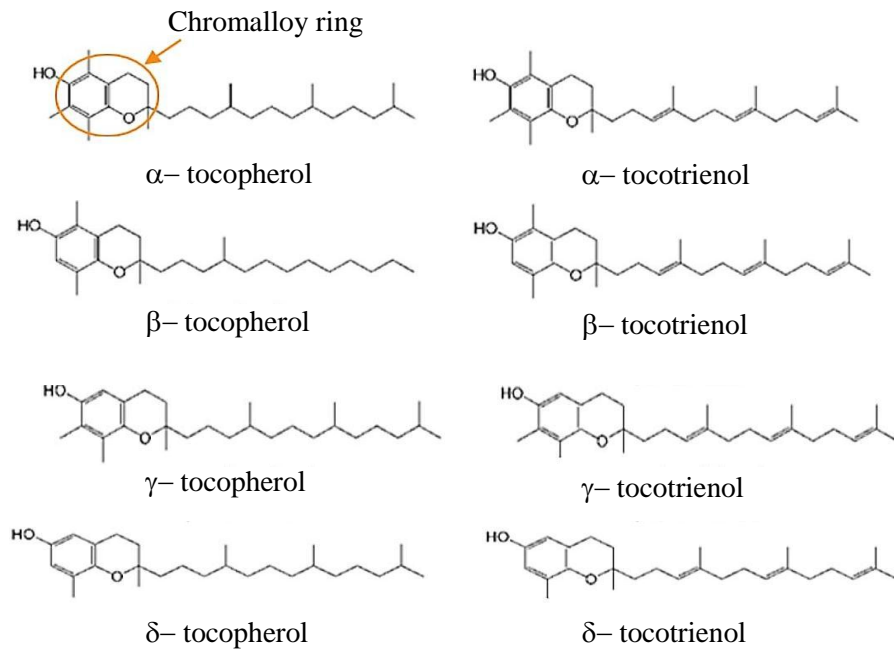


Figure 53

Vitamin E structures.

Reboul (2017).

α -Tocopherol, which contains three methyl groups, is the most biologically active form of tocopherols in humans, while δ -tocopherol, which contains one methyl group, is the least active (Raikos, 2017; Huchzermeyer *et al.*, 2022; Baltusnikiene *et al.*, 2023). The body absorbs all isomers in the small intestine, however, α -tocopherol is the only isomer that the liver can metabolise, the remaining forms are excreted, making it the only compound that meets human dietary requirements and is found in higher concentrations in tissues, thus having greater bioavailability (Galli *et al.*, 2017; Ifeanyi, 2018).

Vitamin E is a powerful antioxidant, lipophilic radical scavenger and chain breaker in lipoproteins and cell membranes (Gugliandolo *et al.*, 2017). Its main function is to protect PUFAs against oxidation through a hydrogen atom transfer reaction, in which vitamin E donates its phenolic hydrogen to $\text{ROO}\cdot$ forming a non-radical product and a vitamin E radical (tocopheroxyl), which can react with another radical to produce a stable product (Fig. 54) (Gugliandolo *et al.*, 2017; He *et al.*, 2017; Huchzermeyer *et al.*, 2022). The same happens with $\text{O}_2\cdot^-$ and $\cdot\text{OH}$, converting them into more stable forms or eliminating them, thus preventing LP and oxidative chain reactions (Montier *et al.*, 2018; Higgins *et al.*, 2020). It also reduces oxidative damage to membranes, lipoproteins, and tissues (Montier *et al.*, 2018). The antioxidant effects of vitamin E isomers depend on the number of methyl groups in the chromanol ring (Miyazawa *et al.*, 2019). A single molecule of α -tocopherol has the capacity to capture two $\text{ROO}\cdot$ molecules and destroy 120 $^1\text{O}_2$ particles (Miyazawa *et al.*, 2019; Huchzermeyer *et al.*, 2022).

Box 62

Vitamin E

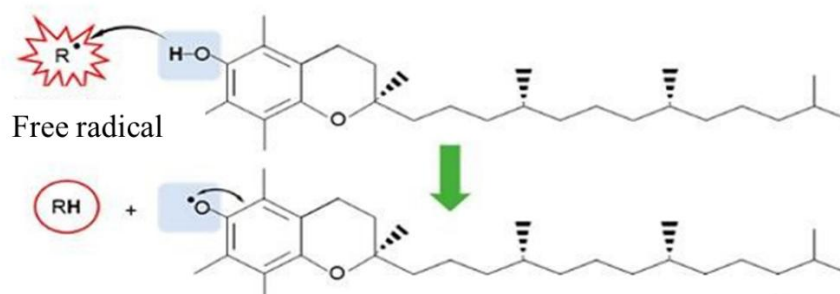


Figure 54

Reaction of Vitamin E with free radicals

Rungratanawanich et al. (2018).

Vitamin E also plays an important role in various processes and in the development of tissues and organs, including the brain (Gugliandolo *et al.*, 2017). The antioxidant activity of vitamin E can influence the regulation of various enzymes involved in signal transduction and gene regulation, as the activity of these enzymes is regulated by the redox state due to their high concentration among the groups of fat-soluble vitamins (Lee & Han, 2018; Miyazawa *et al.*, 2019). Humans must obtain vitamin E through dietary sources (Shahidi *et al.*, 2021), the main sources of which are foods rich in fats such as oils and seeds (Galli *et al.*, 2017). It can also be found in smaller amounts in some fruits, vegetables, seafood, cheese and eggs (Table 9) (Gugliandolo *et al.*, 2017; Reboul, 2017).

Box 63

Table 9

Main foods containing vitamin

Food	Vitamin E content (mg/100g)	Reference
Sunflower oil	58.3	(Reboul, 2017)
Soybean oil	50	(Lee & Han, 2018)
Corn oil	50	(Lee & Han, 2018)
Walnuts	50	(Lee & Han, 2018)
Cotton seed	50	(Lee & Han, 2018)
Palm and wheat germ	50	(Lee & Han, 2018)
Rice bran	50	(Shahidi <i>et al.</i> , 2021)
Sunflower seeds	42.3	(Reboul, 2017)
Almonds	14.6	(Reboul, 2017)
Olive oil	14.3	(Shahidi <i>et al.</i> , 2021)
Pine nuts	9.3	(Baltusnikiene <i>et al.</i> , 2023)
Peanuts	8.3	(Baltusnikiene <i>et al.</i> , 2023)
Fish	0.9-2.0	(Reboul, 2017)
Fruit and vegetables (spinach, tomatoes, etc.)	0.8-2.0	(Reboul, 2017)

Source [in italic]

The recommended dose of vitamin E, established by the FDA, is 13 mg/day for men and 11 mg/day for women (Baltusnikiene *et al.*, 2023). Vitamin E supplementation mainly helps to reduce the risk of developing CVD due to its ability to inhibit LDL cholesterol oxidation and thus reduce the formation of fatty deposits inside the arteries (Sunkara & Raizner, 2019). It also contributes to the prevention of diseases such as diabetes, obesity, hypertension, neurodegenerative diseases such as AD, and ageing (Galli *et al.*, 2017; Sánchez-Valle, 2018). It also has beneficial health effects as an anti-allergic, anti-atherogenic, anti-lipidemic, anti-inflammatory, and anti-carcinogenic agent (Miyazawa *et al.*, 2019), particularly preventing breast, lung, and liver cancer (Shahidi *et al.*, 2021). Additionally, some studies suggest that vitamin E supplementation tends to improve blood glucose levels, decrease glycosylated haemoglobin and LP, and increase antioxidant capacity in diabetics (Montier *et al.*, 2018). On the other hand, although rare, deficiency of this vitamin is related to diseases that affect lipid absorption and can cause peripheral neuropathy, retinopathy, immune system deterioration, and ataxia (Shahidi *et al.*, 2021). It is important to mention that vitamins E and C work together, as vitamin C helps regenerate vitamin E to a reduced state (active form) that allows it to continue oxidising RLs (He *et al.*, 2017; Higgins *et al.*, 2020).

3.4. Minerals

Minerals are essential nutrients that humans need to maintain their functioning. They are known as micronutrients because they are consumed in very small amounts (Kumar *et al.*, 2017) and are essential for life, as they play a fundamental role in metabolic, physiological, growth and developmental functions in the body (Restrepo *et al.*, 2016; Biasi *et al.*, 2020). Among the most important minerals are Se and Zn, because they have antioxidant activity, are an integral part of the enzyme system involved in reducing ROS, and act as cofactors or prosthetic groups of antioxidant enzymes such as SOD and GPx (Casas *et al.*, 2016; Sunkara & Raizner, 2019), which protect cells from oxidative damage and prevent chronic diseases and ageing (Foroughbakhch-Pournavab *et al.*, 2020). Inadequate intake of these nutrients can lead to the proliferation of ROS, causing implications in various pathological processes (Sunkara & Raizner, 2019).

3.4.1. Selenium

Se is an important micronutrient in human nutrition. Although consumed in very small amounts, it is essential, as we could not survive without it (Kumar *et al.*, 2017), because it performs various functions within the body to maintain cell growth and proper functioning (Shahid *et al.*, 2018; Buendía-García *et al.*, 2021), helps maintain normal metabolism (Wang *et al.*, 2017), is essential for protein formation and forms the active site of various enzymes, functions as a cofactor for antioxidant enzymes such as GPx, and is important for protection against EO, demonstrating high activity as a FR scavenger and anticarcinogenic agent (Kumar *et al.*, 2017; Gaucin-Delgado *et al.*, 2021).

Se is found in organic and inorganic forms mainly in soil, plants, H₂O, and some foods (Wang *et al.*, 2017), and has also been found in small amounts in the kidney, liver, spleen, pancreas, heart, and brain (Weaver & Skouta, 2022). Inorganic forms can be found with various minerals such as selenite, selenate, and selenide; selenate is the main inorganic selenium compound present in both animal and plant tissues. On the other hand, Se in food is an integral part of various organic compounds, including the amino acids selenomethionine (SeMet), Se-methylselenocysteine (MeSeCys) and SeCys (Fig. 55) (Yang *et al.*, 2017; Buendía-García *et al.*, 2021). Both organic and inorganic forms are part of human metabolism, can be absorbed by the small intestine and distributed to various tissues in the body, performing important biological functions through the regulation of selenoprotein synthesis (Wang *et al.*, 2017; Gastelum, 2024).

Box 64

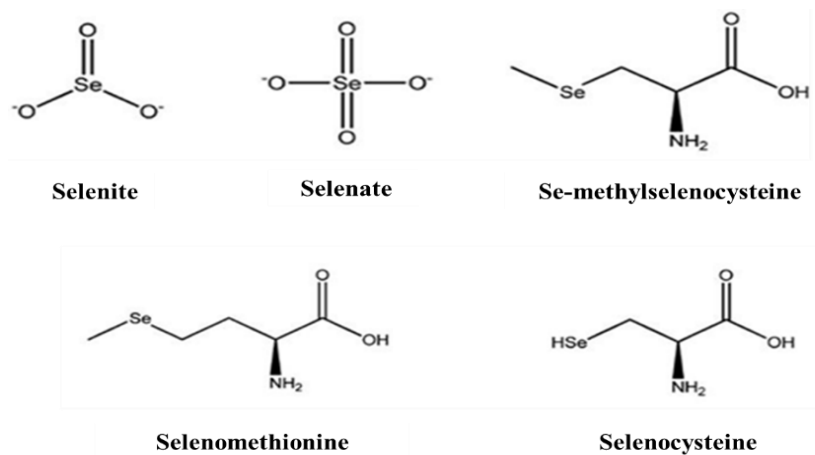


Figure 55

Organic and inorganic forms of selenium.

Yang et al. (2017).

Selenoproteins are proteins that contain Se in the form of SeCys, also known as amino acid 21, which is similar to Cys, differing only in one atom where sulphur is replaced by Se (Fig. 56) (Torres *et al.*, 2017; Tinkov *et al.*, 2020). Selenoproteins are the main proteins in which Se is incorporated as SeCys in the active site or catalytic centre (Schiavon *et al.*, 2020).

Box 65

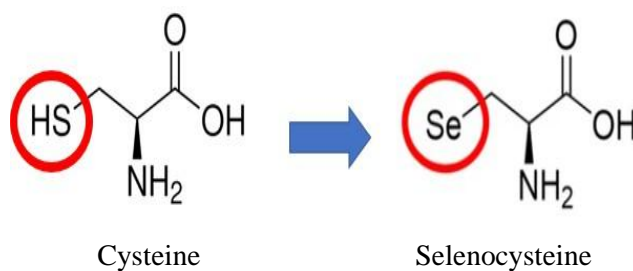


Figure 56

Structure of Selenocysteine

Weaver & Skouta (2022).

To date, more than 50 families of selenoproteins have been found, however, only 25 of them are present in humans and perform various antioxidant, catalytic, anti-inflammatory, antiviral, and antitumour functions (Elmadfa & Meyer, 2019; Gaucin-Delgado *et al.*, 2021). They are characterised by their oxireductase properties, which allow them to act in redox processes to repair cellular damage (Torres *et al.*, 2017; Gastelum, 2024). Among the main selenoproteins are GPx and selenoprotein P, but there are also thioredoxin reductase, iodothyronine deiodinases and selenophosphate synthetase (Yang *et al.*, 2017; Weaver & Skouta, 2022).

Se is involved in the proper functioning of different enzymes and selenoproteins, its main function being to contribute to the antioxidant defence mechanisms of the human body (Gastelum, 2024), through GPx, whose function is to reduce hydroperoxides such as H₂O₂, protecting cells and DNA from the harmful effects of FR and maintaining cellular redox homeostasis, which prevent OS (Torres *et al.*, 2017; Biasi *et al.*, 2020), thereby slowing down the ageing process and increasing tissue flexibility (Kieliszek, 2019). Se is able to act with vitamin E to protect cell membranes and organelles from oxidative damage. It also facilitates the binding between O₂ and H⁺ at the end of the respiratory chain and aids in the transport of ions across cell membranes (Casas *et al.*, 2016).

In addition to its antioxidant functions, Se has the ability to neutralise the negative effect of aflatoxins, reducing their carcinogenic and teratogenic effects and inhibiting the growth of cancer cells (Kieliszek, 2019), and reduces the toxicity of mercury, cadmium and other toxic metals through metal coordination (metal coordination) (Casas *et al.*, 2016). It also plays important roles in health, hormonal balance, immunity, male fertility and resistance to viral infections (Schiavon *et al.*, 2020), plays an important role in modulating insulin signalling, carbohydrate and lipid metabolism (Tinkov *et al.*, 2020), and participates in the prevention of various pathologies such as cancer, CVD, HIV, and rheumatoid arthritis (Torres *et al.*, 2017; Foroughbakhch-Pournavab *et al.*, 2020).

Se accumulates in the body mainly through intake, both in animal and plant products (Table 10). The former are characterised by a diverse amount of Se, while the latter have a relatively low content (Shahid *et al.*, 2018; Buendía-García *et al.*, 2021; Gaucin-Delgado *et al.*, 2021). The most common organic Se compounds in the diet are SeMet, SeCys, MeSeCys and selenite (Dobrzyńska *et al.*, 2023). SeMet is the predominant form in foods such as vegetables, cereals, meat, eggs, dairy products, nuts, grains, legumes and yeast, SeCys is found in meat and other animal products such as liver and kidneys, and MeSeCys is found in spices and foods such as garlic and onions (Table 10). On the other hand, inorganic compounds are acquired through supplementation and are also present in small amounts in both plant and animal products (Tinkov *et al.*, 2020; Dobrzyńska *et al.*, 2023).

Box 66

Table 10

Main dietary sources of selenium

Food	Selenium content (mg/100g)
Brazil nuts	2-20
Fish	0.4-4.3
Liver	0.3-0.4
Kidneys	0.2-2.0
Pork	0.27-0.35
Brussels sprouts	0.25
Chicken	0.15
Garlic	0.15
Broccoli	0.13
Eggs	0.12-0.42
Onions	0.1
Cauliflower	0.1
Bread	0.9-0.25
Beef	0.01-0.73
Milk	0.01-0.06

Kieliszek (2019) & Dobrzyńska et al. (2023).

The amount of Se in the diet varies due to various factors. For example, in animals it depends on where they lived and what they ate, while in plants it depends on geological, geographical and environmental factors such as the region, soil type, agroclimatic conditions, crop type, fertilisation and plant growth (Elmadfa & Meyer, 2019; Dobrzyńska *et al.*, 2023). On the other hand, its bioavailability depends on factors such as source, chemical form and dietary factors such as proteins, fats and heavy metals, with greater bioavailability in its organic form, as it is more easily absorbed and considered less toxic than inorganic compounds; and in the presence of vitamins such as A, C, D and E and low molecular weight proteins containing methionine (Yang *et al.*, 2017). However, in the presence of heavy metals, sulphur and fibre, it is reduced (Kieliszek, 2019). The bioavailability of Se depends not only on its absorption in the intestine but also on its conversion into its biologically active form, which can be affected by age, sex and/or lifestyle, as well as the food preparation process, since cooking in H₂O reduces it by 5-50% depending on the type of product (Dobrzyńska *et al.*, 2023), while the gut microbiota can mediate the effects of Se on selenoprotein metabolism (Tinkov *et al.*, 2020).

According to the WHO, dietary Se intake should be between 55-200 µg/day for adults, which is necessary to perform various functions in the body and prevent certain diseases (Gaucin-Delgado *et al.*, 2021). Se deficiency (<20 µg/day) promotes the accumulation of hydroperoxides that inhibit the enzyme prostacyclin synthase responsible for the production of vasodilator prostacyclins by the endothelium (Vildoso *et al.*, 2021). It induces damage to the cellular redox balance, which can lead to different pathologies (Foroughbakhch-Pournavab *et al.*, 2020), mainly affecting the functioning of the cardiovascular system, causing CVD and myodegenerative diseases (myocardial infarction). also affects the CNS, causing AD, depression or increased anxiety (Kieliszek, 2019), and may lead to increased susceptibility to cancer, male infertility and kidney disorders (Weaver & Skouta, 2022; Gastelum, 2024).

On the other hand, excessive intake (>900 µg/day) acts as a pro-oxidant, producing ROS, which can be toxic, inducing OST and various effects such as insulin resistance and hyperinsulinemia, thereby increasing the risk of diabetes and possibly hypercholesterolemia (Shahid *et al.*, 2018; Vildoso *et al.*, 2021). It also causes symptoms such as emotional instability, nervousness, nausea, vomiting and, in some cases, hair and nail loss (Kumar *et al.*, 2017).

3.4.2. Zinc

Zn is an essential micronutrient for humans because it is important for reproduction, growth, development and cell metabolism (Casas *et al.*, 2016). It is the second most abundant trace element in the body and is essential for health. It is an integral component of many tissues and forms part of a large number of metalloproteins (Restrepo *et al.*, 2016; Lee, 2018). It is necessary for the functioning of numerous metabolic enzymes and transcription factors (Elmadfa & Meyer, 2019). is fundamental for cell proliferation and differentiation, is important for the synthesis of biomolecules such as DNA and cell signalling proteins, as well as for their degradation, performs catalytic, structural and regulatory functions (Jarosz *et al.*, 2017; Elmadfa & Meyer, 2019), prevents the formation of RL, protects biological structures from damage and acts as an anti-inflammatory agent (Rosas-Romero & Covarrubias-Gómez, 2020). On the other hand, its deficiency is strongly related to defects in the neuronal and immune systems, both effects of which are detailed below (Lee, 2018).

Zn is absorbed throughout the digestive tract, mainly in the duodenum, ileum, and jejunum, through specific transporters or by passive diffusion (Jarosz *et al.*, 2017; Pecora *et al.*, 2020). Various authors have determined that the amount of Zn in adults is approximately 1.4 to 3 g, with its content varying significantly between tissues: 85% of Zn is found in muscles and bones, 11% in the skin and liver, and the remaining 4% is distributed in other tissues (Jarosz *et al.*, 2017; Lestegás, 2021).

In the CNS, there are 10 mg/g of tissue and within the neuronal cell there is 15 mM, 80% of which is bound (Lestegás, 2021). Lestegás, 2021). In the CNS, there are 10 mg/g of tissue and within the neuronal cell there is 15mM, 80% of which is bound to transport proteins, known as the inactive form, and the remaining 20% is found in free or chelated form (Restrepo *et al.*, 2016). At the cellular level, 30-40% of Zn is found in the nucleus, 50% in the cytoplasm, and the rest is associated with membranes (Lestegás, 2021).

The Zn homeostatic system is composed of proteins that include the metallothionein (MT) family, which are Cys-rich proteins that have a high affinity for divalent metals such as Zn and Cu (Jarosz *et al.*, 2017). It is made up of three different isoforms distributed throughout the body, characterised by a high content of sulphhydryl groups and a central Zn component, which is important for maintaining their structure and function (Casas *et al.*, 2016; Lestegás, 2021). The main function of MT is to serve as a Zn acceptor and donor, thereby controlling the concentration of readily available Zn ions. They participate in heavy metal detoxification processes, cell membrane stabilisation, apoenzyme activation, and FR capture and elimination (Jarosz *et al.*, 2017). Zn stabilises the tertiary structure of enzymes, giving them a shape known as ‘zinc fingers’, which act as binding sites for other proteins, lipids and nucleic acids, especially DNA, facilitating transcription and gene expression. They perform biological functions related to cell growth and metabolism, sexual development and neuronal growth (Fig. 57) (Rosas-Romero & Covarrubias-Gómez, 2020; Lestegás, 2021).

Box 67

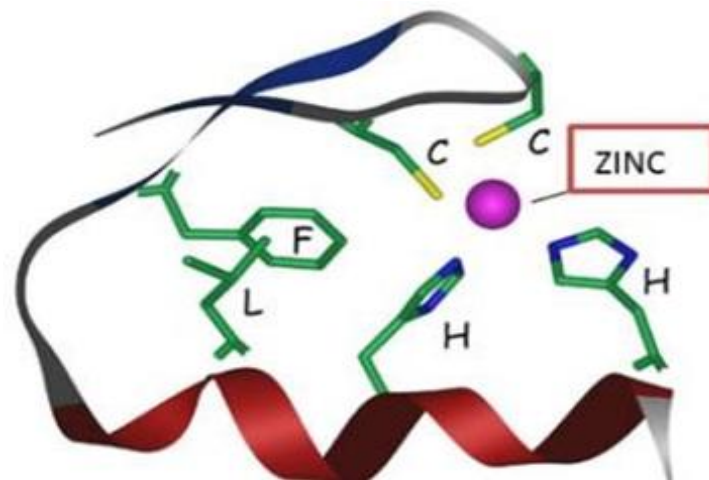


Figure 57

Structure of metallothionein

Casas et al. (2016).

Although Zn is an inert redox metal, it functions as an antioxidant because it acts as a cofactor for enzymes in the antioxidant system through the catalytic action of copper/zinc SOD (Lee, 2018; Biasi *et al.*, 2020; Vildoso *et al.*, 2021), helps reduce OS and protects biological structures from damage during inflammatory processes (Jarosz *et al.*, 2017), regulates the redox state in the body by maintaining Zn homeostasis (Tardy *et al.*, 2020), induces MT synthesis, which is important in reducing and eliminating the formation of $\bullet\text{OH}$ from H_2O_2 by preventing the formation of ROS or as chelators of transition metals such as iron and copper, reducing toxicity and decreasing their intracellular concentrations (He *et al.*, 2017; Biasi *et al.*, 2020; Janciauskiene, 2020), MTs have been shown to be 300 times more effective than GPx at eliminating $\bullet\text{OH}$ (Jarosz *et al.*, 2017).

Another effect of Zn on the antioxidant protection system is its inhibitory action on NADPH oxidase, an enzyme involved in the production of ROS, specifically catalysing the production of 1O_2 (He *et al.*, 2017; Vildoso *et al.*, 2021), also participates in the metabolism of proteins, carbohydrates, lipids, nucleic acids and acts in the inhibition of their oxidation (Tardy *et al.*, 2020; Praharaj *et al.*, 2021), plays a key role in the mechanisms of cell proliferation and differentiation (Rosas-Romero & Covarrubias-Gómez, 2020), RNA and DNA synthesis, as well as cell structures, cell membrane function and stabilisation (Gammoh & Rink, 2017; Pecora *et al.*, 2020), contributes to the production of antibodies, especially immunoglobulin G, influences macrophage activity, regulates lymphocyte apoptosis by modulating susceptibility to infections, improves intestinal absorption, and promotes growth (Casas *et al.*, 2016; Restrepo *et al.*, 2016).

The main source of Zn is found in a variety of foods, with the highest concentrations present in foods of animal origin, especially in the organs and muscles of cattle, pigs, poultry, fish and shellfish such as shrimp, oysters and crabs, and to a lesser extent in eggs and dairy products (López de Romaña *et al.*, 2010; Rosas-Romero & Covarrubias-Gómez, 2020). It is also present in nuts, seeds, legumes, fortified and whole grains, and to a lesser extent in tubers, fruits, and vegetables (Table 11) (Gammoh & Rink, 2017; Pecora *et al.*, 2020). In addition to food, Zn can be ingested through oral supplements, however, not all offer the same bioavailability (Gammoh & Rink, 2017).

Box 68

Table 11

cMain dietary sources of zinc

Food	Zinc content (mg/100g)
Liver, kidney	893
Beef or pork	843
Seeds, nuts	791
Dried fruit	751
Chicken	670
Eggs	327
Bread	247
Fish, seafood	199
Whole grains	156
Dairy products (milk, cheese)	147
Refined grains	125
Root vegetables	118
Vegetables	100
Fruit	94

López de Romaña et al. (2010) y Restrepo et al. (2016).

The bioavailability and absorption of Zn depends on the composition of the diet. Indigestible plant ligands such as phytate, some dietary fibres and lignin chelate Zn and inhibit its absorption (Pecora *et al.*, 2020; Rosas-Romero & Covarrubias-Gómez, 2020). Therefore, it has been established that its bioavailability varies according to the molar ratio of phytate to Zn. When this ratio is greater than 20, it is associated with poor absorption of the micronutrient (Restrepo *et al.*, 2016). Other factors that influence Zn absorption are calcium and iron (Gammoh & Rink, 2017). Therefore, Zn from animal sources has greater bioavailability than that from plant sources and cereals (Pecora *et al.*, 2020), since in addition to containing Zn, they provide lysine, which allows for its solubility and good absorption. On the other hand, cereals, legumes, and oilseeds have a high phytic acid content that makes them insoluble, so they are eliminated in the faeces (Restrepo *et al.*, 2016; Praharaaj *et al.*, 2021). In oral supplements, Zn bound to amino acids such as aspartate, Cys and His has the highest absorption concentration, while zinc oxide has the lowest bioavailability (Gammoh & Rink, 2017).

The recommended daily intake depends on various factors such as age, sex, weight and phytate content in the diet (Restrepo *et al.*, 2016). An intake of 11 mg/day for men and 8 mg/day for women is recommended (Jarosz *et al.*, 2017).

The effect of Zn on the immune system is complex; it can both enhance and inhibit different immune functions to achieve an appropriate balance between pro- and anti-inflammatory effects through different mechanisms (Pecora *et al.*, 2020). Adequate intake is essential to limit the overproduction of inflammatory cytokines, help improve OS levels, and provide antimicrobial action in the gastrointestinal tract (Kumar *et al.*, 2017). On the other hand, its deficiency is associated with high levels of EO in tissues that induce the oxidation of lipids, proteins and DNA, causing apoptosis and cellular dysfunction (Casas *et al.*, 2016). It is considered a health risk factor and is associated with various problems such as teratogenic effects, poor physical growth, increased inflammatory response, weakened immune system, and increased risk of infections such as malaria, HIV, tuberculosis, measles, and pneumonia (Lestegás, 2021; Praharaaj *et al.*, 2021). It has also been linked to metabolic diseases and ECDs such as cancer, diabetes, cognitive impairment, and AD (Gammoh & Rink, 2017; Lee, 2018).

The organs most affected are the CNS, gastrointestinal, skeletal, immune and reproductive systems (Praharaj *et al.*, 2021). Zn deficiency can cause death, and the WHO has defined it as currently the fifth leading cause of mortality and morbidity in developing countries (Gammoh & Rink, 2017).

3.4.3. Melatonin

Melatonin, also known as the ‘sleep hormone,’ is a pleiotropic neuroendocrine hormone produced mainly by the pineal gland, which is located at the base of the brain. It is responsible for regulating the circadian rhythm (the natural cycle of physical, mental, and behavioural changes that the body experiences throughout the day) It is characterised by being an antioxidant, anti-inflammatory, immunomodulatory and neuroprotective hormone (González-Costa & Padrón, 2019; Ferlazzo *et al.*, 2020).

The synthesis and secretion of melatonin increases in darkness and is inhibited by light. Light information is transmitted from the retina to the pineal gland via the suprachiasmatic nucleus of the hypothalamus. In humans, its secretion begins shortly after sunset, peaks in the middle of the night, between 2 and 4 a.m., and gradually decreases during the rest of the day (Kamfar *et al.*, 2024). Almost 80% of melatonin is synthesised during the night, with serum concentrations ranging from 80 to 120 pg/mL (Fig. 58). Levels are high from birth but decrease with age (Tordjman *et al.*, 2017; Kamfar *et al.*, 2024).

Box 69

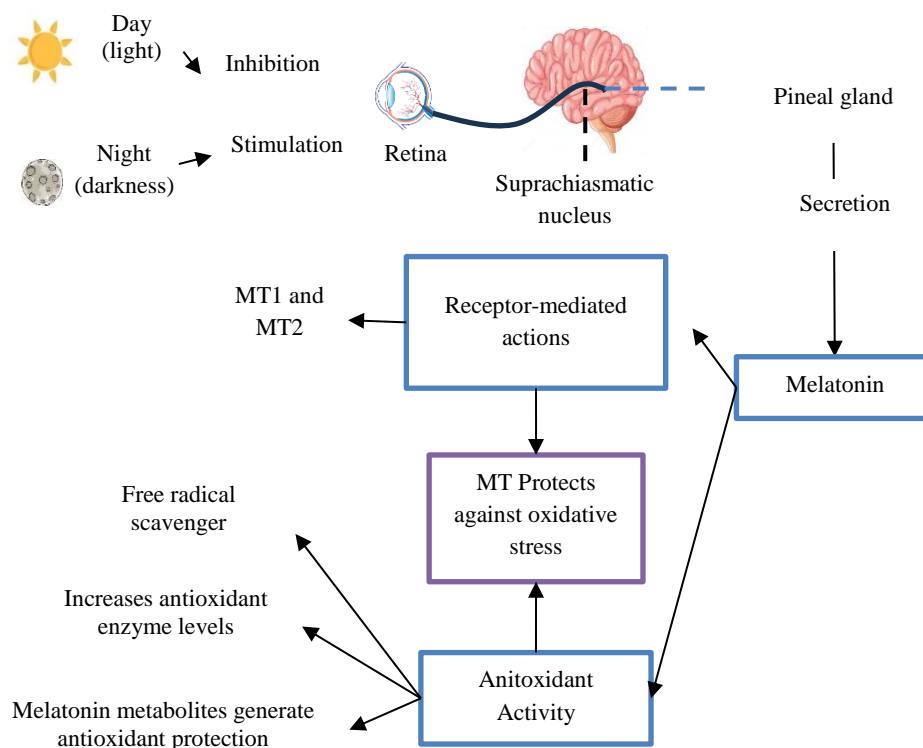


Figure 58

Melatonin production and its functions.

Tordjman et al. (2017).

Melatonin originates from the amino acid tryptophan (Trp), which is hydroxylated in the mitochondria by Trp hydroxylase, resulting in 5-hydroxytryptophan. Subsequently, it is converted into serotonin in the cytosol by the enzyme decarboxylase. Next, N-acetylserotonin undergoes rapid O-methylation thanks to the enzyme hydroxyindole-O-methyltransferase, generating N-acetyl-5-methoxytryptamine, better known as melatonin (Fig. 59) (Argüelles & Bonmatí, 2015; Ferlazzo *et al.*, 2020).

Box 70

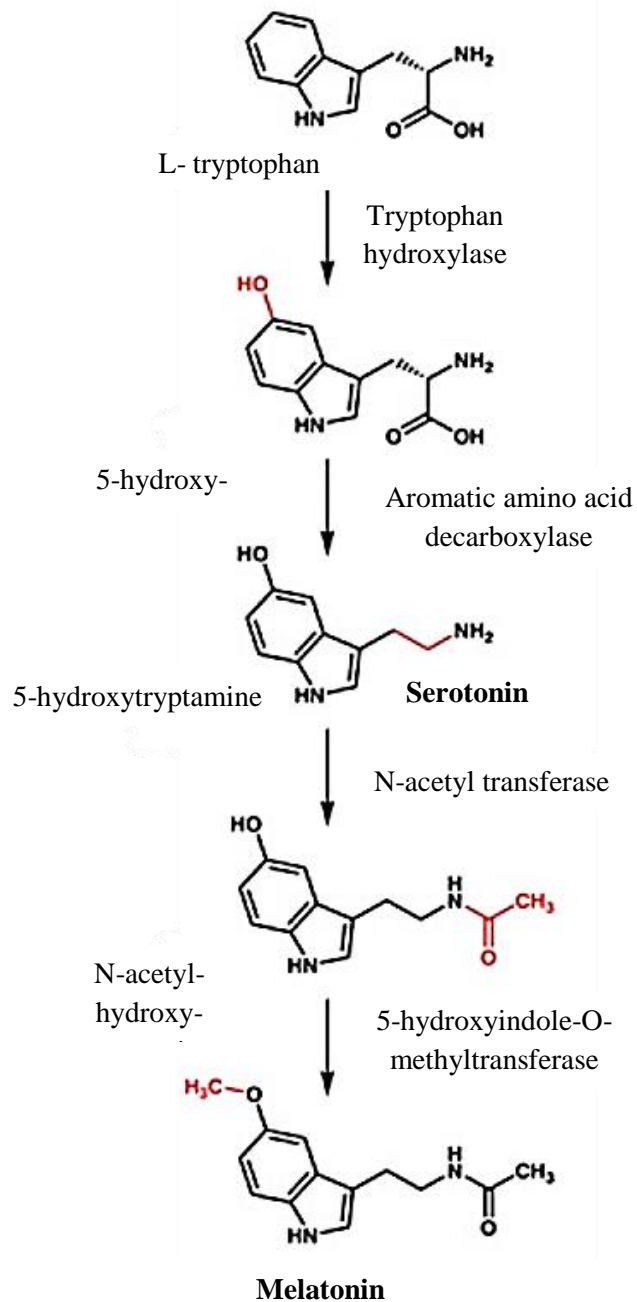
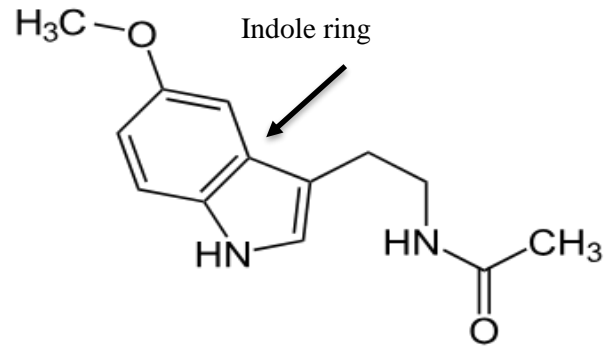


Figure 59
elatonin biosynthesis

Argüelles & Bonmatí (2015).

Melatonin performs various functions, the most important of which is its antioxidant activity. This is mainly due to its aromatic indole ring rich in e-, which makes it a powerful e- donor, thereby significantly reducing OS (Fig. 60). In addition, melatonin can activate MT1 and MT2 melatonin receptors that are coupled to G protein, positively regulating antioxidant defence systems by increasing the expression or activity of antioxidant enzymes such as SOD and GPx (Argüelles & Bonmatí, 2015; Tarocco *et al.*, 2019).

One of the most attractive properties of melatonin, which distinguishes it from most antioxidants, is that its metabolites also have the ability to scavenge ROS and RNS, making it a very effective antioxidant at low concentrations (Leonardo-Mendonça *et al.*, 2017). It also has the ability to chelate transition metals involved in Fenton/Haber-Weiss reactions, thereby reducing the formation of •OH and thus reducing OS (Reiter *et al.*, 2016).

Box 71**Figure 60**

Structure of melatonin

Argüelles & Bonmatí (2015).

Other functions of melatonin include regulating circadian rhythms such as the sleep-wake cycle, neuroendocrine rhythms, and body temperature cycles through its action on MT1 and MT2 receptors. Altered circadian rhythms are associated with sleep disorders and health problems. It may also have important immunostimulatory actions in allergies and possess anticancer activity through antiproliferative effects. For this reason, melatonin may be a candidate for the prevention and treatment of various types of cancer, such as breast, prostate, gastric, and colorectal cancer (Poza et al., 2022).

Chapter 4. Extraction, Identification, and Quantification of Antioxidant Compounds

4.1. Extraction of Antioxidants

The extraction, identification, and quantification of antioxidant compounds are fundamental processes in food, pharmaceutical, and biotechnology research due to the numerous health benefits associated with these compounds, such as the prevention of OE and the reduction of the risk of chronic diseases, including cancer, CVD, and neurodegenerative diseases (Wang & Weller, 2006). However, determining antioxidant capacity is complex, as due to the variety of compounds with antioxidant activity, aspects related to both the chemical nature and the natural reactions that occur in vivo must be considered (Gupta *et al.*, 2015).

It is necessary to consider the chemical structure, stereochemistry, concentration of the antioxidant, intrinsic reactivity towards FR and reactive species (ERO, ERN, ERS), temperature, and kinetics of the redox reactions involved. In addition, the extraction of the antioxidant from the food matrix of interest must be considered (Gupta *et al.*, 2015; Xiao *et al.*, 2020).

To this end, traditional extraction methods are used, such as solvent extraction, maceration, and percolation, which employ solvents such as methanol, ethanol, acetone, and water. The selection of these will be in accordance with the biological matrices (Wang & Weller, 2006; Lefebvre *et al.*, 2020; Shaikh *et al.*, 2020).

In addition, advanced methods such as ultrasound-assisted extraction (UAE), supercritical fluid extraction (SFE), and microwave-assisted extraction (MAE) have significantly improved extraction efficiency, reducing time and minimising the use of toxic solvents (Chemat & Khan, 2011). USE utilises ultrasonic waves to break down cell walls and facilitate the release of antioxidant compounds, while SFE employs supercritical CO₂ as a solvent, which is efficient and environmentally friendly (Carpentieri *et al.*, 2021). On the other hand, MAE uses microwaves to heat the solvent and plant material, accelerating the extraction process (Chemat & Khan, 2011).

4.2. Identification of antioxidants

Once extracted, antioxidants must be identified and quantified using precise techniques. Chromatography, especially high-performance liquid chromatography (HPLC), is essential for the identification of antioxidants due to its ability to separate and detect compounds with high precision (Balentine *et al.*, 1997). Gas chromatography (GC) is used for volatile and thermolabile compounds, although it requires a derivatisation step for non-volatile compounds.

Thin-layer chromatography (TLC) is also used for rapid preliminary identification of antioxidants (Shaikh *et al.*, 2020). When these techniques are inaccessible or costly, conventional qualitative phytochemical tests are inexpensive, easy, and require fewer resources, so they remain a good option for preliminary screening of phytochemicals.

Table 12 shows some tests and their procedures taken from Shaikh *et al.* (2020).

Box 72

Table 12

Conventional qualitative phytochemical tests

Test	Procedure	Results
Dragendorff / Kraut	Filtered mL + 1-2 mL Dragendorff's reagent	Red-copper precipitate
Hager	Filtered mL ^a + 1-2 mL Hage reagent	White-cream precipitate
Mayer / Bertrand / Valser	Filtered mL ^a + 1-2 drops of Mayert's reagent (along the wall of the tube)	Yellow-cream precipitate
Wagner	Filtered mL + 1-2 drops of Wagner's reagent (along the wall of the tube)	Red-copper precipitate
Of picric acid	mL filtered + 3-4 drops of 2% picric acid solution	Orange colour
Iodo	3mL of extract solution + drops of iodine solution	Blue colour that disappears when boiling and reappears when cold
Bouchardat	6mL completely evaporated plant extract + 6mL ethanol (@60 °C) + drops of Bouchardat reagent (in iodine solution)	Reddish brown colour
Of tannic acid	Acidified extract + 10% tannic acid solution	A hastily chosen colour
Barfoed	1mL filtered + 1mL Barfoed reagent + calendar for 2 min.	Red precipitate (monosaccharide)
Molish	2 mL filtered + 2 drops of α -naphthol + 1 mL concentrated H ₂ SO ₄ (along the walls of the tube)	Violet ring
Seliwanoff	1 mL extract solution + 3 mL Seliwanoff reagent + heating in a water bath for 1 min.	Pinkish red colour {ketones}
Resorcinol	2mL aqueous solution of the extract + resorcinol crystals + 1:1 by volume of conc. HCl + heating	Pink colour {ketones}
For pentoses	2mL conc. HCl + fluoroglucinol + 1:1 aqueous extract solution + heating over flame	Red colour
For starch	Aqueous extract + 5mL 5% KOH	Colour: Cyan Blue
Benedict	0.5mL filtered + 0.5mL Benedict's reagent + Boil for 2 min	Colour: green/yellow/red
Fehling	1 mL of each Fehling's reagent A & B + 1 mL filtered in a hot water bath	Red precipitate
Borntrager	2mL filtered hydrolysate + 3mL chloroform + vigorous shaking + separation of the chloroform layer + 10% ammonium solution	Pink solution
Modified Borntrager test	Extract + ferric chloride solution + boil for 5 min. + cool + add benzene 1:1 + separate benzene layer + ammonium solution	Coloured solution ranging from pink to blood red
Legal	Dissolve 50g of plant extract in pyridine + sodium nitroprusside + 10% NaOH.	Pink solution
10% NaOH	1mL diluted H ₂ SO ₄ + 0.2mL extract + boil for 15 min. + cool + neutralise with 10% NaOH + 0.2mL Fehling's reagent A&B	Red brick precipitate
Aqueous NaOH	Extract + dissolve in 1 mL of water + drops of aqueous NaOH solution	Yellow colour
Concentrated H ₂ SO ₄	5mL plant extract + 2mL glacial acetic acid + one drop of 5% FeCl ₃ + conc. H ₂ SO ₄	Coffee ring
Raymond	Extract + di-nitrobenzene in hot methanolic alkali	Purple colour
Detection of cardiotoxic glycosides		
Keller-K illani	1 mL filtrate + 1.5 mL glacial acetic acid + 1 drop of 5% ferric chloride + concentrated H ₂ SO ₄ (along the wall of the tube)	Blue coloured solution (in acetic acid layer)
Kedee	4 mL extract evaporated to dryness + 1-2 mL methanol + 1-2 mL alcoholic KOH + 3-4 drops of 1% alcoholic 3,5-dinitrobenzene + heating	Disappearance of the colour violet
Cardenolides	Extract + pyridine + sodium nitroprusside + 20% NaOH	Red colour fading to yellow-brown
Brominated water	Extract + mL of brominated water	Yellow precipitate
Baljet	2mL extract + 1 drop of Baljet reagent	Colour: Yellow-orange
Detection of proteins and amino acids		
Biuret	2mL filtered + 1 drop of 2% copper sulphate + 1mL of 95% ethanol + KOH lentils	Pink solution (in ethanol layer)
Millionaire	2mL filtered + drops of Millon's reagent	White precipitate
Ninhydrin	2mL filtered + 2 drops ninhydrin solution	Purple solution {Amino acids}
Xanthoproteica	Extract + drops of nitric acid	Yellow solution
Alkaline Reagent	1mL extract + 2mL 2% NaOH	When diluted acid is added, it changes from colourless to a deep yellow colour.
Lead acetate	1mL extract + drops of 10% lead acetate	Yellow precipitate
Shinoda / Reduction of Mg hydrochloride	Extract dissolved in 5 mL of alcohol + magnesium ribbon fragments + drops of conc. HCl.	From pink to crimson
Shibata/ Cyanidin	1g aqueous extract + dissolve in 1-2 mL of 50% methanol with heating + metallic magnesium	Shibata/ Cyanidin
Ferric chloride	Ferric chloride solution + drops of 10% ferric chloride	Green precipitate
Pew	mL of aqueous extract + 0.1g metallic zinc + 8mL conc. H ₂ SO ₄	Red colour {flavonols}
Reduction of Zn hydrochloride	Extract + Zn powder + conc. HCl along the walls of the tube	Magenta colour
Ammonia	Filtering + 5mL diluted ammonia solution + concentrated H ₂ SO ₄	Yellow colour
H ₂ SO ₄ Conc.	Extract + concentrated H ₂ SO ₄ .	Orange colour
From Iodo	1mL extract + drops of iodine solution.	Transient red colour
Ferric chloride	Aqueous extract + drops of 5% ferric chloride	Dark green/bluish black
Jelly	Extract dissolved in 5mL distilled water + 1% gelatin solution + 10% NaCl	White precipitate
Lead acetate	Extract dissolved in 5 mL distilled water + 3 mL 10% lead acetate	White precipitate

Ellagic acid	Aqueous extract + 5% glacial acetic acid + 5% sodium nitrite	The solution becomes muddy/dark brown precipitate.	
Potassium dichromate	Extract + drops of potassium dichromate solution	Dark colour	
Hot water	Hot water in a beaker + submerge the part of the plant + heat for one minute.	Black or dark brown ring on the part that was submerged	
Carotenoids	1g extract + 10mL chloroform, shaken vigorously and filtered.	Blue colour at the interface	
Braymer	1 mL filtered + 3 mL distilled water + 3 drops of 10% ferric chloride solution	Colour: Blue-green	
10% NaOH	0.4 mL extract + 4 mL 10% NaOH + vigorous shaking	Emulsion formation {hydrolysable tannins}	
Brominated water	10 mL brominated water + 0.5 g extract	Brominated colour fading	
Lead subacetate	1mL filtered + 3 drops of lead subacetate solution	Creamy gelatinous precipitate	
Phenazone	(5 mL aqueous extract + 0.5 g sodium acid phosphate heated and allowed to cool + filtered) filtered + 2% phenazone	Hasty	
Mitchell	Extract + iron + sodium tartrate (+ ammonium acetate solution)	Water-soluble iron-tannin complex, insoluble in ammonium acetate solution	
Detection of flobatinins			
HCl	2mL aqueous extract + 2mL 1% HCl (boil)	Red precipitate	
Detección de saponinas			Saponin detection
Foam formation	0.5g extract + 2mL water (shake vigorously)	Foam persists for 10 minutes	
	20mL water in a beaker + 50g extract (shake vigorously for 15 min.)	Formation of a 2 cm layer of foam	
	0.2g extract + 5mL distilled water; shake well; heat to boiling point	Appearance of creamy mist with small bubbles	
NaHCO ₃	Extract + mL sodium bicarbonate solution + distilled water (shake vigorously)	Stable foam like honeycomb	
Olive oil	Aqueous extract + 5mL distilled water; shake vigorously + drops of olive oil + shake vigorously	Foam Appearance	
Haemolysis	Drop of fresh blood on a slide + extract	Haemolysis zone	
Detection of phytosterols			
Salkowski	Filtradoc + drops of H ₂ SO ₄	concentrate (shake and allow to rest)	
Liebermann- Burchard	50g extract dissolved in 2mL anhydrous acetic acid + 1-2 drops of concentrated H ₂ SO ₄ (along the wall of the tube)	Colour change	
Anhydrous acetic acid	0.5 mL extract + 2 mL acetic anhydride + 2 mL conc. H ₂ SO ₄ .	Violet colour change from blue to green	
Hesse	5mL aqueous extract + 2mL chloroform + 2mL conc. H ₂ SO ₄	Pink/red ring (in the lower layer of chloroform)	
Sulphur	Extract + powdered sulphur granules	Sulphur sinks	
Detection of terpenoids			Detection of terpenoids
	2 mL chloroform + 5 mL extract (evaporate in a water bath) + 3 mL conc. H ₂ SO ₄ (boil in a water bath)	Grey colour	
Detection of diterpenes			
Salkowski	Filter + drops of concentrated H ₂ SO ₄ (shake and leave to stand)	Golden yellow layer at the bottom	
Lignin detection			
Labat	Extract + gallic acid	Olive green colour	
Furfuraldehyde	Extract + 2% furfuraldehyde	Red colour	
Carotenoid detection			
Carr-Price	10mL extract evaporated to dryness + 2-3 drops of saturated solution of antimony trichloride in chloroform	Blue-green colour eventually changing to red	
Detection of quinones			
Alcoholic KOH	1 mL extract + mL alcoholic KOH	Colour from red to blue	
Concentrated HCl	Extract + concentrated HCl	Green colour	
Sulphuric acid	10mg extract + dissolve in alcohol + drops of concentrated H ₂ SO ₄	Red colour	
Detection of anthocyanins			
HCl	2 mL extract + 2 mL 2N HCl (+ mL ammonia)	Pink-red solution that turns blue-violet after the addition of ammonia	
Detection of coumarins			
Paper NaOH	0.5 g wet extract in a test tube, the mouth of the tube is covered with filter paper with 1N NaOH, followed by heating in a water bath for a few minutes.	Fluorescent yellow on paper under UV light	
NaOH	Extract + 10% NaOH + Chloroform	Yellow colour	
Detection of gums and mucilages			
Alcohol	Dissolve 100mg of extract in 10mL distilled water + 25mL absolute alcohol (stirring constantly)	White or cream precipitate	

a = 50 g of solvent-free extract is mixed with a few mL of diluted and filtered HCl

b = 100 mg solvent-free extract dissolved with 5 mL in distilled water and filtered

c = plant extract with 1:1 chloroform filtered

{ } = Indicates the presence of specific photo constituents

4.3. Quantification of antioxidants

Spectroscopy is also an invaluable tool for the rapid and non-destructive identification of antioxidants. Techniques such as mass spectrometry (MS), often coupled with HPLC (HPLC-MS), provide detailed information on the molecular structure of antioxidants, offer high sensitivity and specificity, and are essential for the identification of antioxidant compounds in complex mixtures (Zuo *et al.*, 2006). Nuclear magnetic resonance (NMR) spectroscopy provides detailed information on molecular structure, while chromatographic methods such as HPLC with UV-Vis detection allow for the precise quantification of individual compounds in a mixture. Gas chromatography with flame ionisation detection (GC-FID) is used for the quantification of volatile antioxidant compounds (Zuo *et al.*, 2002; Wang & Weller, 2006). Electrochemistry offers additional methods for antioxidant quantification, such as cyclic voltammetry, which measures antioxidant capacity based on e- transfer, and electrochemical biosensors, which provide rapid and accurate results for the specific detection and quantification of antioxidants (Chemat & Khan, 2011), UV-Vis spectroscopy is widely used for the quantification and characterisation of phenolic compounds and flavonoids (Balentine *et al.*, 1997).

The Folin-Ciocalteu method is widely used for the quantification of total phenols and is based on the reduction of the Folin-Ciocalteu reagent by antioxidants, producing a colour change measured spectrophotometrically (Wang & Weller, 2006), while for the group of flavonoids, which contain 5-hydroxy-4-keto, 3-hydroxy-4-keto or o-dihydroxyl systems, they are capable of chelating with AlCl₃, and the reaction manifests itself as a bathochromic shift of the bands in the UV-Visible spectrum), the absorbance peak of quercetin alone, a compound used as a reference standard, is at 260 nm and 370 nm (Matić and Jakobek, 2021; Aparna and Hema, 2022). Aparna and Hema (2022) successfully developed and validated a simple and rapid spectrophotometric method for quantifying the total flavonoid content in the seeds of selected plants of the Apiaceae family.

The method developed proved to be feasible, have a shorter execution time and be low cost, Therefore, small laboratories can rely on this method for routine quality control analyses or use it as a preliminary test to evaluate the flavonoid content in a large number of plant samples in a short time. They recommend performing the spectrum analysis of the standard and the complex with AlCl₃ to determine the ideal wavelength that shows the maximum absorbance, rather than following a previously specified wavelength, since the instruments, chemicals, and other analytical conditions used may vary from person to person (Aparna & Hema, 2022).

For the detection of anthocyanins, the pH differential method is used, which is considered an economical and simple method for the determination of these compounds. This method measures the total content of monomeric anthocyanins based on structural changes from the flavilium cation at pH 1.0 to the carbinol pseudobase at pH 4.5. With this approach, the total anthocyanin content (TAC) can be specified using a summation parameter (Mercedes *et al.*, 2022).

However, a disadvantage of this method lies in the extensive sample preparation and low precision. Although it is suitable for authenticity testing of fruit juices, it must be combined with the quantification of individual anthocyanins using reference methods. Alternatively, the use of near-infrared spectroscopy (NIR) has been proposed as a rapid, non-invasive and economical option, which has become a widely used technique in the pharmaceutical and food industries (Mancini *et al.*, 2020; Singh *et al.*, 2020).

4.4. Antioxidant Activity

Antioxidant capacity assays allow the antioxidant potential to be evaluated directly from plant extracts and biological fluids. They are generally divided into two categories: those based on electron transfer (ET) and those based on hydrogen atom transfer (HAT). The former tests involve a redox reaction with the oxidant as an indicator of the endpoint of the reaction. On the other hand, most HAT-based assays monitor competitive reaction kinetics, and quantification is derived from kinetic curves. HAT-based methods generally consist of a synthetic FR generator, an oxidisable molecule, and an antioxidant. Both HAT- and ET-based assays are intended to measure the radical (or oxidant) scavenging capacity, rather than the preventive antioxidant capacity, of a sample (Xiao *et al.*, 2020; Rumpf *et al.*, 2023).

In most ET-based assays, the antioxidant reaction is simulated with a suitable redox potential molecule, i.e., antioxidants react with a fluorescent or coloured compound (oxidising agent) rather than ROO•. ET-based spectrophotometric assays measure the ability of an antioxidant to reduce an oxidant, which changes colour when reduced; the degree of colour change (either an increase or decrease in the absorbance of the compound at a given wavelength) correlates with the concentration of antioxidants in the sample. ET-based assays include, among others, assays with 2,2'-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), or 2,2-diphenyl-1-picrylhydrazil (DPPH), ferric oxidation with xylenol orange (FOX), ferric thiocyanate (FTC), ferric reducing/antioxidant power (FRAP), potassium ferricyanide reducing power (PFRAP), and cupric reducing antioxidant power (CUPRAC) (Gupta, 2015). Table 13 shows a comparison of two of the most widely used and reported spectrophotometric methods, taken from Becker *et al.* (2019).

Box 73

Table 13

Comparison of the most commonly used spectrophotometric methods

Essay	Biochemical principle	Characteristics
DPPH	Antioxidants neutralize DPPH* radicals through SET and HAT; there is a decrease in absorbance over time, proportional to antioxidant capacity.	Relatively stable radical; highly reproducible and accurate; applied only in organic solvents; easy and fast.
ABTS	Los antioxidantes neutralizan los radicales ABTS por SET y HAT; se trata de una disminución de la absorbancia a lo largo del tiempo, proporcional a la capacidad antioxidante	Wide pH range; applied to hydrophilic and lipophilic antioxidants; prolonged reaction time (>6 min) could give incorrect results due to a short assay; sensitive, easy, and fast.

Becker et al. (2019).

On the other hand, HAT-based assays measure the ability of an antioxidant to neutralize free radicals (generally ROO•, considered biologically more relevant) by donating a hydrogen atom (Eq. 33).



The oxy-aryl radical (ArO•) is formed from the reaction between the antioxidant phenol and ROO•, and is stabilized by resonance. The AH and ArOH species represent protected biomolecules and phenolic antioxidants, respectively. Effective antioxidants must react faster than biomolecules with FRs to protect the latter from oxidation. In HAT-based antioxidant assays, both the fluorescent probe and the antioxidants react with ROO•, allowing antioxidant activity to be determined from the competition kinetics. This is achieved by measuring the fluorescence decay curve of the probe in the absence and presence of antioxidants, integrating the area under these curves, and calculating the difference between them. HAT-based assays include oxygen radical absorbance capacity (ORAC) assays, total peroxyl radical capture (TRAP) assays, thiobarbituric acid (TBA) assays, β -carotene bleaching assays, and cellular antioxidant activity (CAA) assays, among others (Xiao, 2020)). Table 14 presents some of the techniques used and their operating principles.

Box 74

Tabla 14

Técnicas de Cuantificación de Antioxidantes

Essay	Radical/Chromophore	Measurement wavelength	pH measurement	Test mode	Type of transfer
ORAC	AAPH (Fluorescein)	λ_{ex} = 485 nm and λ_{em} = 538 nm	pH 7.4	Fluorescence decay measurement	HAT
TRAP	AAPH (R-ficoeritrin/Luminol)	λ_{ex} = 495 nm and λ_{em} = 575 nm	pH 7.5	Fluorescence decay measurement	HAT
Beta-carotene bleaching test	Peroxyl radicals, ROO	470 nm	pH 5.5 – 7.5	Absorbance	HAT
Crocin bleaching test	Peroxyl radicals, ROO	440 nm	pH 7.0 – 7.5	Absorbance	HAT
Total phenol content	Mo6+ (yellow) → Mo5+ (blue)	765 nm	pH 10	Absorbance	ET
Ferric ion reduction antioxidant assay (FRAP)	Chelation of Fe3+ ions	595 nm	pH 3.6	Absorbance	ET
DPPH	DPPH	515 nm	pH 7.0 – 7.4	Absorbance	ET
Antioxidant capacity in Trolox equivalents (TEAC) (ABTS by radical used)	ABTS+	734 nm	pH 7.4 (phosphate buffer used)	Absorbance	ET
Cu2+ reducing antioxidant power (CUPRAC)	Cu2+ → Cu4 (complexed with neocuproine)	450 nm	Acidic/Neutral /Alkaline	Absorbance	ET
Cerium Antioxidant Reducing Capacity (CERAC)	Ce4+ → Ce3+	λ_{ex} = 256 nm and λ_{em} 360 nm =	Acid (0.3 M H2SO4)	Fluorescence decay measurement	ET
Lipid peroxidation inhibition assay	N-methyl-2-phenylindole	586 nm	pH 7.4	Absorbance	HAT
Hydroxyl radical scavenging capacity (HORAC test) The hydroxyl radical is one of the most reactive free radicals in the atmosphere. It is produced by the interaction of oxygen molecules with ozone and is responsible for the destruction of ozone in the atmosphere. The hydroxyl radical is also responsible for the destruction of ozone in the atmosphere.	Fluorescein HO (p-hydroxybenzoic acid)	λ_{ex} = 488 nm y λ_{em} = 515 nm	Phosphate buffer	Measurement of fluorescence decrease	HAT
Fe2+ ion chelation test	Ferrozine-Fe2+ complex	562 nm	pH 4-10	Absorbance	ET
Nitric oxide free radical scavenging activity	Griess reagent	546 nm	pH 6.6	Absorbance	ET
Potassium ferrocyanide reducing power (PFRAT)	Fe3+ → Fe2+	700 nm	pH 7.2	Absorbance	ET
Thiobarbituric acid reactive substances (TBARS) acronym)	Adducts MDA – TBA	532 nm	pH 2	Absorbance	ET
N,N-dimethyl-p-phenylenediamine (DMPD)	DMPD+ (resided)	505 nm	pH 5.25	Absorbance	Fenton-type ET-based reaction
Photochemiluminescence assay	O2.- (using luminol)	360 nm (luminescence and azul)	pH 10.5	Chemiluminescence	HAT

Conclusions

- The generation of ROS is a normal process during cellular metabolism; however, when there is an imbalance between these species and antioxidants in favour of the former, it causes ODS.
- ROS are mainly generated by exposure to exogenous factors such as alcohol, tobacco, drugs, toxic agents, environmental pollution, ionising radiation, X-rays, gamma rays, ultraviolet radiation, stress, among others. Therefore, recurrent and prolonged exposure to these sources causes deterioration and damage at the cellular, tissue, and molecular levels, leading to: ECD as AD in amyloid plaques and neurofibrillary tangles, EP in dopaminergic neurons located in the substantia nigra, ELA in motor neurons and mitochondria, ECV in the endothelium and mitochondria, liver diseases in hepatocytes and mitochondria, diabetes in the CTE, cancer in cells, and physical activity in skeletal muscle, mitochondrial fibres, sarcolemma, sarcoplasmic reticulum, and T tubules and CTE.
- There are other sources that generate ROS, such as intensive exercise. Therefore, it is advisable to perform this activity in moderation, as people who are not accustomed to this type of activity are more likely to generate ROS, causing premature ageing.
- The consumption of exogenous antioxidants is recommended, which are obtained through diet, mainly from fruits and vegetables, as these contain higher amounts of antioxidants and their activity is greater; in addition, they not only help eliminate ROS, but also play a key role in reinforcing and replenishing endogenous antioxidant enzymes to eliminate excess oxygen metabolites.
- Polyphenols are the most common antioxidants in our diet. They are very numerous and widely distributed in plant-based foods and are considered very efficient antioxidants due to their structural diversity and antioxidant activity.
- It is important to know the antioxidant content of foods in order to have a balanced diet, since at certain concentrations and depending on the sources, they can function as antioxidants or pro-oxidants promoting OE. Therefore, a higher intake of these can have consequences, causing harmful effects on health by increasing damage in certain diseases. In addition to maintaining a healthy lifestyle, a balanced diet and moderate physical activity, this helps to prevent the formation of ROS that cause LO.
- The extraction, identification and quantification of antioxidant compounds are complex processes that require advanced and precise methods. The evolution of techniques such as UAE, SFE and MAE has significantly improved the efficiency and sustainability of antioxidant extraction.
- Chromatographic and spectroscopic techniques, such as HPLC, GC, MS and NMR, allow for the accurate identification and quantification of these compounds, which are essential for developing healthy and effective products.

Recommendations

One recommendation for future studies is the standardisation of units used to measure antioxidant content in foods, as there is variation in the units (mg, meq, etc.) and bases (wet and dry) used by different authors, which makes comparison difficult and is confusing for consumers. Likewise, propose foods that can be integrated into meal plans as dietary recommendations, based on research findings, aimed at the general population, athletes, and people suffering from chronic degenerative diseases with the aim of improving health and athletic performance. and additionally to carry out a more in-depth study to determine the fundamental role of exogenous antioxidants in various industries, including food, cosmetics and pharmaceuticals, to demonstrate their importance in health promotion and disease prevention.

Declarations

Conflict of interest

The authors declare that they have no conflict of interest. They have no financial interests or personal relationships that could have influenced this book.

Author contributions

Morachis-Valdez Ana Gabriela. PhD: Writing and structure research.

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Dublán-García, Octavio. PhD: Conducted the information search and coordinator of the working team.

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Funding

No external funding was received for the preparation of this work.

Acknowledgements

The authors Ana Gabriela Morachis Valdez and Karinne Saucedo Vence are grateful for the support of the Secretariat of Science, Humanities, Technology and Innovation (SECIHTI) for the postdoctoral fellowship.

Abbreviations

=CO	Carbonyl groups
•NO	Nitric oxide radical
•OH	Hydroxyl radical
¹ O ₂	Singlet oxygen radical
AD	Alzheimer's disease
AHD	Alcoholic liver disease
ALS	Amyotrophic lateral sclerosis
APOE	Apolipoprotein E gene
APP	Amyloid precursor protein
Arg	Arginine
ArO•	Oxyaryl radical
BMI	Body mass index
CAA	Cellular antioxidant activity
CAT	Catalase
CDD	Chronic degenerative disease
CNS	Central nervous system
COX	Cyclooxygenases
CVD	Cardiovascular disease

Cys	Cysteine
DA	Dopamine
DAQ's	Dopamine quinones
DM	Diabetes mellitus
DM1	Type 1 diabetes mellitus
DM2	Type 2 diabetes mellitus
e ⁻	Electron
EN	Nitro-oxidative stress
eNOS	Endothelial Nitric Oxide Synthase
ERN	Reactive nitrogen species
ET	Electron transfer
FA	Fatty Acids
FAD	Flavin adenine dinucleotide
FR	Free Radicals
GC	Gas chromatography
GC-FID	Gas chromatography with Flame Ionisation Detection
GDM	Gestational diabetes mellitus
GLUT-2	Glucose transporter-2
GPx	Glutathione peroxidase
GRx	Glutathione reductase
GSH	Glutathione
GSSG	Glutathione disulphides
GST	Glutathione S-transferase
H ₂ O	Water
H ₂ O ₂	Hydrogen Peroxide radical
AIH	Autoimmune hepatitis
HAT	Hydrogen atom transfer
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-Density Lipoproteins
HF	Heart failure
His	Histidine
HNE	4-Hydroxynonenal Aldehyde
HNO	Nitroxyl
HPLC	High-Performance Liquid Chromatography
iNOS	Inducible Nitric Oxide Synthase
LDL	Low-Density Lipoproteins
LGK	Liver-type glucokinase
L-OOH	Lipoperoxides
LOX	Lipoxygenases
LPO	Lipoperoxidation
Lys	Lysine
MAE	Microwave-Assisted Extraction
MAFLD	Metabolic Dysfunction-associated Fatty Liver Disease
MCO	Metal-Catalysed Oxidation
MDA	Malondialdehyde
MeSeCys	Se-methylselenocysteine
Met	Methionine
MS	Mass Spectrometry
MT	Metallothioneins
N ₂ O ₃	Dinitrogen trioxide
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NAFLD	Non-Alcoholic Fatty Liver Disease
NH ₂	Amino group
NIR	Near-Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance Spectroscopy
nNOS	Neuronal nitric oxide synthase
NO ₂ ⁻	Nitrite
NO ₂ ⁻	Nitrogen dioxide

NO ₃ ⁻	Nitrate
NOS	Nitric Oxide Synthase
NOX/DUOX	NADPH oxidase
O ₂	Oxygen
O ₂ • ⁻	Superoxide radical
O ₃	Ozone radical
ONOO ⁻	Peroxynitrite radical
ORAC	Oxygen radical absorbance capacity
OS	Oxidative stress
PC	Protein carbonylation
PD	Parkinson's disease
PLA ₂	Phospholipase A ₂
Pro	Proline
Prx	Peroxiredoxin
PSEN1	Presenilin 1
PSEN2	Presenilin 2
PUFA	Polyunsaturated Fatty Acids
RCS	Reactive Carbonyl Species
RE	Endoplasmic Reticulum
RO•	Alkoxyl radical
ROO•	Peroxyl radical
ROS	Reactive Oxygen Species
Sec	Selenocysteine
SeMet	Selenomethionine
SFE	Supercritical fluid extraction
SOD	Superoxide dismutase
TAC	Total anthocyanin content
TBA	Thiobarbituric acid
Thr	Threonine
TLC	Thin-layer chromatography
TRAP	Total peroxyl radical trapping parameter
Trp	Amino acid tryptophan
Tyr	Tyrosine
UAE	Ultrasound-assisted extraction
XO	Xanthine oxidase

References

Basics

- Abd El-Hack, M. E., de Oliveira, M. C., Attia, Y. A., Kamal, M., Almohmadi, N. H., Youssef, I. M., ... & Taha, A. E. (2023). **The efficacy of polyphenols as an antioxidant agent: An updated review.** *International Journal of Biological Macromolecules*, 250, 126525. <https://doi.org/10.1016/j.ijbiomac.2023.126525>
- Adwas, A. A., Elsayed, A., Azab, A. E., & Quwaydir, F. A. (2019). **Oxidative stress and antioxidant mechanisms in human body.** *Journal of Applied Biotechnology and Bioengineering*, 6(1), 43-47. DOI: 10.15406/jabb.2019.06.00173
- Aggarwal, A., Yadav, A., Saini, N., & Sandhir, R. (2022). **S-nitrosoglutathione alleviates hyperglycemia-induced neurobehavioral deficits involving nitro-oxidative stress and aberrant monoaminergic system.** *Nitric Oxide*, 122, 35-44. <https://doi.org/10.1016/j.niox.2022.03.001>
- Aguilar-Paredes, O. A., Castillo-Guevara, C., Díaz-Godínez, R., Nieto-Camacho, A., Méndez-Iturbide, D., & Tlaxcala, I. (2018). **Antioxidants and inhibition of free radicals: lipoperoxidation and carbonylation** *Antioxidantes e inhibición de radicales libres: lipoperoxidación y carbonilación.* *Mexican Journal of Biotechnology* 2018, 3(1), 60-72. DOI: 10.29267/mxjb.2018.3.1.60
- Akagawa, M. (2021). **Protein carbonylation: molecular mechanisms, biological implications, and analytical approaches.** *Free Radical Research*, 55(4), 307- 320. <https://doi.org/10.1080/10715762.2020.1851027>
- Akhlaghi, M., Ghobadi, S., Hosseini, M. M., Gholami, Z., & Mohammadian, F. (2018). **Flavanols are potential anti-obesity agents, a systematic review and meta-analysis of controlled clinical trials.** *Nutrition, Metabolism and Cardiovascular Diseases*, 28(7), 675-690. <https://doi.org/10.1016/j.numecd.2018.04.001>
- Al-Dashti, Y. A., Holt, R. R., Stebbins, C. L., Keen, C. L., & Hackman, R. M. (2018). **Dietary flavanols: a review of select effects on vascular function, blood pressure, and exercise performance.** *Journal of the American College of Nutrition*, 37(7), 553-567. <https://doi.org/10.1080/07315724.2018.1451788>
- Ali, S. S., Ahsan, H., Zia, M. K., Siddiqui, T., & Khan, F. H. (2020). **Understanding oxidants and antioxidants: Classical team with new players.** *Journal of Food Biochemistry*, 44(3), e13145. <https://doi.org/10.1111/jfbc.13145>
- Al-Kindi, SG, Brook, RD, Biswal, S. y Rajagopalan, S. (2020). **Environmental determinants of cardiovascular disease: lessons learned from air pollution.** *Nature Reviews Cardiology* 17 (10), 656-672. DOI: 10.1038/s41569-020-0371-2
- Al-Madboly, L. A., Ali, S. M., Fakharany, E. M. E., Ragab, A. E., Khedr, E. G., & Elokely, K. M. (2020). **Stress-based production, and characterization of glutathione peroxidase and glutathione S-transferase enzymes from *Lactobacillus plantarum*.** *Frontiers in Bioengineering and Biotechnology*, 8, 78. <https://doi.org/10.3389/fbioe.2020.00078>
- Almeida, A. M., Marchiosi, R., Abrahão, J., Constantin, R. P., dos Santos, W. D., & Ferrarese-Filho, O. (2023). **Revisiting the shikimate pathway and highlighting their enzyme inhibitors.** *Phytochemistry Reviews*, 23, 1-37. <https://doi.org/10.1007/s11101-023-09889-6>
- Alonso Diaz, T., Reyes Reyes, E., & Cuétara Lugo, E. (2023). **Ozonoterapia y cáncer: mito o realidad.** *Revista Cubana de Medicina*, 62(1).
- Alonso, T., Reyes, E., González, J., & Carrasco, J. (2021). **Estrés oxidativo, terapia antioxidante y cáncer.** *Revista Cubana de Oncología*, 19(2).

Alvarado-Villavicencio, M. B., Betancourt-Rubio, E. C., & Villamarín-Ponce, L. R. (2023). [Calidad de vida de los pacientes con cirrosis hepática](#). *Revista Finlay*, 13(3), 149-164. Recuperado de: <https://revfinlay.sld.cu/index.php/finlay/article/view/1304>

Alzheimer's Association. (2017). [Alzheimer's disease facts and figures](#). *Alzheimer's & Dementia*, 13(4), 325-373. <https://doi.org/10.1016/j.jalz.2017.02.001>

Ángeles-Garay, U., Sandoval-Sánchez, J. J., Sánchez-Martínez, L. C., Acosta- Cazares, B., & Ruíz-Betancourt, B. S. (2019). [Conducta sexual y otros factores de riesgo para cáncer de próstata](#). *Revista mexicana de Urología*, 79(5). Recuperado de: http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S2007-40852019000500004&lng=es&nrm=iso

Angelova, P. R., Esteras, N., & Abramov, A. Y. (2021). [Mitochondria and lipid peroxidation in the mechanism of neurodegeneration: Finding ways for prevention](#). *Medicinal Research Reviews*, 41(2), 770-784. <https://doi.org/10.1002/med.21712>

Aparna, B., & Hema, B. P. (2022). [Preliminary Screening and Quantification of Flavonoids in Selected Seeds of Apiaceae by UV-Visible Spectrophotometry with Evaluation Study on Different Aluminium Chloride Complexation Reaction](#). *Indian Journal of Science and Technology*, 15(18), 857-868. DOI: 10.17485/IJST/v15i18.131

Arana, C., Moreno-Fernández, A. M., Gómez-Moreno, G., Morales-Portillo, C., Serrano-Olmedo, I., de la Cuesta Mayor, M. C., & Hernández, T. M. (2017). [Incremento de los parámetros de estrés oxidativo salival en pacientes con diabetes tipo 2: relación con la enfermedad periodontal](#). *Endocrinología, Diabetes y Nutrición*, 64(5), 258-264. <https://doi.org/10.1016/j.endinu.2017.03.005>

Arce Gil, Z., López-López, E., Asalde-Ramos, R., Cortez-Vidal, M., & Loaiza- Chumacero, S. (2023). [Peroxidación lipídica y estrés laboral en trabajadores de una universidad privada del norte de Perú](#). *Horizonte Médico (Lima)*, 23(1). <http://dx.doi.org/10.24265/horizmed.2023.v23n1.08>

Argüelles, R., & Bonmatí Carrión, M. Á. (2015). [Melatonina, la hormona de la noche](#). *Eubacteria*, 33 (2015).

Armstrong, R. A. (2019). [Risk factors for Alzheimer's disease](#). *Folia neuropathologica*, 57(2), 87-105. <https://doi.org/10.5114/fn.2019.85929>

Arroyave-Ospina, J. C., Wu, Z., Geng, Y., & Moshage, H. (2021). [Role of oxidative stress in the pathogenesis of non-alcoholic fatty liver disease: Implications for prevention and therapy](#). *Antioxidants*, 10(2), 174. <https://doi.org/10.3390/antiox10020174>

Arroyo-Hernández, M., Alva-López, L. F., Rendón, A., Barroso-Villafuerte, F. R., Báez- Saldaña, R., Corona-Cruz, J. F., ... & Arrieta, O. (2022). [Guía de Práctica Clínica para el diagnóstico temprano y la referencia oportuna del cáncer de pulmón](#). *Salud Pública de México*, 64(5), 530-538. <https://doi.org/10.21149/13919>

Arteche, L., García, M., Leyva, M., & Martínez, S. (2018). Estandarización de valores de referencia de parámetros de estrés oxidativo. *Revista Cubana de Medicina Militar*, 47(2), 1-7. http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S0138-65572018000200005&lng=es&nrm=iso

Asgher, M., Per, T. S., Masood, A., Fatma, M., Freschi, L., Corpas, F. J., & Khan, N. A. (2017). [Nitric oxide signaling and its crosstalk with other plant growth regulators in plant responses to abiotic stress](#). *Environmental Science and Pollution Research*, 24, 2273-2285. DOI: 10.1007/s11356-016-7947-8

Averill-Bates, D. A. (2023). [The antioxidant glutathione](#). In *Vitamins and hormones*,. *Academic Press*, 121, 109-141. <https://doi.org/10.1016/bs.vh.2022.09.002>

Balendra, V., & Singh, S. K. (2021). [Therapeutic potential of astaxanthin and superoxide dismutase in Alzheimer's disease](#). *Open Biology*, 11(6), 210013. <https://doi.org/10.1098/rsob.210013>

- Balentine, D. A., Wiseman, S. A., & Bouwens, L. C. (1997). [The chemistry of tea flavonoids](#). *Critical Reviews in Food Science & Nutrition*, 37(8), 693-704. DOI: 10.1080/10408399709527797
- Baltusnikiene, A., Staneviciene, I., & Jansen, E. (2023). [Beneficial and adverse effects of vitamin E on the kidney](#). *Frontiers in Physiology*, 14, 1145216. <https://doi.org/10.3389/fphys.2023.1145216>
- Barba, J. R. (2019). [Enfermedad hepática y laboratorio clínico](#). *Revista Mexicana de Patología Clínica y Medicina de Laboratorio*, 66(2), 81-99.
- Barquilla García, A. (2017). [Actualización breve en diabetes para médicos de atención primaria](#). *Revista Española de Sanidad Penitenciaria*, 19(2), 57-65.
- Barragán Martínez, D., García Soldevilla, M. A., Parra Santiago, A., & Tejeiro Martínez, J. (2019). [Enfermedad de alzheimer](#). *Medicine-Programa de Formación Médica Continuada Acreditado*, 12(74), 4338-4346. DOI: <https://doi.org/10.1016/j.med.2019.03.012>
- Barragán Condori, M., Aro Aro, J. M., Muñoz Cáceres, A. E., & Rodríguez Mendoza, J. (2020). [Determinación de antocianinas y capacidad antioxidante en extractos de \(*Muehlenbeckia volcanica*\)](#). *Revista de Investigaciones Altoandinas*, 22(2), 161-169. <http://dx.doi.org/10.18271/ria.2020.604>
- Barreca, D., Gattuso, G., Bellocco, E., Calderaro, A., Trombetta, D., Smeriglio, A., ... & Nabavi, S. M. (2017). [Flavanones: Citrus phytochemical with health-promoting properties](#). *BioFactors*, 43(4), 495-506. <https://doi.org/10.1002/biof.1363>
- Barreca, D., Trombetta, D., Smeriglio, A., Mandalari, G., Romeo, O., Felice, M. R., ... & Nabavi, S. M. (2021). [Food flavonols: Nutraceuticals with complex health benefits and functionalities](#). *Trends in food science & technology*, 117, 194-204. <https://doi.org/10.1016/j.tifs.2021.03.030>
- Barría Ocaranza, R., Morales Ojeda, I. A., & Cerda Aedo, J. (2022). [Estudio epidemiológico de pacientes con diabetes mellitus en el centro de salud familiar Yanequen, Chile](#). *Revista Virtual de la Sociedad Paraguaya de Medicina Interna*, 9(1), 34-44. <https://doi.org/10.18004/rvspmi/2312-3893/2022.09.01.34>
- Becker, M. M., Nunes, G. S., Ribeiro, D. B., Silva, F. E., Catanante, G., & Marty, J. L. (2019). [Determination of the antioxidant capacity of red fruits by miniaturized spectrophotometry assays](#). *Journal of the Brazilian Chemical Society*, 30, 1108- 1114. <https://doi.org/10.21577/0103-5053.20190003>
- Bello-Medina, P. C., Rodríguez-Martínez, E., Prado-Alcalá, R. A., & Rivas-Arancibia, S. (2022). [Contaminación por ozono, estrés oxidativo, plasticidad sináptica y neurodegeneración](#). *Neurología*, 37(4), 277-286. <https://doi.org/10.1016/j.nrl.2018.10.003>
- Berrios-Cárcamo, P., Quezada, M., Quintanilla, M. E., Morales, P., Ezquer, M., Herrera-Marschitz, M., ... & Ezquer, F. (2020). [Oxidative stress and neuroinflammation as a pivot in drug abuse. A focus on the therapeutic potential of antioxidant and anti-inflammatory agents and biomolecules](#). *Antioxidants*, 9(9), 830. <https://doi.org/10.3390/antiox9090830>
- Bhatt, T., & Patel, K. (2020). [Carotenoids: potent to prevent diseases review](#). *Natural Products and Bioprospecting*, 10, 109-117. <https://doi.org/10.1007/s13659-020-00244-2>
- Biasi, A. D. L. M., Vallejos, A., Perez Chaca, M. V., Gil, R. A., & Gomez, N. N. (2020). [Alimentos con elevado contenido de minerales antioxidantes: zinc, cobre y selenio](#). Foro de la Alimentación, la Nutrición y la Salud (FANUS); *Revista del Foro de la Alimentación, la Nutrición y la Salud (RFANUS)*; 2(1), 29-37
- Bisht, K., Sharma, K., & Tremblay, M. È. (2018). [Chronic stress as a risk factor for Alzheimer's disease: roles of microglia-mediated synaptic remodeling, inflammation, and oxidative stress](#). *Neurobiology of Stress*, 9, 9-21. <https://doi.org/10.1016/j.ynstr.2018.05.003>

- Blackadar, C. B. (2016). [Historical review of the causes of cancer](#). *World journal of Clinical Oncology*, 7(1), 54. DOI: 10.5306/wjco.v7.i1.54
- Borrelli, A., Bonelli, P., Tuccillo, F. M., Goldfine, I. D., Evans, J. L., Buonaguro, F. M., & Mancini, A. (2018). [Role of gut microbiota and oxidative stress in the progression of non-alcoholic fatty liver disease to hepatocarcinoma: Current and innovative therapeutic approaches](#). *Redox Biology*, 15, 467-479. <https://doi.org/10.1016/j.redox.2018.01.009>
- Braidy, N., Izadi, M., Sureda, A., Jonaidi-Jafari, N., Banki, A., Nabavi, S. F., & Nabavi, S. M. (2017). [Therapeutic relevance of ozone therapy in degenerative diseases: Focus on diabetes and spinal pain](#). *Journal of Cellular Physiology*, 233(4), 2705- 2714. DOI: 10.1002/jcp.26044
- Bravo Bartra, M. I. (2012). [Actividad física intensa: Dulce o Amargo](#). *Revista Clínica de Medicina de Familia*, 5(1), 76-76. <https://dx.doi.org/10.4321/S1699-695X2012000100016>
- Brigelius-Flohé, R., & Flohé, L. (2020). [Regulatory phenomena in the glutathione peroxidase superfamily](#). *Antioxidants & Redox Signaling*, 33(7), 498-516. <https://doi.org/10.1089/ars.2019.7905>
- Buendía-García, A., Lozano-Cavazos, C. J., Rodríguez-Ortiz, J. C., Carballo-Méndez, F. D. J., Moreno-Reséndez, A., Sariñana-Navarrete, M. D. L. Á., & Preciado- Rangel, P. (2021). [La biofortificación con selenio mejora la calidad nutracéutica y la capacidad antioxidante de la lechuga \(*Lactuca sativa* L.\)](#). *Ecosistemas y Recursos Agropecuarios*, 8(3). <https://doi.org/10.19136/era.a8n3.3104>
- Burgos-Santamaría, D., Sánchez-Aldehuelo, R., Figueroa-Tubío, A., & Mateos Muñoz, B. (2020). [Enfermedad hepática grasa no alcohólica](#). *Medicine - Programa de Formación Médica Continuada Acreditado*, 13(4), 173. <https://doi.org/10.1016/j.med.2020.02.001>
- Caliri, A. W., Tommasi, S., & Besaratinia, A. (2021). [Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer](#). *Mutation Research/Reviews in Mutation Research*, 787, 108365. <https://doi.org/10.1016/j.mrrev.2021.108365>
- Camacho-Beiza, I., Ocaña-Servín, H., Hardy-Pérez, A., Arceo-Guzmán, M. E., Jaimes- García, J., López-Díaz, H. L., & Vilchis-Salazar, E. V. (2022). [Mortalidad por cáncer pulmonar en México de 2000-2020 y su relación con la historia del tabaquismo](#). *Medicina e Investigación Universidad Autónoma del Estado de México*, 10(2), 32-41. <https://doi.org/10.36677/medicinainvestigacion.v10i2.20085>
- Carpentieri, S.; Soltanipour, F.; Ferrari, G.; Pataro, G.; Donsì, F. [Emerging Green Techniques for the Extraction of Antioxidants from Agri-Food By-Products as Promising Ingredients for the Food Industry](#). *Antioxidants* 2021, 10(9), 1417. <https://doi.org/10.3390/antiox10091417>
- Carr, A. C., & Maggini, S. (2017). [Vitamin C and immune function](#). *Nutrients*, 9(11), 1211. <https://doi.org/10.3390/nu9111211>
- Carril C. A, Hardy J., Schott J. M (2017). [Alzheimer's disease](#). *European Journal of Neurology*, 25(1), 59-70. <https://doi.org/10.1111/ene.13439>
- Carrillo Esper, R., Díaz Ponce Medrano, J. A., Peña Pérez, C. A., Flores Rivera, O. I., Neri Maldonado, R., Zepeda Mendoza, A. D., ... & Ortiz Trujillo, A. (2016). [Especies reactivas de oxígeno, sepsis y teoría metabólica del choque séptico](#). *Revista de la Facultad de Medicina (México)*, 59(1), 6-18.
- Carvajal Carvajal, C. (2019). [Especies reactivas del oxígeno: formación, función y estrés oxidativo](#). *Medicina Legal de Costa Rica*, 36(1), 91-100.
- Casas, M. R., Chaire, A. A., Navarro, A. P., & Aguilera, K. G. C. (2016). [Papel inmunomodulador y antioxidante del zinc y el selenio en el tratamiento coadyuvante de infecciones respiratorias graves](#). *Revista de educación bioquímica*, 35(1), 3-10.

- Cassidy, L., Fernandez, F., Johnson, J. B., Naiker, M., Owoola, A. G., & Broszczak, D.A. (2020). [Oxidative stress in alzheimer's disease: A review on emergent natural polyphenolic therapeutics](#). *Complementary therapies in medicine*, 49, 102294. <https://doi.org/10.1016/j.ctim.2019.102294>
- Castera, L., Friedrich-Rust, M., & Loomba, R. (2019). [Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease](#). *Gastroenterology*, 156(5), 1264-1281. <https://doi.org/10.1053/j.gastro.2018.12.036>
- Castillo, R., & Salazar-Lugo, R. (2018). [El estrés oxidativo en la práctica de enfermería](#). *RECIEN: Revista Científica de Enfermería* (España), 15, 50-73. <https://doi.org/10.14198/recien.2018.15.05>
- Castro Acosta, M. L. (2019). [Polifenoles: compuestos bioactivos con efectos benéficos en la prevención de diabetes tipo 2](#). *REDCiEN*, 1, 6-6. <https://redcien.com/index.php/redcien/article/view/5>
- Castro-Arroyave, D. M., Martínez-Gallego, J. A., Montoya-Guzmán, M., Silva, G., & Rojas Arbeláez, C. A. (2023). [Hepatitis B en indígenas de América Latina: una revisión de la literatura](#). *Revista Panamericana de Salud Pública*, 46, 22. <https://doi.org/10.26633/RPSP.2022.22>
- Cedeño Caballero, J. V., Falcones Veliz, K. B., Tircio Esparza, S. S., & Zambrano Soledispa, S. N. (2019). [Atención médica integral en pacientes con enfermedad hepática](#). *RECIAMUC*, 3(3), 208-238. [https://doi.org/10.26820/reciamuc/3.\(3\).julio.2019.208-238](https://doi.org/10.26820/reciamuc/3.(3).julio.2019.208-238)
- Cenini, G., Lloret, A., & Cascella, R. (2020). [Oxidative stress and mitochondrial damage in neurodegenerative diseases: from molecular mechanisms to targeted therapies](#). *Oxidative Medicine and Cellular Longevity*, 2020. <https://doi.org/10.1155/2019/2105607>
- Chaaban, H., Ioannou, I., Paris, C., Charbonnel, C., & Ghoul, M. (2017). [The photostability of flavanones, flavonols and flavones and evolution of their antioxidant activity](#). *Journal of Photochemistry and Photobiology A: Chemistry*, 336, 131-139. <https://doi.org/10.1016/j.jphotochem.2016.12.027>
- Chang, K. H., & Chen, C. M. (2020). [The role of oxidative stress in Parkinson's disease](#). *Antioxidants*, 9(7), 597. <https://doi.org/10.3390/antiox9070597>
- Chang, C., Worley, B. L., Phaëton, R., & Hempel, N. (2020). [Extracellular glutathione peroxidase GPx3 and its role in cancer](#). *Cancers*, 12(8), 2197. <https://doi.org/10.3390/cancers12082197>
- Chasi Toapanta, D. F. (2022). [Consideraciones sobre el entrenamiento de la resistencia a través de actividades físicas rítmicas](#). *Ciencia y Deporte*, 7(1), 30-44. <http://dx.doi.org/10.34982/2223.1773.2022.v7.no1.003>
- Cheemerla, S., & Balakrishnan, M. (2021). [Global epidemiology of chronic liver disease](#). *Clinical liver disease*, 17(5), 365-370. DOI: 10.1002/cld.1061
- Cheignon, C., Tomas, M., Bonnefont-Rousselot, D., Faller, P., Hureau, C., y Collin, F. (2018). [Oxidative stress and the amyloid beta peptide in Alzheimer's disease](#). *Redox Biology*, 14, 450-464. <https://doi.org/10.1016/j.redox.2017.10.014>
- Chemat, F., & Khan, M. K. (2011). [Applications of ultrasound in food technology: Processing, preservation and extraction](#). *Ultrasonics Sonochemistry*, 18(4), 813-835. <https://doi.org/10.1016/j.ultsonch.2010.11.023>
- Chen, Z. Q., Mou, R. T., Feng, D. X., Wang, Z., & Chen, G. (2017). [The role of nitric oxide in stroke](#). *Medical Gas Research*, 7(3), 194. DOI: 10.4103/2045-9912.215750
- Chen, Y., Zhou, Z., & Min, W. (2018). [Mitochondria, oxidative stress and innate immunity](#). *Frontiers in Physiology*, 9, 1487. <https://doi.org/10.3389/fphys.2018.01487>

- Chen, Z., Tian, R., She, Z., Cai, J., & Li, H. (2020). Role of oxidative stress in the pathogenesis of nonalcoholic fatty liver disease. *Free Radical Biology and Medicine*, 152, 116-141. <https://doi.org/10.1016/j.freeradbiomed.2020.02.025>
- Chidambaranathan-Reghupaty, S., Fisher, P. B., & Sarkar, D. (2021). Hepatocellular carcinoma (HCC): Epidemiology, Etiology and Molecular Classification. *Advances in Cancer Research*, 149, 1-61. <https://doi.org/10.1016/bs.acr.2020.10.001>
- Cicero, A., & Colletti, A. (2017). Effects of carotenoids on health: are all the same? Results from clinical trials. *Current Pharmaceutical Design*, 23(17), 2422-2427. DOI: 10.2174/1381612823666170207095459
- Cinelli, M. A., Do, H. T., Miley, G. P., & Silverman, R. B. (2020). Inducible nitric oxide synthase: Regulation, structure, and inhibition. *Medicinal Research Reviews*, 40(1), 158-189. <https://doi.org/10.1002/med.21599>.
- Comino-Sanz, I. M., López-Franco, M. D., Castro, B., & Pancorbo-Hidalgo, P. L. (2021). The role of antioxidants on wound healing: A review of the current evidence. *Journal of Clinical Medicine*, 10(16), 3558. <https://doi.org/10.3390/jcm10163558>
- Cordova Sanchez, G. A., Ugarte Palacios, C. V., Ugarte Palacios, N. A., & Morales Labre, K. O. (2022). Cáncer de pulmón y su importancia en el diagnóstico primario. *RECIAMUC*, 6(2), 208-217. [https://doi.org/10.26820/reciamuc/6.\(2\).mayo.2022.208-217](https://doi.org/10.26820/reciamuc/6.(2).mayo.2022.208-217)
- Corrales, L. C., & Muñoz Ariza, M. M. (2012). Estrés oxidativo: origen, evolución y consecuencias de la toxicidad del oxígeno. *Nova*, 10(18), 213-225.
- Cotignola, Á., Odzak, A., Franchella, J., Bisso, A., Duran, M., Palencia Vizcarra, R.,... & Rodríguez, W. (2023). Actividad física y salud cardiovascular. *Medicina (Buenos Aires)*, 83, 7-10.
- Craig, A. J., Von Felden, J., Garcia-Lezana, T., Sarcognato, S., & Villanueva, A. (2020). Tumour evolution in hepatocellular carcinoma. *Nature reviews Gastroenterology & hepatology*, 17(3), 139-152. DOI: 10.1038/s41575-019-0229-4
- Crotty, G. F., Ascherio, A., & Schwarzschild, M. A. (2017). Targeting urate to reduce oxidative stress in Parkinson disease. *Experimental neurology*, 298, 210-224. <https://doi.org/10.1016/j.expneurol.2017.06.017>
- Cruz Hernández, J., Licea Puig, M. E., Hernández García, P., Abraham Marcel, E. A., & Yanes Quesada, M. (2011). Estrés oxidativo y diabetes mellitus. *Revista Mexicana de Patología Clínica y Medicina de Laboratorio*, 58(1), 4-15.
- Cruz, A. P., Rivero, B. S., Clausell, A. B., & Jorge, M. C. (2020). La enfermedad cerebrovascular y sus factores de riesgo. *Revista Cubana de Medicina Militar*, 49(3). http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S0138-65572020000300009&lng=es&nrm=iso
- Cruz-Rodríguez, J., & López-Solís, R. (2021). El estrés oxidativo en la fisiopatología del síndrome metabólico. *Medicina e Investigación Universidad Autónoma del Estado de México*, 9(2), 88-94.
- Curieses Andrés, C. M., Pérez de Lastra, J. M., Andrés Juan, C., Plou Gasca, F. J., & Pérez-Lebeña, E. (2023). Superoxide Anion Chemistry-Its Role at the Core of the Innate Immunity. *International Journal of Molecular Sciences*, 24(3), 1841. <https://doi.org/10.3390/ijms24031841>
- Damien, & Damien. (2021, 22 septiembre). LUCHAR CONTRA EL ESTRÉS OXIDATIVO - Blog Eric Favre ES. Blog Eric Favre ES. <https://www.ericfavre.com/lifestyle/es/bienvenida/nutricion-deportiva/conceptos-basicos-de-%20nutricion/sobre-radicales-libres-y-los-antioxidante/luchar-contra-el-estres-oxidativo/>

- Da Silva, A., Caldas, A. P. S., Hermsdorff, H. H. M., Bersch-Ferreira, Â. C., Torreglosa, C. R., Weber, B., & Bressan, J. (2019). [Triglyceride-glucose index is associated with symptomatic coronary artery disease in patients in secondary care](#). *Cardiovascular Diabetology*, 18, 1-8. <https://doi.org/10.1186/s12933-019-0893-2>
- Dávila Cervantes, C. A. (2020). [Tendencia e impacto de la mortalidad por enfermedades cardiovasculares en México, 1990-2015](#). *Revista Cubana de Salud Pública*, 45, 1081.
- Del Valle Díaz, S., Piñera Martínez, M., Medina González, N., & Sánchez Vega, J. (2017). [Colestasis: un enfoque actualizado](#). *Medisan*, 21(7), 876-900.
- Deshmukh, A. R., & Kim, B. S. (2019). [Chitosan-vitamin C nanoparticles](#). *KSBB Journal*, 34(4), 221-232. <http://dx.doi.org/10.7841/ksbbj.2019.34.4.221>
- Di Mauro, R., Cantarella, G., Bernardini, R., Di Rosa, M., Barbagallo, I., Distefano, A., ... & Li Volti, G. (2019). [The biochemical and pharmacological properties of ozone: the smell of protection in acute and chronic diseases](#). *International Journal of Molecular Sciences*, 20(3), 634. <https://doi.org/10.3390/ijms20030634>
- Di Meo, S., & Venditti, P. (2020). [Evolution of the knowledge of free radicals and other oxidants](#). *Oxidative Medicine and Cellular Longevity*, 2020(1), 9829176. <https://doi.org/10.1155/2020/9829176>
- Di Meo, S., Venditti, P., Víctor, V. M., & Napolitano, G. (2022). [Harmful and Beneficial role of ROS 2020](#). *Oxidative Medicine and Cellular Longevity*, 2022, 1-3. <https://doi.org/10.1155/2022/9873652>
- Dias, M. D. G., Olmedilla-Alonso, B., Hornero-Méndez, D., Mercadante, A. Z., Osorio, C., Vargas-Murga, L., & Meléndez-Martínez, A. J. (2017). [Tabla de contenido en carotenoides de alimentos iberoamericanos](#). *Carotenoides en Agroalimentación y Salud*, 18, 354-429.
- Díaz-Ramírez, G. S. (2020). [Diagnóstico de hepatitis autoinmune](#). *Hepatología*, 1(1), 23-35. <https://doi.org/10.52784/27112330.113>
- Díaz-Soto, M. T. D., & Calderín-Miranda, J. M. C. (2020). [Síndrome de abstinencia alcohólica: Resultado del estrés oxidativo y desequilibrio neuronal. Estado del arte](#). *Revista Biomedica*, 31(2), 95-107.
- Dionísio, P. A., Amaral, J. D., & Rodrigues, C. M. P. (2021). [Oxidative stress and regulated cell death in Parkinson's disease](#). *Ageing Research Reviews*, 67, 101263. <https://doi.org/10.1016/j.arr.2021.101263>
- Dobrzyńska, M., Drzymała-Czyż, S., Woźniak, D., Drzymała, S., & Przysławski, J. (2023). [Natural Sources of Selenium as Functional Food Products for Chemoprevention](#). *Foods*, 12(6), 1247. <https://doi.org/10.3390/foods12061247>
- Dorszewska, J., Kowalska, M., Prendecki, M., Piekut, T., Kozłowska, J. y Kozubski, W. (2021). [Oxidative stress factors in Parkinson's disease](#). *Neural Regeneration Research*, 16 (7), 1383. DOI: 10.4103/1673-5374.300980
- Doseděl, M., Jirkovský, E., Macáková, K., Krčmová, L. K., Javorská, L., Pourová, J., ... & Oemonom. (2021). [Vitamin C-sources, physiological role, kinetics, deficiency, use, toxicity, and determination](#). *Nutrients*, 13(2), 615. <https://doi.org/10.3390/nu13020615>
- Dubois-Deruy, E., Peugnet, V., Turkieh, A., & Pinet, F. (2020). [Oxidative stress in cardiovascular diseases](#). *Antioxidants*, 9(9), 864. <https://doi.org/10.3390/antiox9090864>
- Durazzo, A., Lucarini, M., Camilli, E., Marconi, S., Gabrielli, P., Lisciani, S., & Marletta, L. (2018). [Dietary lignans: definition, description and research trends in databases development](#). *Molecules*, 23(12), 3251. <https://doi.org/10.3390/molecules23123251>

- Dwivedi, M., & Pandey, A. R. (2020). [Diabetes mellitus and its treatment: An overview](#). *Journal of Advancement in Pharmacology*, 1(1), 48-58.
- Edge, R., & Truscott, T. G. (2021). [The reactive oxygen species singlet oxygen, hydroxy radicals, and the superoxide radical anion-examples of their roles in biology and medicine](#). *Oxygen*, 1(2), 77-95. <https://doi.org/10.3390/oxygen1020009>
- Edwards III, G. A., Gamez, N., Escobedo Jr, G., Calderon, O., & Moreno-Gonzalez, I. (2019). [Modifiable risk factors for Alzheimer's disease](#). *Frontiers in Aging Neuroscience*, 11, 146. <https://doi.org/10.3389/fnagi.2019.00146>
- Eggersdorfer, M., & Wyss, A. (2018). [Carotenoids in human nutrition and health](#). *Archive of Biochemistry and Biophysics*, 652, 18-26. <https://doi.org/10.1016/j.abb.2018.06.001>
- Einarson, T. R., Acs, A., Ludwig, C., & Panton, U. H. (2018). [Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017](#). *Cardiovascular Diabetology*, 17(1), 1-19. DOI: 10.1186/s12933-018-0728-6
- El Khawand, T., Courtois, A., Valls, J., Richard, T., & Krisa, S. (2018). [A review of dietary stilbenes: Sources and bioavailability](#). *Phytochemistry Reviews*, 17(5), 1007-1029. <https://doi.org/10.1007/s11101-018-9578-9>
- Elejalde, E., Villarán, M. C., & Alonso, R.M. (2021). [Grape polyphenols supplementation for exercise-induced oxidative stress](#). *Journal of the International Society of Sports Nutrition*, 18(1), 3. <https://doi.org/10.1186/s12970-020-00395-0>
- Elgailani, I. E. H., Elkareem, M. A. M. G., Noh, E., Adam, O., & Alghamdi, A. (2017). [Comparison of two methods for the determination of vitamin C \(ascorbic acid\) in some fruits](#). *American Journal of Chemistry*, 2(1), 1-7. DOI: 10.20448/812.2.1.1.7
- Elizondo, D. C., Amador, K. A., Ureña, F. S., Robledo, A., & de Microbiología, D. (2020). [Factores de riesgo cardiovascular](#). *CIENCIA Y SALUD*, 4(1). <https://doi.org/10.34192/cienciaysalud.v4i1.108>
- Elmadfa, I., & Meyer, A. L. (2019). [The role of the status of selected micronutrients in shaping the immune function](#). *Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders)*, 19(8), 1100-1115. DOI: 10.2174/1871530319666190529101816
- Enriquez-del-Castillo, L. A., Candia-Lujan, R., Moreno-Brito, V., Fierro, L. G. D. L., Reza-López, S. A., González-Rodríguez, E., & Carrasco-Legleu, C. E. (2019). [Sistema antioxidante, actividad física y consumo máximo de oxígeno en adultos jóvenes](#). *Biocencia*, 21(2), 91-96. DOI: <https://doi.org/10.18633/biocencia.v21i2.934>
- Escalera, E., Bellido, L., Del Barco, E., Cigarral, B., Barrios, B., Casado, D., & Cruz, J. J. (2021). [Cáncer de pulmón microcítico](#). *Medicine-Programa de Formación Médica Continuada Acreditado*, 13(25), 1369-1376. <https://doi.org/10.1016/j.med.2021.02.001>
- Estévez, M., Díaz-Velasco, S., & Martínez, R. (2022). [Protein carbonylation in food and nutrition: a concise update](#). *Amino acids*, 1-15. DOI: 10.1007/s00726-021- 03085-6
- Estrada, J., & Iglesias M. (2017). [Estrés Oxidativo y Oxigenación Hiperbárica](#). *Investigaciones Medicoquirúrgicas*, 9(2), 261-275. <https://revcimeq.sld.cu/index.php/imq/article/view/393>
- Ezhilarasan, D. (2018). [Oxidative stress is bane in chronic liver diseases: Clinical and experimental perspective](#). *Arab Journal of Gastroenterology*, 19(2), 56-64. <https://doi.org/10.1016/j.ajg.2018.03.002>
- Fenech, M., Amaya, I., Valpuesta, V., & Botella, M. A. (2019). [Vitamin C content in fruits: Biosynthesis and regulation](#). *Frontiers in Plant Science*, 9, 413553. <https://doi.org/10.3389/fpls.2018.02006>

- Ferlazzo, N., Andolina, G., Cannata, A., Costanzo, M. G., Rizzo, V., Currò, M., & Caccamo, D. (2020). [Is melatonin the cornucopia of the 21st century?](https://doi.org/10.3390/antiox9111088). *Antioxidants*, 9(11), 1088. <https://doi.org/10.3390/antiox9111088>
- Fernández Pérez, M. D., Regueira Betancourt, S. M., & Torres Fernández, M. (2016). [Factores de riesgo modificables en algunos tipos de cáncer](https://revzoiomarinellosldcu/index.php/zmv/article/view/940). *Revista Electrónica Dr. Zoilo E. Marinello Vidaurreta*, 41(11). <https://revzoiomarinellosldcu/index.php/zmv/article/view/940>
- Fernández González, E. M., & Figueroa Oliva, D. A. (2018). [Tabaquismo y su relación con las enfermedades cardiovasculares](http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1729-519X2018000200008&lng=es&nrm=iso). *Revista Habanera de Ciencias Médicas*, 17(2), 225-235. http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1729-519X2018000200008&lng=es&nrm=iso
- Fernández García, J. J., & Granados Hinojosa, I. (2020). [Enfermedad de Parkinson: Neurodegeneración asociada a Estrés Oxidativo/Parkinson's disease: neurodegeneration associated with Oxidative Stress](https://revpanorama.sld.cu/index.php/panorama/article/view/1222). *Panorama Cuba y Salud*, 15(2). <https://revpanorama.sld.cu/index.php/panorama/article/view/1222>
- Fernández, S., & Zeledón, N. (2020). [Rol del estrés oxidativo en la enfermedad renal crónica](https://doi.org/10.31434/rms.v5i5.481). *Revista Médica Sinergia*, 5(5), 481. <https://doi.org/10.31434/rms.v5i5.481>
- Figueredo Villa, K., Gafas González, C., Pérez Rodríguez, M., Brossard Peña, E., García Ríos, C. A., & Valdiviezo Maygua, M. A. (2020). [Dimensiones de calidad de vida afectadas en pacientes diabéticos](https://doi.org/10.25205/2474-2930.2020.11.01). *Revista Cubana de Enfermería*, 36(1). <https://doi.org/10.25205/2474-2930.2020.11.01>
- Flores Poveda, K. A., Quiñonez García, K. J., Flores Subía, D. L., & Cárdenas Choez, C. A. (2020). [Utilidad de hemoglobina glicosilada en diabetes tipo 2](https://reciamuc.com/index.php/RECIAMUC/article/view/505). *RECIAMUC*, 4(3), 118-126. <https://reciamuc.com/index.php/RECIAMUC/article/view/505>
- Foroughbakhch Pournavab, R., Castillo Godina, R., Benavides Mendoza, A., & Villarreal Garza, J. A. (2020). [Cuantificación de antioxidantes en plantas de tomate \(*Solanum lycopersicon* L. Mill\) enriquecida con selenio](https://doi.org/10.24205/2474-2930.2020.11.01). *Investigación y Desarrollo en Ciencia y Tecnología de Alimentos*, 5, 124-128. <https://doi.org/10.24205/2474-2930.2020.11.01>
- Fortea, J. I., Carrera, I. G., Puente, A., & Crespo, J. (2020). [Cirrosis hepática](https://doi.org/10.1016/j.med.2020.04.001). *Medicine-Programa de Formación Médica Continuada Acreditado*, 13(6), 297-307. <https://doi.org/10.1016/j.med.2020.04.001>
- Galasso, C., Corinaldesi, C., & Sansone, C. (2017). [Carotenoids from marine organisms: Biological functions and industrial applications](https://doi.org/10.3390/antiox6040096). *Antioxidants*, 6(4), 96. <https://doi.org/10.3390/antiox6040096>
- Galasso, M., Gambino, S., Romanelli, M. G., Donadelli, M., & Scupoli, M. T. (2021). [Browsing the oldest antioxidant enzyme: catalase and its multiple regulation in cancer](https://doi.org/10.1016/j.freeradbiomed.2021.06.010). *Free Radical Biology and Medicine*, 172, 264-272. <https://doi.org/10.1016/j.freeradbiomed.2021.06.010>
- Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., ... & Martín, C. (2020). [Pathophysiology of type 2 diabetes mellitus](https://doi.org/10.3390/ijms21176275). *International Journal of Molecular Sciences*, 21(17), 6275. <https://doi.org/10.3390/ijms21176275>
- Galli, F., Azzi, A., Birringer, M., Cook-Mills, J. M., Eggersdorfer, M., Frank, J., & Özer, N. K. (2017). [Vitamin E: Emerging aspects and new directions](https://doi.org/10.1016/j.freeradbiomed.2016.09.017). *Free Radical Biology and Medicine*, 102, 16-36. <https://doi.org/10.1016/j.freeradbiomed.2016.09.017>
- Gammoh, N. Z., & Rink, L. (2017). [Zinc in infection and inflammation](https://doi.org/10.3390/nu9060624). *Nutrients*, 9(6), 624. <https://doi.org/10.3390/nu9060624>
- Gangwar, R. S., Bevan, G. H., Palanivel, R., Das, L., & Rajagopalan, S. (2020). [Oxidative stress pathways of air pollution mediated toxicity: Recent insights](https://doi.org/10.1016/j.redox.2020.101545). *Redox Biology*, 34, 101545. <https://doi.org/10.1016/j.redox.2020.101545>
- Gao, Z., Chen, Z., Sun, A., & Deng, X. (2019). [Gender differences in cardiovascular disease](https://doi.org/10.1016/j.medntd.2019.100025). *Medicine in Novel Technology and Devices*, 4, 100025. <https://doi.org/10.1016/j.medntd.2019.100025>

- García, G. D., Pompeo, D. A., Eid, L. P., Cesarino, C. B., Pinto, M. H., & Gonçalves, L. W. P. (2018). [Relación entre sintomatología ansiosa, depresiva y compulsión alimenticia en pacientes con enfermedades cardiovasculares.](https://doi.org/10.1590/1518-8345.2567.3040) *Revista Latino-Americana de Enfermagem*, 26. <https://doi.org/10.1590/1518-8345.2567.3040>
- García-Giménez, J. L., Cánovas-Cervera, I., & Pallardó, F. V. (2024). [Oxidative stress and metabolism meet epigenetic modulation in physical exercise.](https://doi.org/10.1016/j.freeradbiomed.2024.01.008) *Free Radical Biology and Medicine*, 213, 123-137. <https://doi.org/10.1016/j.freeradbiomed.2024.01.008>
- Gasparovic, A. C., Zarkovic, N., & Bottari, S. P. (2018). [Biomarkers of nitro-oxidation and oxidative stress.](https://doi.org/10.1016/j.cotox.2017.10.002) *Current Opinión in Toxicology*, 7, 73-80. <https://doi.org/10.1016/j.cotox.2017.10.002>
- Gastelum Hernández, A. C. (2024). [Desarrollo de alimentos funcionales de maíz y garbanzo germinado con selenio y su validación en modelos in vitro e in vivo de sus propiedades anticancerígenas, antioxidantes y antiinflamatorias.](#) [Tesis doctoral, Universidad Autónoma de Sinaloa]. Repositorio Institucional Buena.
- Gaucin-Delgado, J. M., Preciado-Rangel, P., González-Salas, U., Sifuentes-Ibarra, E., Núñez-Ramírez, F., & Vidal, J. A. O. (2021). [La biofortificación con selenio mejora los compuestos bioactivos y la actividad antioxidante en chile jalapeño.](https://doi.org/10.29312/remexca.v12i8.3066) *Revista Mexicana de Ciencias Agrícolas*, 12(8), 1339-1349. <https://doi.org/10.29312/remexca.v12i8.3066>
- Gebicka, L., & Krych-Madej, J. (2019). [The role of catalases in the prevention/promotion of oxidative stress.](https://doi.org/10.1016/j.jinorgbio.2019.110699) *Journal of Inorganic Biochemistry*, 197, 110699. <https://doi.org/10.1016/j.jinorgbio.2019.110699>
- Gegotek, A., & Skrzydlewska, E. (2022). [Antioxidative and anti-inflammatory activity of ascorbic acid.](https://doi.org/10.3390/antiox11101993) *Antioxidants*, 11(10), 1993. <https://doi.org/10.3390/antiox11101993>
- Gerrard, G., Martí, M. B., Diviani, R., Ceruti, M. J., Lioi, S., Beloscar, J., & D'Arrigo, M. (2019). [Miocardiopatía chagásica: rol de la inflamación y el estrés oxidativo.](https://doi.org/10.62073/bypc.v83i2.49) *Revista Bioquímica y Patología Clínica*, 83(2), 31-35. <https://doi.org/10.62073/bypc.v83i2.49>
- Ghasemi, M., & Brown Jr, R. H. (2018). [Genetics of amyotrophic lateral sclerosis.](https://doi.org/10.1101/cshperspect.a024125) *Cold Spring Harbor Perspectives in Medicine*, 8(5). DOI: 10.1101/cshperspect.a024125
- Glorieux, C., & Calderon, P. B. (2017). [Catalase, a remarkable enzyme: targeting the oldest antioxidant enzyme to find a new cancer treatment approach.](https://doi.org/10.1515/hsz-2017-0131) *Biological Chemistry*, 398(10), 1095-1108. <https://doi.org/10.1515/hsz-2017-0131>
- Godoy Martínez, M. D. M. (2023). [Ejercicio físico, radicales libres y estrés oxidativo. Suplementación con antioxidantes naturales derivados del consumo de arándanos](#) [Master's thesis, Universidad Internacional de Andalucía].
- Goff, S. L., & Danforth, D. N. (2021). [The role of immune cells in breast tissue and immunotherapy for the treatment of breast cancer.](https://doi.org/10.1016/j.clbc.2020.06.011) *Clinical Breast Cancer*, 21(1), 63-73. <https://doi.org/10.1016/j.clbc.2020.06.011>
- Gonos, E. S., Kapetanou, M., Sereikaite, J., Bartosz, G., Naparło, K., Grzesik, M., & Sadowska-Bartos, I. (2018). [Origin and pathophysiology of protein carbonylation, nitration and chlorination in age-related brain diseases and aging.](https://doi.org/10.18632/aging.101450) *Aging* (Albany NY), 10(5), 868. DOI: 10.18632/aging.101450
- González-Costa, M., & Padrón González, A. A. (2019). [La melatonina y su rol en los procesos inflamatorios.](#) *Revista Cubana de Reumatología*, 21(2).
- Goutman, S. A., Hardiman, O., Al-Chalabi, A., Chió, A., Savelieff, M. G., Kiernan, M. C., & Feldman, E. L. (2022). [Emerging insights into the complex genetics and pathophysiology of amyotrophic lateral sclerosis.](https://doi.org/10.1016/S1474-4422(21)00414-2) *The Lancet Neurology*, 21(5), 465-479. [https://doi.org/10.1016/S1474-4422\(21\)00414-2](https://doi.org/10.1016/S1474-4422(21)00414-2)

- Granger, M., & Eck, P. (2018). **Dietary vitamin C in human health**. *Advances in food and nutrition research*, 83, 281-310. <https://doi.org/10.1016/bs.afnr.2017.11.006>
- Guamán-Montero, N. A., Mesa-Cano, I. C., Peña-Cordero, S. J., & Ramírez-Coronel, A.A. (2021). **Factores que influyen en la adherencia al tratamiento de la diabetes mellitus II**. *Archivos Venezolanos de Farmacología y Terapéutica*, 40(3), 290-297. <https://doi.org/10.5281/zenodo.5039487>
- Guerra-Ruiz, A. R., Casals, G., Iruzubieta, P., Lalana, M., Leis, A., López, R. M., ... & Morales-Ruiz, M. (2021). **Valoración bioquímica en la enfermedad hepática grasa asociada a la disfunción metabólica**. *Advances in Laboratory Medicine/Avances en Medicina de Laboratorio*, 2(2), 209-219. <https://doi.org/10.1515/almed-2020-0062>
- Guevara, D. N., Dominguez, J. E., & Salazar, J. M. (2021). **Cirrosis hepática causas y complicaciones en mayores de 40 años de edad**. *RECIAMUC*, 5(1), 63-69. DOI:10.26820/reciamuc/5.(1).ene.2021.63-69
- Gugliandolo, A., Bramanti, P., & Mazzon, E. (2017). **Role of vitamin E in the treatment of Alzheimer's disease: Evidence from animal models**. *International Journal of Molecular Sciences*, 18(12), 2504. <https://doi.org/10.3390/ijms18122504>
- Gulcin, İ. (2020). **Antioxidants and antioxidant methods: An updated overview**. *Archives of Toxicology*, 94(3), 651-715. <https://doi.org/10.1007/s00204-020-02689-3>
- Guo, J. D., Zhao, X., Li, Y., Li, G. R., & Liu, X. L. (2018). **Damage to dopaminergic neurons by oxidative stress in Parkinson's disease**. *International journal of molecular medicine*, 41(4), 1817-1825. <https://doi.org/10.3892/ijmm.2018.3406>
- Gupta, D. (2015). **Methods for determination of antioxidant capacity: A review**. *International Journal of Pharmaceutical Sciences and Research*, 6(2), 546. DOI: 10.13040/IJPSR.0975-8232.6(2).546-66
- Gutiérrez, R., Reyes, C., Martínez, J., López, J., & Lazalde, B. (2018). **Estrés oxidativo: promotor de enfermedades**. *IBN SINA*, 9(1), 1-9. <https://doi.org/10.48777/ibnsina.v9i1.91>
- Hadwan, M. H. (2018). **Simple spectrophotometric assay for measuring catalase activity in biological tissues**. *BMC Biochemistry*, 19, 1-8. <https://doi.org/10.1186/s12858-018-0097-5>
- Han, C. H., Kim, H., Lee, S., & Chung, J. H. (2019). **Knowledge and poor understanding factors of stroke and heart attack symptoms**. *International Journal of Environmental Research and Public Health*, 16(19), 3665. <https://doi.org/10.3390/ijerph16193665>
- Hano, C., & Tungmunnithum, D. (2020). **Plant polyphenols, more than just simple natural antioxidants: Oxidative stress, aging and age-related diseases**. *Medicines*, 7(5), 26. <https://doi.org/10.3390/medicines7050026>
- Hauck, A. K., Huang, Y., Hertzfel, A. V., & Bernlohr, D. A. (2019). **Adipose oxidative stress and protein carbonylation**. *Journal of Biological Chemistry*, 294(4), 1083-1088. <https://doi.org/10.1074/jbc.R118.003214>
- He, L., He, T., Farrar, S., Ji, L., Liu, T., & Ma, X. (2017). **Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species**. *Cellular Physiology and Biochemistry*, 44(2), 532-553. <https://doi.org/10.1159/000485089>
- He, Z., Li, Q., Xu, Y., Zhang, D., & Pan, X. (2023). **Production of extracellular superoxide radical in microorganisms and its environmental implications: A review**. *Environmental Pollution*, 338, 122563. <https://doi.org/10.1016/j.envpol.2023.122563>
- Hecker, M., & Wagner, A. H. (2017). **Role of protein carbonylation in diabetes**. *Journal of inherited metabolic disease*, 41, 29-38. <https://doi.org/10.1007/s10545-017-0104-9>

- Hemmati-Dinarvand, M., Valilo, M., Kalantary-Charvadeh, A., Sani, M. A., Kargar, R., Safari, H., & Samadi, N. (2019). **Oxidative stress and Parkinson's disease: conflict of oxidant-antioxidant systems.** *Neuroscience Letters*, 709, 134296. <https://doi.org/10.1016/j.neulet.2019.134296>
- Henning, R. J. (2018). **Type-2 diabetes mellitus and cardiovascular disease.** *Future Cardiology*, 14(6), 491-509. <https://doi.org/10.2217/fca-2018-0045>
- Hernández García, F., Robaina Castillo, J. I., & Vázquez Almoguera, E. (2017). **Estrés oxidativo y diabetes mellitus, un acercamiento al tema.** *Universidad Médica Pinareña*, 13(2), 69-85.
- Hernández Espinosa, D. R., Barrera Morín, V., Briz Tena, O., González Herrera, E. A., Laguna Maldonado, K. D., Jardínez Díaz, A. S., & Matuz Mares, D. (2019). **El papel de las especies reactivas de oxígeno y de nitrógeno en algunas enfermedades neurodegenerativas.** *Revista de la Facultad de Medicina (México)*, 62(3), 6-19. <https://doi.org/10.22201/fm.24484865e.2019.62.3.03>
- Hernández-Martínez, J. C., Varona-Uribe, M., & Hernández, G. (2020). **Prevalencia de factores asociados a la enfermedad cardiovascular y su relación con el ausentismo laboral de los trabajadores de una entidad oficial.** *Revista Colombiana de Cardiología*, 27(2), 109-116. <https://doi.org/10.1016/j.rccar.2018.11.004>
- Hernández, Y., Rodríguez, A., Villafuerte, J., Marrero, I., & Mora, C. (2020). **Influencia de los radicales libres en la génesis de la aterosclerosis.** *Revista de Enfermedades no Transmisibles Finlay*, 10(2), 170-178.
- Herrscher, C., Roingard, P., & Blanchard, E. (2020). **Hepatitis B virus entry into cells.** *Cells*, 9(6), 1486. <https://doi.org/10.3390/cells9061486>
- Higashi, Y. (2022). **Roles of oxidative stress and inflammation in vascular endothelial dysfunction-related disease.** *Antioxidants*, 11(10), 1958. <https://doi.org/10.3390/antiox11101958>
- Higgins, M.R., Izadi, A., Kaviani, M. (2020) **Antioxidants and Exercise Performance: With a Focus on Vitamin E and C Supplementation.** *International Journal of Environmental Research and Public Health*, 17, 8452. <https://doi.org/10.3390/ijerph17228452>
- Holotiuk, V. V., Kryzhanivsk, A. Y., Churpiy, I. K., Tataryn, B. B., & Ivasiutyn, D. Y. (2019). **Role of nitric oxide in pathogenesis of tumor growth and its possible application in cancer treatment.** *Experimental Oncology*, 41(3), 210-215. <https://doi.org/10.32471/exp-oncology.2312-8852.vol-41-no-3.13515>
- Hong, Y. A., Lim, J. H., Kim, M. Y., Kim, Y., Park, H. S., Kim, H. W., & Park, C. W. (2018). **Extracellular superoxide dismutase attenuates renal oxidative stress through the activation of adenosine monophosphate-activated protein kinase in diabetic nephropathy.** *Antioxidants & Redox Signaling*, 28(17), 1543-1561. <https://doi.org/10.1089/ars.2017.7207>
- Hu, J., Protzer, U., & Siddiqui, A. (2019). **Revisiting hepatitis B virus: challenges of curative therapies.** *Journal of Virology*, 93(20), 10-1128. <https://doi.org/10.1128/jvi.01032-19>
- Huchzermeyer, B., Menghani, E., Khardia, P., & Shilu, A. (2022). **Metabolic pathway of natural antioxidants, antioxidant enzymes and ROS providence.** *Antioxidants*, 11(4), 761. <https://doi.org/10.3390/antiox11040761>
- Ifeanyi, O. E. (2018). **A review on free radicals and antioxidants.** *International Journal of Current Research in Medical Sciences*, 4(2), 123-133. <http://dx.doi.org/10.22192/ijcrms.2018.04.02.019>
- Ighodaro, O. M., & Akinloye, O. A. (2018). **First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid.** *Alexandria Journal of Medicine*, 54(4), 287-293. DOI: 10.1016/j.ajme.2017.09.001

- Islam, M. N., Rauf, A., Fahad, F. I., Emran, T. B., Mitra, S., Olatunde, A., & Mubarak, M. S. (2021). [Superoxide dismutase: an updated review on its health benefits and industrial applications](#). *Critical Reviews in Food Science and Nutrition*, 62(26), 7282-7300. <https://doi.org/10.1080/10408398.2021.1913400>
- Islas Pérez, L. Á., Martínez Reséndiz, J. I., Ruiz Hernández, A., Ruvalcaba Ledezma, J. C., Benítez Medina, A., Beltran Rodríguez, M. G., & Reynoso Vázquez, J. (2021). [Epidemiology of prostate cancer, its determinants and prevention](#). *Journal of Negative and No Positive Results*, 5(9), 1010-1022. <https://dx.doi.org/10.19230/jonnpr.3686>
- Jahandideh, F., & Wu, J. (2020). [Perspectives on the potential benefits of antihypertensive peptides towards metabolic syndrome](#). *International Journal of Molecular Sciences*, 21(6), 2192. DOI: 10.3390/ijms21062192
- Jakubczyk, K., Dec, K., Kałduńska, J., Kawczuga, D., Kochman, J., & Janda, K. (2020). [Reactive oxygen species-sources, functions, oxidative damage](#). *Polski merkuriusz lekarski: organ Polskiego Towarzystwa Lekarskiego*, 48(284), 124- 127. <https://pubmed.ncbi.nlm.nih.gov/32352946/>
- Jamshidi-Kia, F., Wibowo, J. P., Elachouri, M., Masumi, R., Salehifard-Jouneghani, A., Abolhassanzadeh, Z., & Lorigooini, Z. (2020). [Battle between plants as antioxidants with free radicals in human body](#). *Journal of Herbmed Pharmacology*, 9(3), 191-199. DOI: 10.34172/jhp.2020.25 <https://herbmedpharmacol.com/Article/jhp-36627>
- Jamshidovich, A. S. (2023). [Ascorbic acid: its role in immune system, chronic inflammation diseases and on the antioxidant effects](#). *European Journal of Modern Medicine and Practice*, 3(11), 57-60.
- Janciauskiene, S. (2020). [The beneficial effects of antioxidants in health and diseases](#). *Chronic Obstructive Pulmonary Diseases*, 7(3), 182. DOI: 10.15326/jcopdf.7.3.2019.0152
- Jarosz, M., Olbert, M., Wyszogrodzka, G., Młyniec, K., & Librowski, T. (2017). [Antioxidant and anti-inflammatory effects of zinc. Zinc-dependent NF-κB signaling](#). *Inflammopharmacology*, 25, 11-24. <https://doi.org/10.1007/s10787-017-0309-4>
- Jávega Martínez, B. (2022). [Aplicación de la citometría de flujo al estudio en tiempo real de las interacciones entre especies reactivas de oxígeno y nitrógeno en el estrés oxidativo inducido por xenobióticos](#). [Tesis doctoral, Universitat de València. Facultat de Ciències Biològiques].
- Jiang, P., & Dickson, D. W. (2018). [Parkinson's disease: experimental models and reality](#). *Acta Neuropathologia*, 135, 13-32. DOI: 10.1007/s00401-017-1788-5
- Jiménez, I. (2019). [Fosforilación oxidativa y proteinopatías neurodegenerativas](#). [Tesis de maestría, Universidad de Zaragoza] Repositorio de la Universidad de Zaragoza. <https://zaguan.unizar.es/record/86840>
- Jinez-Sorroza, L. D., Sorroza-Rojas, N. A., Barberán Torres, J. P., & Jinez Jinez, H. E. (2017). [Factores de riesgo de cáncer de próstata: Revisión de Literatura](#). *RECIMUNDO: Revista Científica de la Investigación y el Conocimiento*, 1(5), 893-943. <https://doi.org/10.26820/recimundo/1.5.2017.893-943>
- Jîtcă, G., Ósz, B. E., Tero-Vescan, A., & Vari, C. E. (2021). [Psychoactive drugs—from chemical structure to oxidative stress related to dopaminergic neurotransmission. A review](#). *Antioxidants*, 10(3), 381. <https://doi.org/10.3390/antiox10030381>
- Joe, E., & Ringman, J. M. (2019). [Cognitive symptoms of Alzheimer's disease: clinical management and prevention](#). *BMJ*, 367(367) 16217. <https://doi.org/10.1136/bmj.16217>
- Jorquera, A., Wilhelm, J., & Conca, N. (2022). [Hepatitis de etiología no precisada en población pediátrica](#). *Revista Chilena de Infectología*, 39(4), 448-456. <http://dx.doi.org/10.4067/s0716-10182022000400448>

- Juszczuk, G., Mikulska, J., Kasperek, K., Pietrzak, D., Mrozek, W., & Herbet, M. (2021). [Chronic stress and oxidative stress as common factors of the pathogenesis of depression and Alzheimer's disease: The role of antioxidants in prevention and treatment.](#) *Antioxidants*, 10(9), 1439. <https://doi.org/10.3390/antiox10091439>
- Kabir, M. T., Rahman, M. H., Shah, M., Jamiruddin, M. R., Basak, D., Al-Harrasi, A., ... & Abdel-Daim, M. M. (2022). [Therapeutic promise of carotenoids as antioxidants and anti-inflammatory agents in neurodegenerative disorders.](#) *Biomedicine & Pharmacotherapy*, 146, 112610. <https://doi.org/10.1016/j.biopha.2021.112610>
- Kalpage, H. A., Wan, J., Morse, P. T., Zurek, M. P., Turner, A. A., Khobeir, A., & Hüttemann, M. (2020). [Cytochrome c phosphorylation: Control of mitochondrial electron transport chain flux and apoptosis.](#) *The International Journal of Biochemistry & Cell Biology*, 121, 105704. <https://doi.org/10.1016/j.biocel.2020.105704>
- Kamfar, W. W., Khraiwesh, H. M., Ibrahim, M. O., Qadhi, A. H., Azhar, W. F., Ghafouri, K. J., ... & Azzeh, F. S. (2024). [Comprehensive review of melatonin as a promising nutritional and nutraceutical supplement.](#) *Heliyon*. <https://doi.org/10.1016/j.heliyon.2024.e24266>
- Kamm, A., Przychodzen, P., Kuban-Jankowska, A., Jacewicz, D., Dabrowska, A. M., Nussberger, S., ... & Gorska-Ponikowska, M. (2019). [Nitric oxide and its derivatives in the cancer battlefield.](#) *Nitric oxide*, 93, 102-114. <https://doi.org/10.1016/j.niox.2019.09.005>
- Kashyap, D., Pal, D., Sharma, R., Garg, V. K., Goel, N., Koundal, D., ... & Belay, A. (2022). [Global Increase in Breast Cancer Incidence: Risk Factors and Preventive Measures.](#) *BioMed Research International*, 2022(1), 9605439. <https://doi.org/10.1155/2022/9605439>
- Katiyar, S., & Kumar, A. (2019). [Purification of Catalase Enzyme from Chilli Plants and its Physiochemical Properties.](#) *International Journal of Engineering Sciences and Advanced Research*, 5, 25-30.
- Katsarou, A., Gudbjörnsdóttir, S., Rawshani, A., Dabelea, D., Bonifacio, E., Anderson, B. J., ... & Lernmark, Å. (2017). [Type 1 diabetes mellitus.](#) *Nature Reviews Disease Primers*, 3(1), 1-17. DOI: 10.1038/nrdp.2017.16
- Katsumoto, A., Takeuchi, H., Takahashi, K., & Tanaka, F. (2018). [Microglia in Alzheimer's disease: risk factors and inflammation.](#) *Frontiers in Neurology*, 9, 978. <https://doi.org/10.3389/fneur.2018.00978>
- Kaushal, J., Mehandia, S., Singh, G., Raina, A., & Arya, S. K. (2018). [Catalase enzyme: Application in bioremediation and food industry.](#) *Biocatalysis and agricultural biotechnology*, 16, 192-199. <https://doi.org/10.1016/j.bcab.2018.07.035>
- Kaźmierczak-Barańska, J., Boguszewska, K., Adamus-Grabicka, A., & Karwowski, B. T. (2020). [Two faces of vitamin C—antioxidative and pro-oxidative agent.](#) *Nutrients*, 12(5), 1501. <https://doi.org/10.3390/nu12051501>
- Kehm, R., Baldensperger, T., Raupbach, J., & Höhn, A. (2021). [Protein oxidation- formation mechanisms, detection and relevance as biomarkers in human diseases.](#) *Redox Biology*, 42, 101901. <https://doi.org/10.1016/j.redox.2021.101901>
- Khadim, R. M., & Al-Fartusie, F. S. (2021). [Antioxidant vitamins and their effect on immune system.](#) *In Journal of Physics: Conference Series* 1853, 1, 012065. IOP Publishing. DOI: 10.1088/1742-6596/1853/1/012065
- Khan, R.M.M.; Chua, Z.J.Y.; Tan, J.C.; Yang, Y.; Liao, Z.; Zhao, Y. (2019). [From Pre- Diabetes to Diabetes: Diagnosis, Treatments and Translational Research.](#) *Medicina*, 55, 546. <https://doi.org/10.3390/medicina55090546>

- Khan, A., Ikram, M., Hahm, J. R., & Kim, M. O. (2020). Antioxidant and anti-inflammatory effects of citrus flavonoid hesperetin: Special focus on neurological disorders. *Antioxidants*, 9(7), 609. <https://doi.org/10.3390/antiox9070609>
- Khatun, M., & Ray, R. B. (2019). Mechanisms underlying hepatitis C virus-associated hepatic fibrosis. *Cells*, 8(10), 1249. <https://doi.org/10.3390/cells8101249>
- Kieliszek, M. (2019). Selenium—fascinating microelement, properties and sources in food. *Molecules*, 24(7), 1298. <https://doi.org/10.3390/molecules24071298>
- Kim, I. S. (2021). Current perspectives on the beneficial effects of soybean isoflavones and their metabolites for humans. *Antioxidants*, 10(7), 1064. <https://doi.org/10.3390/antiox10071064>
- Kiyose, C. (2021). Absorption, transportation, and distribution of vitamin E homologs. *Free Radical Biology and Medicine*, 177, 226-237. <https://doi.org/10.1016/j.freeradbiomed.2021.10.016>
- Koliaki, C., Liatis, S., & Kokkinos, A. (2019). Obesity and cardiovascular disease: revisiting an old relationship. *Metabolism*, 92, 98-107. <https://doi.org/10.1016/j.metabol.2018.10.011>
- Konno, T., Melo, E. P., Chambers, J. E., & Avezov, E. (2021). Intracellular sources of ROS/H₂O₂ in health and neurodegeneration: spotlight on endoplasmic reticulum. *Cells*, 10(2), 233. <https://doi.org/10.3390/cells10020233>
- Koo, M. M., Swann, R., McPhail, S., Abel, G. A., Elliss-Brookes, L., Rubin, G. P., & Lyratzopoulos, G. (2020). Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study. *The Lancet Oncology*, 21(1), 73-79. DOI: 10.1016/S1470-2045(19)30595-9
- Kovacs, G. G. (2018). Concepts and classification of neurodegenerative diseases. In *Handbook of Clinical Neurology*, 145, 301-307. <https://doi.org/10.1016/B978-0-12-802395-2.00021-3>
- Křížová, L., Dadáková, K., Kašparovská, J., Kašparovský, T. (2019). Isoflavones. *Molecules*, 24(6), 1076. <https://doi.org/10.3390/molecules24061076>
- Kulik, L., & El-Serag, H. B. (2019). Epidemiology and management of hepatocellular carcinoma. *Gastroenterology*, 156(2), 477-491. <https://doi.org/10.1053/j.gastro.2018.08.065>
- Kumar, S., Sharma, S., & Vasudeva, N. (2017). Review on antioxidants and evaluation procedures. *Chinese Journal of Integrative Medicine*, 1-12. <https://doi.org/10.1007/s11655-017-2414-z>
- Kumar, S., Singh, R. K., & Bhardwaj, T. R. (2017). Therapeutic role of nitric oxide as emerging molecule. *Biomedicine & Pharmacotherapy*, 85, 182-201. <https://doi.org/10.1016/j.biopha.2016.11.125>
- Kumar, A., Sidhu, J., Goyal, A., & Tsao, J. W. (2018). Alzheimer disease. *Europe PMC*.
- Kumar, N., & Goel, N. (2019). Phenolic acids: Natural versatile molecules with promising therapeutic applications. *Biotechnology Reports*, 24, e00370. <https://doi.org/10.1016/j.btre.2019.e00370>
- Laube, R., Sabih, A. H., Strasser, S. I., Lim, L., Cigolini, M., & Liu, K. (2021). Palliative care in hepatocellular carcinoma. *Journal of Gastroenterology and Hepatology*, 36(3), 618-628. <https://doi.org/10.1111/jgh.15169>
- Lee, G. Y., & Han, S. N. (2018). The role of vitamin E in immunity. *Nutrients*, 10(11), 1614. <https://doi.org/10.3390/nu10111614>
- Lee, S. R. (2018). Critical role of zinc as either an antioxidant or a prooxidant in cellular systems. *Oxidative Medicine and Cellular Longevity*, 2018. <https://doi.org/10.1155/2018/9156285>

- Lefebvre, T., Destandau, E., & Lesellier, E. (2020). [Selective extraction of bioactive compounds from plants using recent extraction techniques: A Review](#). *Journal of Chromatography A*, 1635 461770. <https://doi.org/10.1016/j.chroma.2020.46177>
- León, M., Cedeño, R., Rivero, R., Rivero J., García, D., & Bordón, L. (2018). [La teoría del estrés oxidativo como causa directa del envejecimiento celular](#). *Medisur*, 16(5), 699-710.
- Leonardo-Mendonça, R. C., Ocaña-Wilhelmi, J., de Haro, T., de Teresa-Galván, C., Guerra-Hernández, E., Rusanova, I., ... & Acuña-Castroviejo, D. (2017). [The benefit of a supplement with the antioxidant melatonin on redox status and muscle damage in resistance-trained athletes](#). *Applied Physiology, Nutrition, and Metabolism*, 42(7), 700-707. <https://doi.org/10.1139/apnm-2016-0677>
- Lestegás Soto, A. (2021). [Funciones biológicas del zinc](#). [Trabajo fin de grado, Universidad de León]. *Repositorio Institucional Bulberia*. <https://buleria.unileon.es/handle/10612/13826>
- Li, S., Tan, H. Y., Wang, N., Zhang, Z. J., Lao, L., Wong, C. W., & Feng, Y. (2015). [The role of oxidative stress and antioxidants in liver diseases](#). *International Journal of Molecular Sciences*, 16(11), 26087-26124. <https://doi.org/10.3390/ijms161125942>
- Li, C., Deng, X., Xie, X., Liu, Y., Friedmann Angeli, J. P., & Lai, L. (2018). [Activation of glutathione peroxidase 4 as a novel anti-inflammatory strategy](#). *Frontiers in Pharmacology*, 9, 385435. <https://doi.org/10.3389/fphar.2018.01120>
- Liguori, I., Russo, G., Curcio, F., Bulli, G., Aran, L., Della-Morte, D., Gargiulo, G., Testa, G., Cacciatore, F., Bonaduce, D., & Abete, P. (2018). [Oxidative stress, aging, and diseases](#). *Clinical Interventions in Aging*, 13, 757-772.
- Liu, W., Feng, Y., Yu, S., Fan, Z., Li, X., Li, J., & Yin, H. (2021). [The flavonoid biosynthesis network in plants](#). *International Journal of Molecular Sciences*, 22(23), 12824. <https://doi.org/10.3390/ijms222312824>
- Lolas Stepke, F. (2020). [Perspectivas bioéticas en un mundo en pandemia](#). *Acta Bioethica*, 26(1), 7-8. <http://dx.doi.org/10.4067/S1726-569X2020000100007>
- Longinetti, E., & Fang, F. (2019). [Epidemiology of amyotrophic lateral sclerosis: an update of recent literature](#). *Current Opinion in Neurology*, 32(5), 771-776. DOI: 10.1097/WCO.0000000000000730
- Loomba, R., Friedman, S. L., & Shulman, G. I. (2021). [Mechanisms and disease consequences of nonalcoholic fatty liver disease](#). *Cell*, 184(10), 2537-2564. <https://doi.org/10.1016/j.cell.2021.04.015>
- López de Romaña, D., Castillo, C., & Diazgranados, D. (2010). [El zinc en la salud humana-1](#). *Revista chilena de nutrición*, 37(2), 234-239. <http://dx.doi.org/10.4067/S0717-75182010000200013>
- López-Quesada, J. (2018). [Purificación y caracterización de la enzima glutatión reductasa de levadura](#). [Trabajo de fin de grado, Universidad de Jaén]. <https://hdl.handle.net/10953.1/8735>
- López, E. (2019). [Peroxidación lipídica y evaluación del efecto de las vitaminas antioxidantes en internos de medicina con somnolencia diurna en hospitales de Lambayeque-2018](#). [Tesis doctoral, Universidad Nacional Pedro Ruiz Gallo]. Repositorio Institucional UNPRG. <http://repositorio.unprg.edu.pe/handle/20500.12893/5024>
- López, E. O., Ballard, B. D., & Jan, A. (2022). [Cardiovascular disease](#). In *StatPearls* [Internet]. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK535419/>
- López-Plaza, B., Loria-Kohen, V., González-Rodríguez, L. G., & Fernández-Cruz, E. (2022). [Alimentación y estilo de vida en la prevención del cáncer](#). *Nutrición Hospitalaria*, 39(3), 74-77. <https://dx.doi.org/10.20960/nh.04317>

- Losada-Barreiro, S., & Bravo-Diaz, C. (2017). Free radicals and polyphenols: The redox chemistry of neurodegenerative diseases. *European Journal of Medicinal Chemistry*, 133, 379-402. <https://doi.org/10.1016/j.ejmech.2017.03.061>
- Lozano-Picazo, C. M., & Fernández-Belda, F. (2018). Especies reactivas de oxígeno y su implicación en Biomedicina. In *Anales de Veterinaria de Murcia* 34, 17-26. <https://doi.org/10.6018/analesvet.332621>
- Luna-Ortiz, P., Pilar-Báez, S., Lazcano-Vázquez, M. F., & Martínez-Rosas, M. (2024). El estrés oxidativo en el perioperatorio: implicaciones clínicas. *Revista Mexicana de Anestesiología*, 47(1), 23-29. DOI: 10.35366/114093
- Lutkus, L. V., Rickenbach, S. S., & McCormick, T. M. (2019). Singlet oxygen quantum yields determined by oxygen consumption. *Journal of Photochemistry and Photobiology A: Chemistry*, 378, 131-135. <https://doi.org/10.1016/j.jphotochem.2019.04.029>
- Mach, N., & Fuster-Botella, D. (2017). Endurance exercise and gut microbiota: A review. *Journal of Sport and Health Science*, 6(2), 179-197. <https://doi.org/10.1016/j.jshs.2016.05.001>
- Magkos, F., Hjorth, M. F., & Astrup, A. (2020). Diet and exercise in the prevention and treatment of type 2 diabetes mellitus. *Nature Reviews Endocrinology*, 16(10), 545-555. DOI: 10.1038/s41574-020-0381-5
- Magliano, D. J., Sacre, J. W., Harding, J. L., Gregg, E. W., Zimmet, P. Z., & Shaw, J. E. (2020). Young-onset type 2 diabetes mellitus—Implications for morbidity and mortality. *Nature Reviews Endocrinology*, 16(6), 321-331. DOI: 10.1038/s41574-020-0334-z
- Magrone, T., Magrone, M., Russo, M. A., & Jirillo, E. (2019). Recent advances on the anti-inflammatory and antioxidant properties of red grape polyphenols: in vitro and in vivo studies. *Antioxidants*, 9(1), 35. <https://doi.org/10.3390/antiox9010035>
- Mahecha Matsudo, S. M. (2019). Recomendaciones de actividad física: un mensaje para el profesional de la salud. *Revista de Nutrición Clínica y Metabolismo*, 2(2).
- Mahomoodally, M. F., & MA-L, E. R. (2022). Catalase. In *Antioxidants effects in health*, 81-90. <https://doi.org/10.1016/B978-0-12-819096-8.00022-7>
- Maiorino, M., Conrad, M., & Ursini, F. (2018). GPx4, lipid peroxidation, and cell death: discoveries, rediscoveries, and open issues. *Antioxidants & Redox Signaling*, 29(1), 61-74. <https://doi.org/10.1089/ars.2017.7115>
- Maldonado, J. C. (2018). Epidemiología de la insuficiencia cardíaca. *Revista Médica Vozandes*, 29(1), 51-3.
- Mancini, M., Mazzoni, L., Gagliardi, F., Balducci, F., Duca, D., Toscano, G., & Capocasa, F. (2020). Application of the non-destructive NIR technique for the evaluation of strawberry fruits quality parameters. *Foods*, 9(4), 441 <https://doi.org/10.3390/foods9040441>
- Mantovani, A., Scorletti, E., Mosca, A., Alisi, A., Byrne, C. D., & Targher, G. (2020). Complications, morbidity and mortality of nonalcoholic fatty liver disease. *Metabolism*, 111, 154170. <https://doi.org/10.1016/j.metabol.2020.154170>
- Martemucci, G., Costagliola, C., Mariano, M., D'andrea, L., Napolitano, P., & D'Alessandro, A. G. (2022). Free radical properties, source and targets, antioxidant consumption and health. *Oxygen*, 2(2), 48-78. <https://doi.org/10.3390/oxygen2020006>
- Martinez-Castillo, M., Altamirano-Mendoza, I., Sánchez-Valle, S., García-Islas, L., Sánchez-Barragán, M., Hernández-Santillán, M., ... & Gutierrez-Reyes, G. (2023). Desregulación inmunológica y fisiopatología del consumo de alcohol y la enfermedad hepática alcohólica. *Revista de Gastroenterología de México*, 88(2), 136-154. <https://doi.org/10.1016/j.rgmx.2023.01.002>

- Martínez-Orgado, J., Martínez-Vega, M., Silva, L., Romero, A., de Hoz-Rivera, M., Villa, M., & Del Pozo, A. (2023). [Protein carbonylation as a biomarker of oxidative stress and a therapeutic target in neonatal brain damage](#). *Antioxidants*, 12(10), 1839. <https://doi.org/10.3390/antiox12101839>
- Martins, T. F., Palomino, O. M., Álvarez-Cilleros, D., Martín, M. A., Ramos, S., & Goya, L. (2020). [Cocoa flavanols protect human endothelial cells from oxidative stress](#). *Plant Foods for Human Nutrition*, 75, 161-168. <https://doi.org/10.1007/s11130-020-00807-1>
- Masarone, M., Rosato, V., Dallio, M., Gravina, A. G., Aglitti, A., Loguercio, C., & Persico, M. (2018). [Role of oxidative stress in pathophysiology of nonalcoholic fatty liver disease](#). *Oxidative medicine and cellular longevity*, 2018(1). <https://doi.org/10.1155/2018/9547613>
- Masrori, P., & Van Damme, P. (2020). [Amyotrophic lateral sclerosis: a clinical review](#). *European Journal of Neurology*, 27(10), 1918-1929. <https://doi.org/10.1111/ene.14393>
- Matamoros, M. A., Kim, A., Peñuelas, M., Ihling, C., Griesser, E., Hoffmann, R., & Becana, M. (2018). [Proteincarbonylation and glycation in legume nodules](#). *Plant Physiology*, 177(4), 1510-1528. <https://doi.org/10.1104/pp.18.00533>
- Mateos Muñoz, B., Martínez Ortega, A., Sanchez Aldehuelo, R., & Guerrero García, A. (2020). [Hepatitis víricas: virus de la hepatitis A, B y E](#). *Medicine-Programa de Formación Médica Continuada Acreditado*, 13(5), 237-244. <https://doi.org/10.1016/j.med.2020.03.001>.
- Mathesius, U. (2018). [Flavonoid functions in plants and their interactions with other organisms](#). *Plants*, 7(2), 30. <https://doi.org/10.3390/plants7020030>
- Mathis, S., Goizet, C., Soulages, A., Vallat, J. M., & Le Masson, G. (2019). [Genetics of amyotrophic lateral sclerosis: A review](#). *Journal of the Neurological Sciences*, 399, 217-226. <https://doi.org/10.1016/j.jns.2019.02.030>
- Matic, P., & Jakobek, L. (2021). [Spectrophotometric Folin-Ciocalteu and aluminium chloride method validation for the determination of phenolic acid, flavan-3-ol, flavonol, and anthocyanin content](#). *Croatian Journal of Food Science and Technology*, 13(2), 176-183. DOI: 10.17508/CJFST.2021.13.2.06
- McCartney, D. L., Stevenson, A. J., Walker, R. M., Gibson, J., Morris, S. W., Campbell, A., ... & Marioni, R. E. (2018). [Investigating the relationship between DNA methylation age acceleration and risk factors for Alzheimer's disease](#). *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 10, 429-437. <https://doi.org/10.1016/j.dadm.2018.05.006>
- McGlynn, K.A., Petrick, J.L. y El-Serag, H.B. (2021). [Epidemiología del carcinoma hepatocelular](#). *Hepatología*, 73, 4-13. <https://doi.org/10.1002/hep.31288>
- Medeiros, M. S., Schumacher-Schuh, A., Cardoso, A. M., Bochi, G. V., Baldissarelli, J., Kegler, A., ... & Figuera, M. R. (2016). [Iron and oxidative stress in Parkinson's disease: an observational study of injury biomarkers](#). *PloS one*, 11(1), 0146129. DOI: 10.1371/journal.pone.0146129
- Medina-Chávez, J. H., Vázquez-Parrodi, M., Mendoza-Martínez, P., Ríos-Mejía, E. D., de Anda-Garay, J.C., & Balandrán-Duarte, D.A. (2022). [Protocolo de Atención Integral: prevención, diagnóstico y tratamiento de diabetes mellitus 2](#). *Revista Médica del Instituto Mexicano del Seguro Social*, 60(1), 4. DOI: <https://doi.org/10.5281/>
- Meitha, K., Pramesti, Y., & Suhandono, S. (2020). [Reactive oxygen species and antioxidants in postharvest vegetables and fruits](#). *International Journal of Food Science*, 2020(1) 8817778. <https://doi.org/10.1155/2020/8817778>
- Meléndez Martínez, A. J., Mercadante, Adriana, A. Z., Pérez Gálvez, A., Roca, M., Estévez Santiago, R., Olmedilla-Alonso, B., & Ornelas-Paz, J. de J. (2017). [Carotenoides en agroalimentación y salud](#). En *Carotenoides en agroalimentación y salud* (pp. 574-608). Programa Iberoamericano de Ciencia y Tecnología para el Desarrollo.

- Mendez, M. F. (2019). [Early-onset Alzheimer disease and its variants](#). *CONTINUUM: Lifelong Learning in Neurology*, 25(1), 34-51. DOI: 10.1212/CON.0000000000000687
- Mendoza-Herrera, K., Pedroza-Tobías, A., Hernández-Alcaraz, C., Ávila-Burgos, L., Aguilar-Salinas, CA, & Barquera, S. (2019). [Carga y gasto atribuibles de las enfermedades cardiovasculares y factores de riesgo asociados en México y otros megapaíses seleccionados](#). *Revista Internacional de Investigación ambiental y salud pública*, 16 (20), 4041. <https://doi.org/10.3390/ijerph16204041>
- Mensah, G. A., Roth, G. A., & Fuster, V. (2019). [The global burden of cardiovascular diseases and risk factors: 2020 and beyond](#). *Journal of the American College of Cardiology*, 74(20), 2529-2532. DOI: 10.1016/j.jacc.2019.10.009
- Meñaca-Guerrero, L., Suarez-Causado, A., & José Díaz-Caballero, A. (2020). [Reactive species of oxygen, oxidative stress and its relationship with tissular destruction in periodontitis](#). *CES Odontología*, 33(2), 112-127. <https://doi.org/10.21615/cesodon.33.2.10>
- Mercedes, B. F. A., Santos, G. S. J., Nydia, C. B. O., Isabel, S. M. D., Jaime, L. C., & Karina, B. R. A. (2022). [Validation of a micro-assay based on the pH differential method to quantify total monomeric anthocyanins in red cabbage \(*Brassica oleracea var. capitata f rubra*\)](#). *Journal of Food Measurement and Characterization*, 16(5), 3967-3976. DOI: 10.1007/s11694-022-01505-z
- Metro, D., Corallo, F., Fedele, F., Buda, M., Manasseri, L., Buono, V. L., & Bonanno, L. (2022). [Effects of Alcohol Consumption on Oxidative Stress in a Sample of Patients Recruited in a Dietary Center in a Southern University Hospital: A Retrospective Study](#). *Medicina*, 58(11), 1670. <https://doi.org/10.3390/medicina58111670>
- Milani, A., Basirnejad, M., Shahbazi, S., & Bolhassani, A. (2016). Carotenoids: biochemistry, pharmacology and treatment. *British Journal of Pharmacology*, 174(11), 1290-1324. <https://doi.org/10.1111/bph.13625>
- Miłek, J. (2020). [Thermodynamics and kinetics of thermal deactivation of catalase *Aspergillus niger*](#). *Green Sciences*, 22(2). 67-72. <https://doi.org/10.2478/pjct-2020-0018>
- Miller, M. R., & Newby, D. E. (2020). [Air pollution and cardiovascular disease: car sick](#). *Cardiovascular Research*, 116(2), 279-294. <https://doi.org/10.1093/cvr/cvz228>
- Miranda, L., & Guerrero, J. (2021). [Fracción de óxido nítrico exhalado: una herramienta clínica para las enfermedades pulmonares](#). *Revista Médica de Chile*, 149(8), 1173-1181. <http://dx.doi.org/10.4067/s0034-98872021000801173>
- Mitra, S., De, A., & Chowdhury, A. (2020). [Epidemiology of non-alcoholic and alcoholic fatty liver diseases](#). *Translational gastroenterology and hepatology*, 5(16). DOI: 10.21037/tgh.2019.09.08
- Miyazawa, T., Burdeos, G. C., Itaya, M., Nakagawa, K., & Miyazawa, T. (2019). [Vitamin E: regulatory redox interactions](#). *IUBMB life*, 71(4), 430-441. <https://doi.org/10.1002/iub.2008>
- Moldogazieva, N. T., Mokhosoev, I. M., Melnikova, T. I., Porozov, Y. B., & Terentiev, A. A. (2019). [Oxidative stress and advanced lipoxidation and glycation end products \(ALEs and AGEs\) in aging and age-related diseases](#). *Oxidative medicine and cellular longevity*, 2019(1), 3085756. <https://doi.org/10.1155/2019/3085756>
- Möller, M. N., Rios, N., Trujillo, M., Radi, R., Denicola, A., & Alvarez, B. (2019). [Detection and quantification of nitric oxide-derived oxidants in biological systems](#). *Journal of Biological Chemistry*, 294(40), 14776-14802. <https://doi.org/10.1074/jbc.REV119.006136>
- Montalvo-Jave, EE, Hoyos-Lazaro, AE, Espejel-Deloiza, M., Chernitzky-Camano, J., Rodriguez-Baez, A., & Ortega-Leon, LH (2021). [Actualización en supervivencia del carcinoma hepatocelular](#). *Cirugía y Cirujanos*, 89 (1), 104-114. <https://doi.org/10.24875/ciru.19001375>

- Montero, M. (2023). [El estrés oxidativo y su relación con enfermedades neurodegenerativas](#). [Tesis de licenciatura, Universidad Técnica de Ambato]. Repositorio Universidad Técnica de Ambato. <https://repositorio.uta.edu.ec:8443/handle/123456789/38782>
- Montier Iglesias, A., Ramos Arencibia, A. L., Gómez García, M. L., Pérez Cardoso, J. J., & Quintana Pérez, Q. (2015). [Estrés oxidativo en la diabetes mellitus papel de la vitamina E y antioxidantes endógenos](#). *Revista de Ciencias Médicas de Pinar del Río*, 19(5), 973-985.
- Montier Iglesias, A., Cabezas Alfonso, I., Díaz Cabrera, J. C., Linares Guerra, E. M., & Jerez Hernández, E. (2018). [Efecto de la vitamina E sobre antioxidantes endógenos en ratas Wistar diabéticas](#). *Revista de Ciencias Médicas de Pinar del Río*, 22(3), 25-39.
- Moon, J., Posada-Quintero, H. F., & Chon, K. H. (2023). [A literature embedding model for cardiovascular disease prediction using risk factors, symptoms, and genotype information](#). *Expert Systems with Applications*, 213, 118930. <https://doi.org/10.1016/j.eswa.2022.118930>
- Mora, S., Zeledón, A., & Vargas, T. (2019). [Estrés oxidativo y antioxidantes: efectos en el embarazo](#). *Revista Médica Sinergia*, 4(05), 89-100. <https://doi.org/10.31434/rms.v4i5.211>
- Morachis, A. G. (2014). [Evaluación de las características fisicoquímicas, texturales y nutrimentales de carpa común \(*Cyprinus carpio*\) por exposición a diversos contaminantes presentes de presa Madín](#) [Tesis de maestría, Universidad Autónoma del Estado de México]. Repositorio Institucional de la Universidad Autónoma del Estado de México. <http://ri.uaemex.mx/handle/20.500.11799/14963>
- Morales-Romero, J., Ortíz-León, M. C., Hernández-Gutiérrez, H., Bahena-Cerón, R. A., Miranda-Reza, A., Marín-Carmona, J. A., ... & García-Román, R. (2023). [Factores de riesgo de la enfermedad hepática grasa asociada a disfunción metabólica en población hispano-mexicana](#). *Revista Española de salud pública*, 97.
- Muchtaridi, M., Az-Zahra, F., Wongso, H., Setyawati, L. U., Novitasari, D., & Ikram, E. H. K. (2024). [Molecular Mechanism of Natural Food Antioxidants to Regulate ROS in Treating Cancer: A Review](#). *Antioxidants*, 13(2), 207. <https://doi.org/10.3390/antiox13020207>
- Nair, D., Nedungadi, D., Mishra, N., Nair, B. G., & Nair, S. S. (2021). [Identification of carbonylated proteins from monocytic cells under diabetes-induced stress conditions](#). *Biomedical Chromatography*, 35(6), 5065. DOI: 10.1002/bmc.5065
- Nakayama, T., Takahashi, S., & Waki, T. (2019). [Formation of flavonoid metabolons: functional significance of protein-protein interactions and impact on flavonoid chemodiversity](#). *Frontiers in Plant Science*, 10, 460916. <https://doi.org/10.3389/fpls.2019.00821>
- National Cancer Institute. (2019). [Cancer Types](#). National Cancer Institute; Cancer.gov. <https://www.cancer.gov/types>
- Navarro-González, I., Periago, M. J., & García-Alonso, F. J. (2017). [Estimación de la capacidad antioxidante de los alimentos ingeridos por la población española](#). *Revista Chilena de Nutrición*, 44(2), 183-188. <http://dx.doi.org/10.4067/S0717-75182017000200010>
- Nayak, A. P., Kapur, A., Barroilhet, L., & Patankar, M. S. (2018). [Oxidative phosphorylation: a target for novel therapeutic strategies against ovarian cancer](#). *Cancers*, 10(9), 337. <https://doi.org/10.3390/cancers10090337>
- Nazario Dolz, A. M., Álvarez Matos, D., Castillo Toledo, L., Miyares Peña, M. V., & Garbey Nazario, A. (2021). [Algunas especificidades en torno al cáncer de pulmón](#). *Revista Cubana de Medicina Militar*, 50(1).
- Nizama Mena, T. D. P. (2019). [Contenido de compuestos carotenoides y determinación de la capacidad antioxidante in vitro de *Physalis peruviana* l “Aguaymanto”](#). [Tesis de licenciatura]. Universidad César Vallejo.

- Njus, D., Kelley, P. M., Tu, Y. J., & Schlegel, H. B. (2020). [Ascorbic acid: The chemistry underlying its antioxidant properties.](#) *Free Radical Biology and Medicine*, 159, 37-43. <https://doi.org/10.1016/j.freeradbiomed.2020.07.013>
- Nolfi-Donagan, D., Braganza, A., & Shiva, S. (2020). [Mitochondrial electron transport chain: Oxidative phosphorylation, oxidant production, and methods of measurement.](#) *Redox biology*, 37, 101674. <https://doi.org/10.1016/j.redox.2020.101674>
- Núñez-Liza, J.C, Díaz-Vélez, C., & Velásquez J. E. (2017). [Frecuencia de factores de riesgo para cáncer de próstata en un distrito de alta incidencia.](#) *Revista Venezolana de Oncología*, 29(4), 244-251.
- Núñez-Troconis, J. (2017). [Cigarrillo y cáncer de cuello uterino.](#) *Revista Chilena de Obstetricia y Ginecología*, 82(2), 232-240. <http://dx.doi.org/10.4067/S0717-75262017000200014>
- Núñez Martín, M., & Castillo Gualda, R. (2019). [El papel de la inteligencia emocional en la enfermedad cardiovascular.](#) *Gaceta Sanitaria*, 33(4), 377-380. <https://dx.doi.org/10.1016/j.gaceta.2018.04.008>
- Obrador, E., Salvador, R., López-Blanch, R., Jihad-Jebbar, A., Vallés, S. L., & Estrela, J.M. (2020). [Oxidative stress, neuroinflammation and mitochondria in the pathophysiology of amyotrophic lateral sclerosis.](#) *Antioxidants*, 9(9), 901. <https://doi.org/10.3390/antiox9090901>
- Ogunwobi, O. O., Harricharran, T., Huaman, J., Galuza, A., Odumuwagon, O., Tan, Y., ... & Nguyen, M. T. (2019). [Mechanisms of hepatocellular carcinoma progression.](#) *World Journal of Gastroenterology*, 25(19), 2279. DOI: 10.3748/wjg.v25.i19.2279
- Olivas, I., Rodríguez-Tajes, S., & Londoño, M. C. (2022). [Hepatitis autoinmune: retos y novedades.](#) *Medicin Clínica*, 159(6), 289-298. <https://doi.org/10.1016/j.medcli.2022.04.004>
- Olszowy, M. (2019). [What is responsible for antioxidant properties of polyphenolic compounds from plants?.](#) *Plant Physiology and Biochemistry*, 144, 135-143. <https://doi.org/10.1016/j.plaphy.2019.09.039>
- Onofrio, F. Q., & Hirschfield, G. M. (2020). [The pathophysiology of cholestasis and its relevance to clinical practice.](#) *Clinical Liver Disease*, 5(3), 110-114. DOI: 10.1002/cld.894
- Ordoñez-Gómez, E. S., Reátegui-Díaz, D., & Villanueva-Tiburcio, J. E. (2018). [Polifenoles totales y capacidad antioxidante en cáscara y hojas de doce cítricos.](#) *Scientia Agropecuaria*, 9(1), 113-121. <http://dx.doi.org/10.17268/sci.agropecu.2018.01.13>
- Ore, A., & Akinloye, O. A. (2019). [Oxidative stress and antioxidant biomarkers in clinica and experimental models of non-alcoholic fatty liver disease.](#) *Medicina*, 55(2), 26. <https://doi.org/10.3390/medicina55020026>
- Oskarsson, B., Gendron, T. F., & Staff, N. P. (2018). [Amyotrophic lateral sclerosis: an update for 2018.](#) *In Mayo Clinic Proceedings* 93(11), 1617-1628. <https://doi.org/10.1016/j.mayocp.2018.04.007>
- Osorio B.N., Bello H.C., & Vega B.L., (2020). [Factores de riesgo asociados al cáncer de mama.](#) *Revista Cubana de Medicina General Integral*, 36(2), 1147. Recuperado a partir de <https://revmgi.sld.cu/index.php/mgi/article/view/1147>
- Palmero Picazo, J., Lassard Rosenthal, J., Juárez Aguilar, L. A., & Medina Núñez, C. A. (2021). [Cáncer de mama: una visión general.](#) *Acta Médica Grupo Ángeles*, 19(3), 354-360.
- Panche, A. N., Diwan, A. D., & Chandra, S. R. (2016). [Flavonoids: an overview.](#) *Journal of Nutritional Science*, 5, 47. <https://doi.org/10.1017/jns.2016.41>
- Parcheta, M., Świsłocka, R., Orzechowska, S., Akimowicz, M., Choińska, R. y Lewandowski, W. (2021). [Desarrollos recientes en antioxidantes efectivos: Estructura y propiedades antioxidantes.](#) *Materials*, 14 (8), 1984. <https://doi.org/10.3390/ma14081984>

- Park, H. R., & Yang, E. J. (2021). **Oxidative stress as a therapeutic target in amyotrophic lateral sclerosis: Opportunities and limitations.** *Diagnostics*, 11(9), 1546. <https://doi.org/10.3390/diagnostics11091546>
- Patel, H., Alkhawam, H., Madanieh, R., Shah, N., Kosmas, C. E., & Vittorio, T. J. (2017). **Aerobic vs anaerobic exercise training effects on the cardiovascular system.** *World Journal of Cardiology*, 9(2), 134. doi: 10.4330/wjc.v9.i2.134
- Pavlek, L. R., Dillard, J., & Rogers, L. K. (2020). **The role of oxidative stress in toxicities due to drugs of abuse.** *Current Opinion in Toxicology*, 20, 29-35. DOI: 10.1016/j.cotox.2020.04.003
- Pawlowska, E., Szczepanska, J., & Blasiak, J. (2019). **Pro-and antioxidant effects of vitamin C in cancer in correspondence to its dietary and pharmacological concentrations.** *Oxidative Medicine and Cellular Longevity*, 2019. <https://doi.org/10.1155/2019/7286737>
- Pecora, F., Persico, F., Argentiero, A., Neglia, C., & Esposito, S. (2020). **The role of micronutrients in support of the immune response against viral infections.** *Nutrients*, 12(10), 3198. <https://doi.org/10.3390/nu12103198>
- Peña García, Y., Maceo González, M., Ávila Céspedes, D., Utria Velázquez, L., & Más López, Y. (2017). **Factores de riesgo para padecer cáncer de mama en la población femenina.** *Revista Finlay*, 7(4), 283-289.
- Peña-Bautista, C., Baquero, M., Vento, M., & Cháfer-Pericás, C. (2019). **Free radicals in Alzheimer's disease: Lipid peroxidation biomarkers.** *Clinica Química Acta*, 491, 85-90. <https://doi.org/10.1016/j.cca.2019.01.021>
- Percário, S., Da Silva Barbosa, A., Varela, E. L. P., Gomes, A. R. Q., Ferreira, M. E. S., De Nazaré Araújo Moreira, T., & Dolabela, M. F. (2020). **Oxidative stress in Parkinson's Disease: Potential benefits of antioxidant supplementation.** *Oxidative Medicine and Cellular Longevity*, 2020, 1-23. <https://doi.org/10.1155/2020/2360872>
- Pereira, R., Silva, A. M., Ribeiro, D., Silva, V. L., & Fernandes, E. (2023). **Bis- chalcones: A review of synthetic methodologies and anti-inflammatory effects.** *European Journal of Medicinal Chemistry*, 252, 115280. <https://doi.org/10.1016/j.ejmech.2023.115280>
- Pérez-Gálvez, A., Viera, I., & Roca, M. (2020). **Carotenoids and chlorophylls as antioxidants.** *Antioxidants*, 9(6), 505. <https://doi.org/10.3390/antiox9060505>
- Piacenza, L., Zeida, A., Trujillo, M., & Radi, R. (2022). **The superoxide radical switch in the biology of nitric oxide and peroxynitrite.** *Physiological Reviews*, 102(4), 1881-1906. <https://doi.org/10.1152/physrev.00005.2022>
- Piñate, S., Diaz, L., & Contreras, F. (2020). **Educación terapéutica en pacientes con diabetes y trastornos emocionales.** *Revista Digital de Postgrado*, 9(1). <https://doi.org/10.37910/RDP.2020.9.1.e202>
- Poblete-Aro, C., Russell-Guzmán, J., Parra, P., Soto-Muñoz, M., Villegas-González, B., Cofré-Bolados, C., & Herrera-Valenzuela, T. (2018). **Efecto del ejercicio físico sobre marcadores de estrés oxidativo en pacientes con diabetes mellitus tipo 2.** *Revista Médica de Chile*, 146(3), 362-372. <http://dx.doi.org/10.4067/s0034-98872018000300362>
- Poderoso, J.J., Helfenberger, K., & Poderoso, C. (2019). **The effect of nitric oxide on mitochondrial respiration.** *Nitric Oxide*, 88, 61-72. <https://doi.org/10.1016/j.niox.2019.04.005>
- Pol, S. (2022). **Hepatitis vírica C.** *EMC-Tratado de Medicina*, 26(4), 1-9. [https://doi.org/10.1016/S1636-5410\(22\)47172-8](https://doi.org/10.1016/S1636-5410(22)47172-8)
- Poza, J. J., Pujol, M., Ortega-Albás, J. J., & Romero, O. (2022). **Melatonina en los trastornos de sueño.** *Neurología*, 37(7), 575-585. <https://doi.org/10.1016/j.nrl.2018.08.002>

- Prado, G. (2019). [Relaciones entre el Estrés Oxidativo y la Salud](#). *Sociedades Rurales, Producción y Medio Ambiente*, 19(38), 34-34.
- Praharaj, S., Skalicky, M., Maitra, S., Bhadra, P., Shankar, T., Brestic, M., & Hossain, A. (2021). [Zinc biofortification in food crops could alleviate the zinc malnutrition in human health](#). *Molecules*, 26(12), 3509. <https://doi.org/10.3390/molecules26123509>
- Quisirumbay-Gaibor, J., & Vílchez Perales, C. (2019). [Selenio y glutatión peroxidasa en la nutrición porcina](#). *CES Medicina Veterinaria y Zootecnia*, 14(1), 57-69. <https://doi.org/10.21615/cesmvz.14.1.5>
- Radi, R. (2018). [Oxygen radicals, nitric oxide, and peroxynitrite: Redox pathways in molecular medicine](#). *Proceedings of the National Academy of Sciences*, 115(23), 5839-5848. <https://doi.org/10.1073/pnas.1804932115>
- Raikos, V. (2017). [Encapsulation of vitamin E in edible orange oil-in-water emulsion beverages: Influence of heating temperature on physicochemical stability during chilled storage](#). *Food Hydrocolloids*, 72, 155-162. <https://doi.org/10.1016/j.foodhyd.2017.05.027>
- Ramadori, P., Cubero, F. J., Liedtke, C., Trautwein, C., & Nevzorova, Y. A. (2017). [Alcohol and hepatocellular carcinoma: adding fuel to the flame](#). *Cancers*, 9(10), 130. DOI: 10.3390/cancers9100130
- Ramblado Valiente, M. (2022). [Selenio como antioxidante frente a la posible resistencia a la insulina generada por el atracón de alcohol durante la adolescencia](#). [Trabajo de fin de grado, Universidad de Sevilla].
- Ramírez García, M. C., Anlehu Tello, A., & Rodríguez León, A. (2019). [Factores que influyen en el comportamiento de adherencia del paciente con Diabetes Mellitus Tipo 2](#). *Horizonte sanitario*, 18(3), 383-392.
- Rao, X., Zhong, J., Brook, R. D., & Rajagopalan, S. (2018). [Effect of particulate matter air pollution on cardiovascular oxidative stress pathways](#). *Antioxidants & Redox Signaling*, 28(9), 797-818. <https://doi.org/10.1089/ars.2017.7394>
- Reboul, E. (2017). [Vitamin E bioavailability: mechanisms of intestinal absorption in the spotlight](#). *Antioxidants*, 6(4), 95. <https://doi.org/10.3390/antiox6040095>
- Reiter, R. J., Mayo, J. C., Tan, D. X., Sainz, R. M., Alatorre-Jimenez, M., & Qin, L. (2016). [Melatonin as an antioxidant: under promises but over delivers](#). *Journal of Pineal Research*, 61(3), 253-278. <https://doi.org/10.1111/jpi.12360>
- Rekatsina, M., Paladini, A., Piroli, A., Zis, P., Pergolizzi, J. V., & Varrassi, G. (2020). [Pathophysiology and therapeutic perspectives of oxidative stress and neurodegenerative diseases: a narrative review](#). *Advances in Therapy*, 37(1), 113-139. <https://doi.org/10.1007/s12325-019-01148-5>
- Restrepo Caro, C., Coronell, M. D. C., Arrollo, J., Martínez, G., Sánchez Majana, L., & Sarmiento-Rubiano, L. A. (2016). [La deficiencia de zinc: un problema global que afecta la salud y el desarrollo cognitivo](#). *Archivos Latinoamericanos de Nutrición*, 66(3), 165-175. <https://doi.org/10.37527/2016.66.3.002>
- Revilla Flores, E. M. (2021). [Especies reactivas de oxígeno, importancia e implicación patológica](#). *Revista Científica Ciencia Médica*, 24(2), 125-132. <https://doi.org/10.51581/rccm.v24i2.401>
- Reyes Sanamé, F. A., Pérez Álvarez, M. L., Alfonso Figueredo, E., Núñez Molina, B., & Jiménez Rodríguez, K. (2018). [Fibrilación auricular. Panorámica sobre un tema actualizado](#). *Correo Científico Médico*, 22(4), 695-718.

- Reynoso-Noverón, N., & Torres-Domínguez, J. A. (2017). [Epidemiología del cáncer en México: carga global y proyecciones 2000-2020](#). *Revista Latinoamericana de Medicina Conductual/Latin American Journal of Behavioral Medicine*, 8(1), 9-15. Recuperado a partir de <https://www.revistas.unam.mx/index.php/rlmc/article/view/65111>
- Ribeiro, D., Freitas, M., Silva, A. M., Carvalho, F., & Fernandes, E. (2018). [Antioxidant and pro-oxidant activities of carotenoids and their oxidation products](#). *Food and Chemical Toxicology*, 120, 681-699. <https://doi.org/10.1016/j.fct.2018.07.060>
- Rivas, S., & Armisen, R. (2022). [El cáncer de pulmón de células no pequeñas en la era de la medicina de precisión](#). *Revista Médica Clínica Las Condes*, 33(1), 25-35. <https://doi.org/10.1016/j.rmcl.2022.01.001>
- Rodríguez Núñez, A., Calá Fernández, J., Cruz Vadell, H., & Montoya Deler, M. Á. (2021). [Marcadores de estrés oxidativo en pacientes con síndrome metabólico](#). *Revista Finlay*, 11(1), 23-30. http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S2221-24342021000100023&lng=es&nrm=iso
- Rojas-Díaz, S., Jiménez Martínez, C., Saenz Ramírez, V., & Arias Amador, K. (2021). [Hepatitis autoinmune: manifestaciones, diagnóstico y tratamiento](#). *Revista Ciencia y Salud Integrando Conocimientos*, 5(3), 6-17. <https://doi.org/10.34192/cienciaysalud.v5i3.288>
- Rojas Peláez, Y., Trujillo Pérez, Y. L., Reyes Escobar, A. D., & Bembibre Mozo, D. (2021). [Algunas consideraciones sobre las hepatitis virales crónicas como problema de salud](#). *Medisan*, 25(4), 965-981. Epub 27 de agosto de 2021. Recuperado en 08 de noviembre de 2024, de http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1029-30192021000400965&lng=es&tlng=es.
- Romano, M., Nissen, M. D., Del Huerto, N., & Parquet, C. (2007). [Enfermedad de Alzheimer](#). *Revista de posgrado de la vía cátedra de medicina*, 75, 9-12.
- Romero, A. P., & Garrido, S. G. (2018). [La importancia de los síntomas psicológicos y conductuales \(SPCD\) en la enfermedad de Alzheimer](#). *Neurología*, 33(6), 378-384. <https://doi.org/10.1016/j.nrl.2016.02.024>
- Rosa, G. P., Seca, A. M., Barreto, M. D. C., Silva, A. M., & Pinto, D. C. (2019). [Chalcones and flavanones bearing hydroxyl and/or methoxyl groups: Synthesis and biological assessments](#). *Applied Sciences*, 9(14), 2846. <https://doi.org/10.3390/app9142846>
- Rosas-Romero, R., & Covarrubias-Gómez, A. (2020). [El papel del zinc en la salud humana](#). *Revista Médica del Instituto Mexicano del Seguro Social*, 58(4), 477-485. <https://www.redalyc.org/articulo.oa?id=457768632015>
- Rubbo, H. (2013). [Nitro-fatty acids: novel anti-inflammatory lipid mediators](#). *Brazilian Journal of Medical and Biological Research*, 46(9), 728-734. <https://doi.org/10.1590/1414-431X20133202>
- Rubio del Peral, J. A., & Gracia Josa, M. (2018). [Ejercicios de resistencia en el tratamiento y prevención de la sarcopenia en ancianos. Revisión sistemática](#). *Gerokomos*, 29(3), 133-137.
- Rudzińska, M., Parodi, A., Balakireva, A. V., Chepikova, O. E., Venanzi, F. M., & Zamyatnin Jr, A. A. (2020). [Cellular aging characteristics and their association with age-related disorders](#). *Antioxidants*, 9(2), 94. <https://doi.org/10.3390/antiox9020094>
- Rumpf, J., Burger, R., & Schulze, M. (2023). [Statistical evaluation of DPPH, ABTS, FRAP, and Folin-Ciocalteu assays to assess the antioxidant capacity of lignins](#). *International Journal of Biological Macromolecules*, 233, 123470. <https://doi.org/10.1016/j.ijbiomac.2023.123470>
- Rungratanawanich, W., Memo, M., & Uberti, D. (2018). Redox homeostasis and natural dietary compounds: Focusing on antioxidants of rice (*Oryza sativa* L.). *Nutrients*, 10(11), 1605.

- Sacristán, H., García, J. G., & Joaquín, J (2019). [La melatonina y su papel en la enfermedad de Alzheimer](https://zaguan.unizar.es/record/111776). [Tesis de grado en medicina, Universidad de Zaragoza] <https://zaguan.unizar.es/record/111776>
- Sadasivam, N., Kim, Y. J., Radhakrishnan, K., & Kim, D. K. (2022). [Oxidative stress, genomic integrity, and liver diseases](https://doi.org/10.3390/molecules27103159). *Molecules*, 27(10), 3159. <https://doi.org/10.3390/molecules27103159>
- Sahay, S., & Gupta, M. (2017). [An update on nitric oxide and its benign role in plant responses under metal stress](https://doi.org/10.1016/j.niox.2017.04.011). *Nitric Oxide*, 67, 39-52. <https://doi.org/10.1016/j.niox.2017.04.011>
- Saini, A., Kumar, M., Bhatt, S., Saini, V., & Malik, A. (2020). [Cancer causes and treatments](https://dx.doi.org/10.13040/IJPSR.0975-8232.11(7).3121-34). *International Journal of Pharmacology of Science Reserarch*, 11,3121-3134. [https://dx.doi.org/10.13040/IJPSR.0975-8232.11\(7\).3121-34](https://dx.doi.org/10.13040/IJPSR.0975-8232.11(7).3121-34)
- Sánchez-Valle, V., & Méndez-Sánchez, N. (2018). [Estrés oxidativo, antioxidantes y enfermedad](#). *Médica Sur*, 20(3), 161-168.
- Sandamalika, W. G., Kwon, H., Lim, C., Yang, H., & Lee, J. (2021). [The possible role of catalase in innate immunity and diminution of cellular oxidative stress: Insights into its molecular characteristics, antioxidant activity, DNA protection, and transcriptional regulation in response to immune stimuli in yellowtail clownfish \(*Amphiprion clarkii*\)](https://doi.org/10.1016/j.fsi.2021.03.022). *Fish & Shellfish Immunology*, 113, 106-117. <https://doi.org/10.1016/j.fsi.2021.03.022>
- Sandmann, G. (2019). [Antioxidant protection from UV-and light-stress related to carotenoid structures](https://doi.org/10.3390/antiox8070219). *Antioxidants*, 8(7), 219. <https://doi.org/10.3390/antiox8070219>
- Santos, K. L., Bragança, V. A., Pacheco, L. V., Ota, S. S., Aguiar, C. P., & Borges, R. S. (2022). [Essential features for antioxidant capacity of ascorbic acid \(vitamin C\)](https://doi.org/10.1007/s00894-021-04994-9). *Journal of Molecular Modeling*, 28, 1-8. <https://doi.org/10.1007/s00894-021-04994-9>
- Sarmiento Salinas, F. L. (2020). [Estudio de la secreción de citocinas mediada por Especies Reactivas de Oxígeno \(ERO\) en cáncer de mama](https://hdl.handle.net/20.500.12371/10605). [Tesis doctoral, Benemérita Universidad Autónoma de Puebla]. Repositorio Institucional de Acceso Abierto RIAA-BUAP. <https://hdl.handle.net/20.500.12371/10605>
- Sarre-Álvarez, D., Cabrera-Jardines, R., Rodríguez-Weber, F., & Díaz-Greene, E. (2018). [Enfermedad cardiovascular aterosclerótica](https://doi.org/10.24245/mim.v34i6.2136). Revisión de las escalas de riesgo y edad cardiovascular. *Medicina Interna de México*, 34(6), 910-923. <https://doi.org/10.24245/mim.v34i6.2136>
- Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C. E., & van der Flier, W. M. (2021). [Alzheimer's disease](https://doi.org/10.1016/S0140-6736(20)32205-4). *The Lancet*, 397(10284), 1577-1590. [https://doi.org/10.1016/S0140-6736\(20\)32205-4](https://doi.org/10.1016/S0140-6736(20)32205-4)
- Schiavon, M., Nardi, S., Dalla Vecchia, F., & Ertani, A. (2020). [Selenium biofortification in the 21 st century: status and challenges for healthy human nutrition](https://doi.org/10.1007/s11104-020-04635-9). *Plant and soil*, 453, 245-270. <https://doi.org/10.1007/s11104-020-04635-9>
- Sekhoacha, M., Riet, K., Motloun, P., Gumenku, L., Adegoke, A., & Mashele, S. (2022). [Prostate cancer review: genetics, diagnosis, treatment options, and alternative approaches](https://doi.org/10.3390/molecules27175730). *Molecules*, 27(17), 5730. <https://doi.org/10.3390/molecules27175730>
- Senoner, T., & Dichtl, W. (2019). [Oxidative stress in cardiovascular diseases: still a therapeutic target?](https://doi.org/10.3390/nu11092090). *Nutrients*, 11(9), 2090. <https://doi.org/10.3390/nu11092090>
- Shahid, M., Niazi, N. K., Khalid, S., Murtaza, B., Bibi, I., & Rashid, M. I. (2018). [A critical review of selenium biogeochemical behavior in soil-plant system with an inference to human health](https://doi.org/10.1016/j.envpol.2017.12.019). *Environmental Pollution*, 234, 915-934. <https://doi.org/10.1016/j.envpol.2017.12.019>

- Shahidi, F., Pinaffi-Langley, A. C. C., Fuentes, J., Speisky, H., & de Camargo, A. C. (2021). **Vitamin E as an essential micronutrient for human health: Common, novel, and unexplored dietary sources.** *Free Radical Biology and Medicine*, 176, 312-321. <https://doi.org/10.1016/j.freeradbiomed.2021.09.025>
- Shaikh, J. R., & Patil, M. (2020). **Qualitative tests for preliminary phytochemical screening: An overview.** *International Journal of Chemical Studies*, 8(2), 603-608. DOI: <https://doi.org/10.22271/chemi.2020.v8.i2i.8834>
- Sharifi-Rad, M., Anil Kumar, N. V., Zucca, P., Varoni, E. M., Dini, L., Panzarini, E., & Sharifi-Rad, J. (2020). Lifestyle, oxidative stress, and antioxidants: Back and forth in the pathophysiology of chronic diseases. *Frontiers in Physiology*, 11, 694. <https://doi.org/10.3389/fphys.2020.00694>
- Sharma, G. N., Dave, R., Sanadya, J., Sharma, P., & Sharma, K. (2010). **Various types and management of breast cancer: an overview.** *Journal of Advanced Pharmaceutical Technology & Research*, 1(2), 109-126. <https://pubmed.ncbi.nlm.nih.gov/22247839/>
- Sharma, P., & Arora, A. (2020). **Clinical presentation of alcoholic liver disease and non-alcoholic fatty liver disease: spectrum and diagnosis.** *Translational Gastroenterology and Hepatology*, 5(19). DOI: [10.21037/tgh.2019.10.02](https://doi.org/10.21037/tgh.2019.10.02)
- Sharma, A., Weber, D., Raupbach, J., Dakal, T. C., Fließbach, K., Ramirez, A., & Wüllner, U. (2020). **Advanced glycation end products and protein carbonyl levels in plasma reveal sex-specific differences in Parkinson's and Alzheimer's disease.** *Redox biology*, 34, 101546. <https://doi.org/10.1016/j.redox.2020.101546>
- Sharma, A., & Nagalli, S. (2023). **Chronic liver disease.** In *StatPearls* [Internet]. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK554597/>
- Shein, M., & Jeschke, G. (2019). **Comparison of free radical levels in the aerosol from conventional cigarettes, electronic cigarettes, and heat-not-burn tobacco products.** *Chemical Research in Toxicology*, 32(6), 1289-1298. <https://doi.org/10.1021/acs.chemrestox.9b00085>
- Shen, Y., Wu, Q., Shi, J., & Zhou, S. (2020). **Regulation of SIRT3 on mitochondrial functions and oxidative stress in Parkinson's disease.** *Biomedicine & Pharmacotherapy*, 132, 110928. <https://doi.org/10.1016/j.biopha.2020.110928>
- Shin, S. K., Cho, H. W., Song, S. E., & Song, D. K. (2018). **Catalase and nonalcoholic fatty liver disease.** *Pflügers Archiv-European Journal of Physiology*, 470, 1721-1737. <https://doi.org/10.1007/s00424-018-2195-z>
- Sienes Bailo, P., Llorente Martín, E., Calmarza, P., Montolio Brevia, S., Bravo Gómez, A., Pozo Giráldez, A., & Fort Gallifa, I. (2022). **The role of oxidative stress in neurodegenerative diseases and potential antioxidant therapies.** *Advances in Laboratory Medicine/Avances en Medicina de Laboratorio*, 3(4), 342-350. <https://doi.org/10.1515/almed-2022-0111>
- Sies, H., Berndt, C., & Jones, D.P. (2017). **Oxidative Stress.** *Annual Review of Biochemistry*, 86, 715-748. DOI: [10.1146/annurev-biochem-061516-045037](https://doi.org/10.1146/annurev-biochem-061516-045037)
- Silva, M. V. F., Loures, C. D. M. G., Alves, L. C. V., de Souza, L. C., Borges, K. B. G., & Carvalho, M. D. G. (2019). **Alzheimer's disease: risk factors and potentially protective measures.** *Journal of Biomedical Science*, 26, 1-11. <https://doi.org/10.1186/s12929-019-0524-y>
- Simioni, C., Zauli, G., Martelli, A. M., Vitale, M., Sacchetti, G., Gonelli, A., & Neri, L. M. (2018). **Oxidative stress: role of physical exercise and antioxidant nutraceuticals in adulthood and aging.** *Oncotarget*, 9(24), 17181. DOI: [10.18632/oncotarget.24729](https://doi.org/10.18632/oncotarget.24729)
- Sinbad, O. O., Folorunsho, A. A., Olabisi, O. L., Ayoola, O. A., & Temitope, E. J. (2019). **Vitamins as antioxidants.** *Journal of Food Science and Nutrition Research*, 2(3), 214-235. DOI: [10.26502/jfsnr.2642-11000021](https://doi.org/10.26502/jfsnr.2642-11000021)

- Singh, A., Kukreti, R., Saso, L., & Kukreti, S. (2019). [Oxidative stress: a key modulator in neurodegenerative diseases](#). *Molecules*, 24(8), 1583. <https://doi.org/10.3390/molecules24081583>
- Singh, M. C., Kelso, C., Price, W. E., & Probst, Y. (2020). [Validated liquid chromatography separation methods for identification and quantification of anthocyanins in fruit and vegetables: A systematic review](#). *Food Research International*, 138, 109754. DOI: 10.1016/j.foodres.2020.109754
- Smeriglio, A., Calderaro, A., Denaro, M., Laganà, G., & Bellocco, E. (2019). [Effects of isolated isoflavones intake on health](#). *Current Medicinal Chemistry*, 26(27), 5094-5107. <https://doi.org/10.2174/0929867324666171006143047>
- Smith, E. F., Shaw, P. J., & De Vos, K. J. (2019). [The role of mitochondria in amyotrophic lateral sclerosis](#). *Neuroscience letters*, 710, 132933. <https://doi.org/10.1016/j.neulet.2017.06.052>
- Sosa, V., Aicardo, A., & Valez, V. (2022). [Estrés oxidativo en saliva generado por el humo de tabaco: impacto en la periodontitis y perspectivas hacia el uso de farmacología redox](#). *Odontostomatología*, 24(39). <https://doi.org/10.22592/ode2022n39e307>
- Soledad, P. (2017). [Efecto de flavonoides frente al estrés oxidativo inducido por antibióticos](#). [Tesis de doctorado, Universidad Nacional de Córdoba]. Repositorio digital UNC. <https://rdu.unc.edu.ar/handle/11086/15312>
- Spaas, J., Van Veggel, L., Schepers, M., Tiane, A., Van Horsen, J., Wilson III, D. M. & Vanmierlo, T. (2021). [Oxidative stress and impaired oligodendrocyte precursor cell differentiation in neurological disorders](#). *Cellular and Molecular Life Sciences*, 78(10), 4615-4637. <https://doi.org/10.1007/s00018-021-03802-0>
- Srivastava, S., Ahmad, R., & Khare, S. K. (2021). [Alzheimer's disease and its treatment by different approaches: A review](#). *European Journal of Medicinal Chemistry*, 216, 113320. <https://doi.org/10.1016/j.ejmech.2021.113320>
- Stagos, D. (2019). [Antioxidant activity of polyphenolic plant extracts](#). *Antioxidants*, 9(1), 19. <https://doi.org/10.3390/antiox9010019>
- Steven, S., Frenis, K., Oelze, M., Kalinovic, S., Kuntic, M., Bayo Jimenez, M. T., ... & Daiber, A. (2019). [Vascular inflammation and oxidative stress: major triggers for cardiovascular disease](#). *Oxidative Medicine and Cellular Longevity*, 2019(1), 7092151. <https://doi.org/10.1155/2019/7092151>
- Sticova, E., Jirsa, M., & Pawłowska, J. (2018). [New insights in genetic cholestasis: from molecular mechanisms to clinical implications](#). *Canadian Journal of Gastroenterology and Hepatology*, 2018(1), 1-12. <https://doi.org/10.1155/2018/2313675>
- Storino, M. A., Contreras, M. A., Rojano, J., Serrano, R., & Nouel, A. (2014). [Complicaciones de la diabetes y su asociación con el estrés oxidativo: un viaje hacia el daño endotelial](#). *Revista colombiana de cardiología*, 21(6), 392-398. <https://doi.org/10.1016/j.rccar.2014.09.004>
- Su, L. J., Zhang, J. H., Gomez, H., Murugan, R., Hong, X., Xu, D., ... & Peng, Z. Y. (2019). [Reactive oxygen species-induced lipid peroxidation in apoptosis, autophagy, and ferroptosis](#). *Oxidative medicine and cellular longevity*, 2019(1), 5080843. <https://doi.org/10.1155/2019/5080843>
- Sunkara, A., & Raizner, A. (2019). [Supplemental vitamins and minerals for cardiovascular disease prevention and treatment](#). *Methodist Deakey Cardiovascular Journal*, 15(3), 179. DOI: 10.14797/mdcj-15-3-179
- Sutrisno, S., Miryani, I., Dwijayasa, P. M., Suprobo, N. R., & Wiyasa, I. W. A. (2022). [Genistein administration increases the level of superoxide dismutase and glutathione peroxidase in the endometriosis mice model: An experimental study](#). *International Journal of Reproductive BioMedicine*, 20(10), 873. DOI: 10.18502/ijrm.v20i10.12271

- Tardy, A. L., Pouteau, E., Marquez, D., Yilmaz, C., & Scholey, A. (2020). [Vitamins and minerals for energy, fatigue and cognition: A narrative review of the biochemical and clinical evidence](#). *Nutrients*, 12(1), 228. <https://doi.org/10.3390/nu12010228>
- Tarocco, A., Caroccia, N., Morciano, G., Wieckowski, M. R., Ancora, G., Garani, G., & Pinton, P. (2019). [Melatonin as a master regulator of cell death and inflammation: molecular mechanisms and clinical implications for newborn care](#). *Cell Death & Disease*, 10(4), 1-12. <https://doi.org/10.1038/s41419-019-1556-7>
- Tehrani, H. S., & Moosavi-Movahedi, A. A. (2018). [Catalase and its mysteries](#). *Progress in Biophysics and Molecular Biology*, 140, 5-12. <https://doi.org/10.1016/j.pbiomolbio.2018.03.001>
- Teleanu, D. M., Niculescu, A. G., Lungu, I. I., Radu, C. I., Vladâcenco, O., Roza, E., ... & Teleanu, R. I. (2022). [An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases](#). *International Journal of Molecular Sciences*, 23(11), 5938. <https://doi.org/10.3390/ijms23115938>
- Testai, L., & Calderone, V. (2017). [Nutraceutical value of citrus flavanones and their implication in cardiovascular disease](#). *Nutrients*, 9(5), 502. <https://doi.org/10.3390/nu9050502>
- Thirupathi, A., Pinho, R. A., Ugbole, U. C., He, Y., Meng, Y., & Gu, Y. (2021). [Effect of running exercise on oxidative stress biomarkers: a systematic review](#). *Frontiers in Physiology*, 11, 610112. <https://doi.org/10.3389/fphys.2020.610112>
- Tinkov, A. A., Ajsuvakova, O. P., Filippini, T., Zhou, J. C., Lei, X. G., Gatiatulina, E. R., ... & Skalny, A. V. (2020). [Selenium and selenoproteins in adipose tissue physiology and obesity](#). *Biomolecules* 10(4), 658. <https://doi.org/10.3390/biom10040658>
- Tirichen, H., Yaigoub, H., Xu, W., Wu, C., Li, R., & Li, Y. (2021). [Mitochondrial reactive oxygen species and their contribution in chronic kidney disease progression through oxidative stress](#). *Frontiers in Physiology*, 12, 398. <https://doi.org/10.3389/fphys.2021.627837>
- Tola, A. J., Jaballi, A., & Missihoun, T. D. (2021). [Protein carbonylation: Emerging roles in plant redox biology and future prospects](#). *Plants*, 10(7), 1451. <https://doi.org/10.3390/plants10071451>
- Tordjman, S., Chokron, S., Delorme, R., Charrier, A., Bellissant, E., Jaafari, N., & Fougerou, C. (2017). [Melatonin: pharmacology, functions and therapeutic benefits](#). *Current Neuropharmacology*, 15(3), 434-443. <https://doi.org/10.2174/1570159X14666161228122115>
- Torres Martínez, J., Flores Villavicencio, L., Barbosa Sabanero, G., Cruz Jiménez, G. & Sabanero López, M. (2017). [Micronutrientes la Lucha por la Salud: Las Selenoproteínas](#). *Naturaleza y Tecnología*, 1(1)
- Townsend, N., Kazakiewicz, D., Lucy Wright, F., Timmis, A., Huculeci, R., Torbica, A., ... & Vardas, P. (2022). [Epidemiology of cardiovascular disease in Europe](#). *Nature Reviews Cardiology*, 19(2), 133-143. DOI: 10.1038/s41569-021-00607-3
- Travica, N., Ried, K., Sali, A., Scholey, A., Hudson, I., & Pipingas, A. (2017). [Vitamin C status and cognitive function: a systematic review](#). *Nutrients*, 9(9), 960. <https://doi.org/10.3390/nu9090960>
- Trist, B. G., Hilton, J. B., Hare, D. J., Crouch, P. J., & Double, K. L. (2021). [Superoxide dismutase 1 in health and disease: how a frontline antioxidant becomes neurotoxic](#). *Angewandte Chemie International Edition*, 60(17), 9215-9246. <https://doi.org/10.1002/anie.202000451>
- Troncoso-Pantoja, C., Martínez-Sanguinetti, M. A., Ulloa, N., & Celis-Morales, C. (2020). [La mayoría de las enfermedades cardiovasculares se atribuyen a factores de riesgo que podrían ser modificados con cambios de los estilos de vida](#). *Revista Médica de Chile*, 148(1), 126-128. <http://dx.doi.org/10.4067/S0034-98872020000100126>

- Tsermpini, E. E., Plemenitaš Ilješ, A., & Dolžan, V. (2022). Alcohol-induced oxidative stress and the role of antioxidants in alcohol use disorder: a systematic review. *Antioxidants*, 11(7), 1374. <https://doi.org/10.3390/antiox11071374>
- Tsukuda, S., & Watashi, K. (2020). Hepatitis B virus biology and life cycle. *Antiviral research*, 182, 104925. <https://doi.org/10.1016/j.antiviral.2020.104925>
- Tvrđá, E., & Benko, F. (2020). Free radicals: what they are and what they do. *Pathology*, 3–13. <https://doi.org/10.1016/B978-0-12-815972-9.00001-9>
- Ursini, F., & Maiorino, M. (2020). Lipid peroxidation and ferroptosis: The role of GSH and GPx4. *Free Radical Biology and Medicine*, 152, 175-185. <https://doi.org/10.1016/j.freeradbiomed.2020.02.027>
- Uyaguari-Matute, G. M., Mesa-Cano, I. C., Ramírez-Coronel, A. A., & Martínez-Suárez, P. C. (2021). Factores de riesgo para desarrollar diabetes mellitus II. *Vive Revista de Salud*, 4(10), 96-106. <https://doi.org/10.33996/revistavive.v4i10.79>
- Valencia-Avilés, E., Ignacio-Figueroa, I., Sosa-Martínez, E., Bartolomé-Camacho, M. C., Martínez-Flores, H. E., & García-Pérez, M. E. (2017). Polifenoles: propiedades antioxidantes y toxicológicas. *Revista de la Facultad de Ciencias Químicas*, (16), 15-29.
- Valencia Rico, C. L., Alzate Beltrán, M. C., Vargas Rosas, C. E., Álvarez Ramírez, L. C., Montes Rivera, A. K., Arbeláez Gallego, J. C., & Botero Galindo, M. (2022). Cáncer de pulmón, tendencias desde la perspectiva del cuidado. *Revista Uruguaya de Enfermería*, 17(2). <https://doi.org/10.33517/rue2022v17n2a6>
- Valenzuela, M. J., Münzenmayer, B., Osorio, T., Arancibia, M., & Madrid, E. (2018). Sintomatología depresiva y control metabólico en pacientes ambulatorios portadores de diabetes mellitus tipo 2. *Revista médica de Chile*, 146(12), 1415- 1421.
- Van Gorkom, G. N., Lookermans, E. L., Van Elssen, C. H., & Bos, G. M. (2019). The effect of vitamin C (ascorbic acid) in the treatment of patients with cancer: a systematic review. *Nutrients*, 11(5), 977. <https://doi.org/10.3390/nu11050977>
- Vasconcelos-de Dios, C. E., De La Cruz-López, A. A., & Acosta-Pérez, L. I. (2022). Estrés oxidativo y mecanismos moleculares/celulares en pacientes de 40-60 años con síndrome metabólico en Latinoamérica. *Journal of Basic Sciences*, 8(23), 57-71. <https://doi.org/10.19136/jobs>
- Vázquez, Y., Piña, J., Lozano, J., Mederos, I., & Savín, K. (2019). Relación de la peroxidación lipídica con parámetros glucémicos en pacientes diabéticos tipo 2. *Revista Mexicana de Patología Clínica y Medicina de Laboratorio*, 66(2), 61- 67. <http://medigraphic.com/pdfs/COMPLETOS/patol/2019/pt192.pdf>
- Veloza, L., Jiménez, C., Quiñones, D., Polanía, F., Pachón-Valero, L. C., & Rodríguez- Triviño, C. Y. (2019). Variabilidad de la frecuencia cardiaca como factor predictor de las enfermedades cardiovasculares. *Revista Colombiana de Cardiología*, 26(4), 205-210. <https://doi.org/10.1016/j.rccar.2019.01.006>
- Vera-Mesias, M. M., Parrales-Carvajal, J. M., & Rodríguez-Parrales, D. H. (2021). Hepatitis autoinmune, formas clínicas, diagnóstico y pronóstico. *Polo del Conocimiento: Revista científico-profesional*, 6(7), 61-77.
- Viada Pupo, E., Gómez Robles, L., & Campaña Marrero, I. R. (2017). Estrés oxidativo. *Correo científico médico*, 21(1), 171-186. http://scielo.sld.cu/scielo.php?script=sci_abstract&pid=S1560-43812017000100014
- Vignolo, P., Elgueta, K., López, G., Durruty, P., Gómez, P., & Sanzana, G. (2020). Enfermedades hepáticas y su relación con hiperglicemia. *Revista Chilena de Endocrinología y Diabetes*, 13(2), 64-71.

- Vildoso, P. S. V., Junior, J. D. S. P., Mattos, A. P. A. D., Rocha, G. D. S., Barroso, S. G., Huguenin, G. V. B., & Cardoso de Matos, A. (2021). [Análisis del perfil bioquímico y antropométrico, y de la ingesta de micronutrientes antioxidantes en pacientes con hipertensión arterial resistente.](#) *Nutrición Hospitalaria*, 37(6), 1209-1216. <https://dx.doi.org/10.20960/nh.02962>
- Villafuerte Reinante, J., Hernández Guerra, Y., Ayala Reina, Z. E., Naranjo Hernández, L., González Alonso, J. Á., & Brito Méndez, M. (2019). [Aspectos bioquímicos y factores de riesgo asociados con el cáncer cervicouterino.](#) *Revista Finlay*, 9(2), 138-146.
- Villagrán, M., Muñoz, M., Díaz, F., Troncoso, C., Celis-Morales, C., & Mardones, L. (2019). [Una mirada actual de la vitamina C en salud y enfermedad.](#) *Revista Chilena de Nutrición*, 46(6), 800-808. <http://dx.doi.org/10.4067/S0717-75182019000600800>
- Wang, L., & Weller, C. L. (2006). [Recent advances in extraction of nutraceuticals from plants.](#) *Trends in Food Science & Technology*, 17(6), 300-312. <https://doi.org/10.1016/j.tifs.2005.12.004>
- Wang, N., Tan, H. Y., Li, S., Xu, Y., Guo, W., & Feng, Y. (2017). [Supplementation of micronutrient selenium in metabolic diseases: its role as an antioxidant.](#) *Oxidative Medicine and Cellular Longevity*, 2017. <https://doi.org/10.1155/2017/7478523>
- Wang, Y., Branicky, R., Noë, A., & Hekimi, S. (2018). [Superoxide dismutases: Dual roles in controlling ROS damage and regulating ROS signaling.](#) *Journal of Cell Biology*, 217(6), 1915-1928. <https://doi.org/10.1083/jcb.201708007>
- Wang, Y., Lin, Y., He, S., Wu, S., & Yang, C. (2024). [Singlet oxygen: Properties, generation, detection, and environmental applications.](#) *Journal of Hazardous Materials*, 461, 132538. <https://doi.org/10.1016/j.jhazmat.2023.132538>
- Weaver, K., & Skouta, R. (2022). [The selenoprotein glutathione peroxidase 4: from molecular mechanisms to novel therapeutic opportunities.](#) *Biomedicines*, 10(4), 891. <https://doi.org/10.3390/biomedicines10040891>
- Wei, Z., Li, X., Li, X., Liu, Q., & Cheng, Y. (2018). [Oxidative stress in Parkinson's disease: a systematic review and meta-analysis.](#) *Frontiers in Molecular Neuroscience*, 11, 236. DOI: 10.3389/fnmol.2018.00236
- Wen, L., Zhao, Y., Jiang, Y., Yu, L., Zeng, X., Yang, J., ... & Yang, B. (2017). [Identification of a flavonoid C-glycoside as potent antioxidant.](#) *Free Radical Biology and Medicine*, 110, 92-101. <https://doi.org/10.1016/j.freeradbiomed.2017.05.027>
- World Health Organization. (2021). Guide to cancer early diagnosis 2017. Available at apps.who.int/iris/handle/10665/254500.
- Xiao, F., Xu, T., Lu, B., & Liu, R. (2020). [Guidelines for antioxidant assays for food components.](#) *Food Frontiers*, 1(1), 60-69. DOI:10.1002/fft2.10
- Xiong, Y. L., & Guo, A. (2020). [Animal and plant protein oxidation: Chemical and functional property significance.](#) *Foods*, 10(1), 40. DOI: 10.3390/foods10010040
- Xu, L., Li, Y., Dai, Y., & Peng, J. (2018). [Natural products for the treatment of type 2 diabetes mellitus: Pharmacology and mechanisms.](#) *Pharmacological Research*, 130, 451-465. <https://doi.org/10.1016/j.phrs.2018.01.015>
- Xu, X., Lai, Y., & Hua, Z. C. (2019). [Apoptosis and apoptotic body: disease message and therapeutic target potentials.](#) *Bioscience reports*, 39(1). <https://doi.org/10.1042/BSR20180992>

Yalcinkaya, T., Uzilday, B., Ozgur, R., Turkan, I., & Mano, J. I. (2019). Lipid peroxidation-derived reactive carbonyl species (RCS): Their interaction with ROS and cellular redox during environmental stresses. *Environmental and Experimental Botany*, 165, 139-149. <https://doi.org/10.1016/j.envexpbot.2019.06.004>

Yaman, S. O., & Ayhanci, A. (2021). Lipid peroxidation. *Accenting Lipid Peroxidation*, 1-11. DOI: 10.5772/intechopen.95802

Yang, R., Liu, Y., & Zhou, Z. (2017). Selenium and selenoproteins, from structure, function to food resource and nutrition. *Food Science and Technology Research*, 23(3), 363-373. <https://doi.org/10.3136/fstr.23.363>

Yang, C. S., Ho, C. T., Zhang, J., Wan, X., Zhang, K., & Lim, J. (2018). Antioxidants: Differing meanings in food science and health science. *Journal of Agricultural and Food Chemistry*, 66(12), 3063-3068. <https://doi.org/10.1021/acs.jafc.7b05830>

Yonekura-Sakakibara, K., Higashi, Y., & Nakabayashi, R. (2019). The origin and evolution of plant flavonoid metabolism. *Frontiers in Plant Science*, 10, 468057. <https://doi.org/10.3389/fpls.2019.00943>

Young, A. J., & Lowe, G.L. (2018). Carotenoids-antioxidant properties. *Antioxidants*, 7(2), 28. <https://doi.org/10.3390/antiox7020028>

Younus, H. (2018). Therapeutic potentials of superoxide dismutase. *International Journal of Health sciences*, 12(3), 88.

Zaragozá, C., Villaescusa, L., Monserrat, J., Zaragozá, F., & Álvarez-Mon, M. (2020). Potential therapeutic anti-inflammatory and immunomodulatory effects of dihydroflavones, flavones, and flavonols. *Molecules*, 25(4), 1017. <https://doi.org/10.3390/molecules25041017>

Zuo, Y., Chen, H., & Deng, Y. (2002). Simultaneous determination of catechins, caffeine and gallic acids in green, Oolong, black and pu-erh teas using HPLC with a photodiode array detector. *Talanta*, 57(2), 307–316. [https://doi.org/10.1016/s0039-9140\(02\)00030-9](https://doi.org/10.1016/s0039-9140(02)00030-9)

Zhang, X. X., Tian, Y., Wang, Z. T., Ma, Y. H., Tan, L., & Yu, J. T. (2021). The epidemiology of Alzheimer's disease modifiable risk factors and prevention. *The Journal of Prevention of Alzheimer's disease*, 8(8), 313-321. DOI: 10.14283/jpad.2021.15

Zhao, Y., Wang, H., Zhou, J., & Shao, Q. (2022). Glutathione peroxidase GPX1 and its dichotomous roles in cancer. *Cancers*, 14(10), 2560. <https://doi.org/10.3390/cancers14102560>

Zinellu, A., & Mangoni, A. A. (2021). A systematic review and meta-analysis of the effect of statins on glutathione peroxidase, superoxide dismutase, and catalase. *Antioxidants*, 10(11), 1841. <https://doi.org/10.3390/antiox10111841>

Supports

Abbas, M., Saeed, F., Anjum, F. M., Afzaal, M., Tufail, T., Bashir, M. S., ... & Suleria, H. A. R. (2017). Natural polyphenols: An overview. *International Journal of Food Properties*, 20(8), 1689-1699. <https://doi.org/10.1080/10942912.2016.1220393>

Aguilar-Paredes, O. A., Castillo-Guevara, C., Díaz-Godínez, R., Nieto-Camacho, A., Méndez-Iturbide, D., & Tlaxcala, I. (2018). Antioxidants and inhibition of free radicals: lipoperoxidation and carbonylation. *Antioxidantes e inhibición de radicales libres: lipoperoxidación y carbonilación. Mexican Journal of Biotechnology* 2018, 3(1), 60-72. DOI: 10.29267/mxjb.2018.3.1.60

Arancibia-Hernández, Y. L., Loyola-Mondragón, D. Y., Yaquelin, E., & Hernández- Cruz, J. P. C. (2022). Especies reactivas de oxígeno y antioxidantes: Aspectos básicos. *Tequío*, 5(15), 5–20. <https://doi.org/10.53331/teq.v5i15.4905>

- Authoritative Neurology Information. (2024, 7 noviembre). *MedLink Neurology*. <https://www.medlink.com/media/dlgs6>.
- Ayala-Mata, F., Barrera-Mendoza, C. C., Cortés-Rojo, C., Montoya-Pérez, R. D. C., García-Pérez, M. E., & Rodríguez-Orozco, A. R. (2019). *Antioxidantes en asma: polifenoles*. *Medicina Interna de México*, 35(2), 223-234. <https://doi.org/10.24245/mim.v35i2.2291>
- Barbosa, K., Bressan, J., Zulet, M., & Martínez, J. (2008). *Influencia de la dieta sobre marcadores plasmáticos de estrés oxidativo en humanos*. In *Anales del sistema sanitario de Navarra*, 31(3), 259-280. Gobierno de Navarra. Departamento de Salud.
- Belščak-Cvitanović, A., Durgo, K., Huđek, A., Bačun-Družina, V., & Komes, D. (2018). *Overview of polyphenols and their properties*. In *Polyphenols: Properties, recovery, and applications*, 3-44. <https://doi.org/10.1016/B978-0-12-813572-3.00001-4>
- Beltrán Ramírez, R., Espinoza Jr, J., Arellano, M. D. R. M., Larios Rosillo, V. M., Martínez Mendoza, J. D. J., & Zepeda Gómez, J. R. Z. (2018). *Tecnología para la prevención y cuidado de personas con diabetes*. *Avances: Investigación en Ingeniería*, 15(1), 194-203. <https://doi.org/10.18041/1794-4953/avances.1.4736>
- Blesa, J., Trigo-Damas, I., Quiroga-Varela, A., & Jackson-Lewis, V. R. (2015). *Oxidative stress and Parkinson's disease*. *Frontiers in Neuroanatomy*, 9, 91. <https://doi.org/10.3389/fnana.2015.00091>
- Calderón Salinas, J. V., Muñoz Reyes, E. G., & Quintanar Escorza, M. A. (2013). *Estrés oxidativo y diabetes mellitus*. *REB. Revista de educación bioquímica*, 32(2), 53-66.
- Carvajal Martínez, F., Bioti Torres, Y., & Carvajal Aballe, M. (2020). *Diabetes mellitus tipo 2: una problemática actual de salud en la población pediátrica*. *Ciencia y Salud*, 4(1), 17-26. <https://doi.org/10.22206/cysa.2020.v4i1.pp17-26>
- Castillo-Velarde, E. R. (2019). *Vitamina C en la salud y en la enfermedad*. *Revista de la Facultad de Medicina Humana*, 19(4), 95-100. <http://dx.doi.org/10.25176/RFMH.v19i4.235>
- Chagas, M. D. S. S., Behrens, M. D., Moragas-Tellis, C. J., Penedo, G. X., Silva, A. R., & Gonçalves-de-Albuquerque, C. F. (2022). *Flavonols and flavones as potential anti-inflammatory, antioxidant, and antibacterial compounds*. *Oxidative medicine and cellular longevity*, 2022. <https://doi.org/10.1155/2022/9966750>
- Clemente-Suárez, V. J., Bustamante-Sanchez, Á., Mielgo-Ayuso, J., Martínez-Guardado, I., Martín-Rodríguez, A., & Tornero-Aguilera, J. F. (2023). *Antioxidants and Sports Performance*. *Nutrients*, 15(10), 2371. <https://doi.org/10.3390/nu15102371>
- Cunha-Oliveira, T., Montezinho, L., Mendes, C., Firuzi, O., Saso, L., Oliveira, P. J., & Silva, F. S. (2020). *Oxidative stress in amyotrophic lateral sclerosis: pathophysiology and opportunities for pharmacological intervention*. *Oxidative Medicine and Cellular Longevity*, 2020(1), 5021694. <https://doi.org/10.1155/2020/5021694>
- De Luis, D. A., & Aller, R. (2008). *Papel de los flavonoides del té en la protección cardiovascular*. In *Anales de Medicina Interna*, 25(3), 105-107.
- Dos Santos, C. N. D., Menezes, R., Carregosa, D., Valentova, K., Foito, A., McDougall, G., & Stewart, D. (2020). *Flavonols and Flavones*. En *Dietary Polyphenols: Their Metabolism and Health Effects* (pp. 163-198). John Wiley & Sons, Ltd. <https://doi.org/10.1002/9781119563754.ch5>
- Flohé, L., Toppo, S., & Orian, L. (2022). *The glutathione peroxidase family: Discoveries and mechanism*. *Free Radical Biology and Medicine*, 187, 113-122. <https://doi.org/10.1016/j.freeradbiomed.2022.05.003>
- García-Allen, J. (2025, 14 septiembre). *Tabla de aminoácidos: funciones, tipos y características*. *Psicología y Mente*. <https://psicologiyamente.com/neurociencias/tabla-de-aminoacidos>

- Grigoras, A. G. (2017). *Catalase immobilization-A review*. *Biochemical Engineering Journal*, 117, 1-20. <https://doi.org/10.1016/j.bej.2016.10.021>
- Guija-Guerra, H., & Guija-Poma, E. (2023). *Radicales libres y sistema antioxidante*. *Horizonte Médico (Lima)*, 23(2). <http://dx.doi.org/10.24265/horizmed.2023.v23n2.12>
- Kay, C. D., Pereira-Caro, G., Ludwig, I. A., Clifford, M. N., & Crozier, A. (2017). *Anthocyanins and flavanones are more bioavailable than previously perceived: A review of recent evidence*. *Annual Review of Food Science and Technology*, 8, 155-180. <https://doi.org/10.1146/annurev-food-030216-025636>
- Lizárraga-Velázquez, C. E., Hernández, C., González-Aguilar, G. A., & Basilio-Heredia, J. (2018). *Propiedades antioxidantes e inmunoestimulantes de polifenoles en peces carnívoros de cultivo*. *CienciaUAT*, 12(2), 127-136.
- López, J. A. S., González, H. M., & Léger, G. C. (2019). *Alzheimer's disease*. *Handbook of Clinical Neurology*, 167, 231-255. <https://doi.org/10.1016/B978-0-12-804766-8.00013-3>
- Luo, Y., Jian, Y., Liu, Y., Jiang, S., Muhammad, D., & Wang, W. (2022). *Flavanols from nature: A phytochemistry and biological activity review*. *Molecules*, 27(3), 719. <https://doi.org/10.3390/molecules27030719>
- Matus, G., Pablo, J., Guerra, G., Buendía, K., Matus, M., González, J., & Romero, L. (2021). *Un vistazo a la morfología y dinámica de la mitocondria ya los sitios de producción de las especies reactivas de oxígeno*. *Revista de Educación Bioquímica*, 40 (3), 111-127. https://www.researchgate.net/publication/355094750_Un_vistazo_a_la_morfologia_y_dinamica_de_la_mitocondria_y_a_los_sitios_de_produccion_de_las_especies_reactivas_de_oxigeno
- Muñoz Verbel, D., Cueto Almeida, E., Morales Meléndez, V., García Lombana, A., Aparicio Marenco, D., & Márquez Lázaro, J. (2022). *Proteínas oxidadas de origen animal y su impacto sobre la salud intestinal*. *Medicina UPB*, 42(1), 49- 56. <https://doi.org/10.18566/medupb.v42n1.a07>
- Mordi, R. C., Ademosun, O. T., Ajanaku, C. O., Olanrewaju, I. O., & Walton, J. C. (2020). *Free radical mediated oxidative degradation of carotenes and xanthophylls*. *Molecules*, 25(5), 1038. <https://doi.org/10.3390/molecules25051038>
- Nandi, A., Yan, L. J., Jana, C. K., & Das, N. (2019). *Role of catalase in oxidative stress-and age-associated degenerative diseases*. *Oxidative Medicine and Cellular Longevity*, 2019. <https://doi.org/10.1155/2019/9613090>
- Ortiz Escarza, J. M., & Medina López, M. E. (2020). *Estrés oxidativo ¿un asesino silencioso?*. *Educación química*, 31(1), 1-11. <https://doi.org/10.22201/fq.18708404e.2020.1.69709>
- Proteintech. What is the difference between necrosis and apoptosis? (2023, 12 julio). Proteintech. <https://www.ptglab.com/news/blog/what-is-the-difference-between-necrosis-and-apoptosis>
- Powers, S. K., Deminice, R., Ozdemir, M., Yoshihara, T., Bomkamp, M. P., & Hyatt, H. (2020). *Exercise-induced oxidative stress: Friend or foe?*. *Journal of sport and health science*, 9(5), 415-425. <https://doi.org/10.1016/j.jshs.2020.04.001>
- Puig, R. P. (2023). Superóxido dismutasa. Lifereder. <https://www.lifereder.com/superoxido-dismutasa/#estructura-de-la-superoxido-dismutasa>.
- Rodríguez-Amaya, D. B. (2019). *Update on natural food pigments-A mini-review on carotenoids, anthocyanins, and betalains*. *Food Research International*, 124, 200-205. <https://doi.org/10.1016/j.foodres.2018.05.028>
- Rodríguez-García, A., García-Vicente, R., Morales, M. L., Ortiz-Ruiz, A., Martínez- López, J., & Linares, M. (2020). *Protein carbonylation and lipid peroxidation in hematological malignancies*. *Antioxidants*, 9(12), 1212. <https://doi.org/10.3390/antiox9121212>

Ronsisvalle, S., Panarello, F., Longhitano, G., Siciliano, E. A., Montenegro, L., & Panico, A. (2020). Natural flavones and flavonols: Relationships among antioxidant activity, glycation, and metalloproteinase inhibition. *Cosmetics*, 7(3), 71. <https://doi.org/10.3390/cosmetics7030071>

Rosa, A. C., Corsi, D., Cavi, N., Bruni, N., & Dosio, F. (2021). Superoxide dismutase administration: A review of proposed human uses. *Molecules*, 26(7), 1844. <https://doi.org/10.3390/molecules26071844>

Rudrapal, M., Khairnar, S. J., Khan, J., Dukhyil, A. B., Ansari, M. A., Alomary, M. N., ... & Devi, R. (2022). Dietary polyphenols and their role in oxidative stress-induced human diseases: Insights into protective effects, antioxidant potentials and mechanisms of action. *Frontiers in Pharmacology*, 13, 806470. <https://doi.org/10.3389/fphar.2022.806470>

Swallah, M. S., Sun, H., Affoh, R., Fu, H., & Yu, H. (2020). Antioxidant potential overviews of secondary metabolites (polyphenols) in fruits. *International Journal of Food Science*, 2020. <https://doi.org/10.1155/2020/9081686>

Zheng, M., Liu, Y., Zhang, G., Yang, Z., Xu, W., & Chen, Q. (2023). The applications and mechanisms of superoxide dismutase in medicine, food, and cosmetics. *Antioxidants*, 12(9), 1675. <https://doi.org/10.3390/antiox12091675>

Discussions

Cioffi, F., Adam, R. H. I., & Broersen, K. (2019). Molecular mechanisms and genetics of oxidative stress in Alzheimer's disease. *Journal of Alzheimer's Disease*, 72(4), 981-1017. DOI: 10.3233/JAD-190863

Conde de la Rosa, L., Goicoechea, L., Torres, S., Garcia-Ruiz, C., & Fernandez- Checa, J. C. (2022). Role of oxidative stress in liver disorders. *Livers*, 2(4), 283- 314. <https://doi.org/10.3390/livers2040023>

Eslam, M., Newsome, P. N., Sarin, S. K., Anstee, Q. M., Targher, G., Romero-Gomez, M., ... & George, J. (2020). A new definition for metabolic dysfunction- associated fatty liver disease: An international expert consensus statement. *Journal of hepatology*, 73(1), 202-209. <https://doi.org/10.1016/j.jhep.2020.03.039>.

Granado Serrano, A. B. (2010). Estudio de los mecanismos de acción molecular de polifenoles de la dieta en cultivos celulares y animales de experimentación. [Tesis doctoral, Universidad Complutense de Madrid. Repositorio Docta Complutense. <https://docta.ucm.es/entities/publication/1d46f31f-3794-4dac-b42b-437e87f40fb2>

Hancock, J. T. (2021). Oxygen is instrumental for biological signaling: An overview. *Oxygen*, 1(1), 3-15. <https://doi.org/10.3390/oxygen1010002>

Incalza, M. A., D'Oria, R., Natalicchio, A., Perrini, S., Laviola, L., & Giorgino, F. (2018). Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. *Vascular pharmacology*, 100, 1-19. <https://doi.org/10.1016/j.vph.2017.05.005>

Misrani, A., Tabassum, S., & Yang, L. (2021). Mitochondrial dysfunction and oxidative stress in Alzheimer's disease. *Frontiers Aging Neuroscience*, (13)57. <https://doi.org/10.3389/fnagi.2021.617588>

Zvěřová, M. (2019). Clinical aspects of Alzheimer's disease. *Clinical Biochemistry*, 72, 3-6. <https://doi.org/10.1016/j.clinbiochem.2019.04.015>




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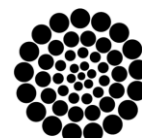
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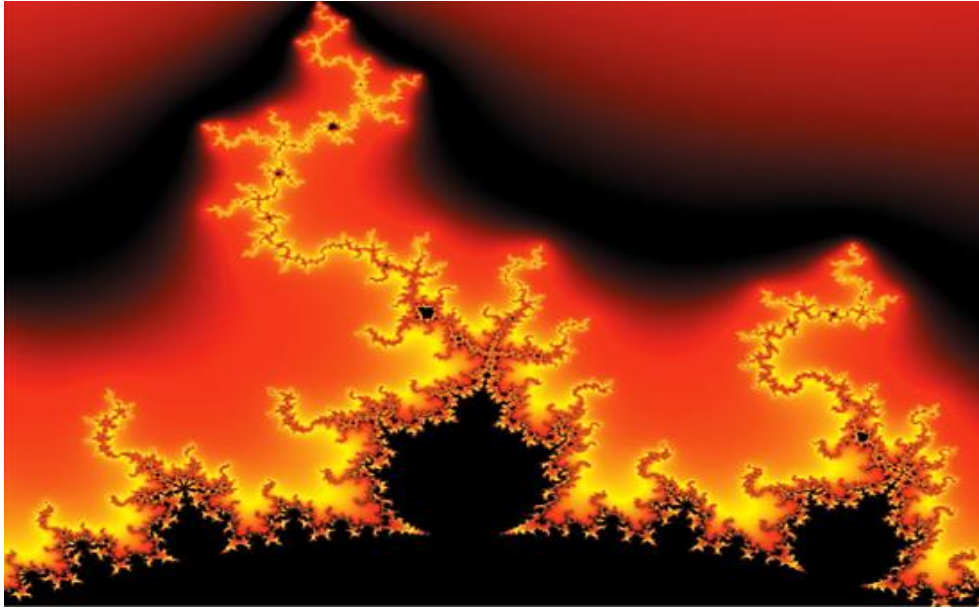


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