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Review

Plant Antioxidants: Therapeutic Potential in Cardiovascular Diseases

Hilda Aguayo-Morales *, Joan Poblano, Lia Berlanga, Ileana Castillo-Tobías, Sonia Yesenia Silva-Belmares and Luis E. Cobos-Puc *

Facultad de Ciencias Químicas, Unidad Saltillo, Universidad Autónoma de Coahuila, Boulevard Venustiano Carranza S/N Esquina Con Ing, José Cárdenas Valdés, República Oriente, Saltillo 25290, Mexico; joanhernandezpoblan@uadec.edu.mx (J.P.); lia.berlanga@uadec.edu.mx (L.B.); ileana.castillo@uadec.edu.mx (I.C.-T.); yesenia_silva@uadec.edu.mx (S.Y.S.-B.)

* Correspondence: aguayohilda@uadec.edu.mx (H.A.-M.); luis.cobos@uadec.edu.mx (L.E.C.-P.); Tel.: +52-844-415-5752 (L.E.C.-P.); Fax: +52-844-415-9534 (L.E.C.-P.)

Abstract: Cardiovascular diseases (CVDs) are a global health problem. The mortality associated with them is one of the highest. Essentially, CVDs occur when the heart or blood vessels are damaged. Oxidative stress is an imbalance between the production of reactive oxygen species (free radicals) and antioxidant defenses. Increased production of reactive oxygen species can cause cardiac and vascular injuries, leading to CVDs. Antioxidant therapy has been shown to have beneficial effects on CVDs. Plants are a rich source of bioactive antioxidants on our planet. Several classes of these compounds have been identified. Among them, carotenoids and phenolic compounds are the most potent antioxidants. This review summarizes the role of some carotenoids (a/β-carotene, lycopene and lutein), polyphenols such as phenolic acids (caffeic, p-coumaric, ferulic and chlorogenic acids), flavonoids (quercetin, kaempferol and epigallocatechin gallate), and hydroxytyrosol in mitigating CVDs by studying their biological antioxidant mechanisms. Through detailed analysis, we aim to provide a deeper understanding of how these natural compounds can be integrated into cardiovascular health strategies to help reduce the overall burden of CVD.

Keywords: cardiovascular diseases; reactive oxygen species; plant antioxidants; carotenoids; phenolic acids; flavonoids

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1. Introduction

Cardiovascular diseases (CVDs) are a general term for diseases that involve dysfunction of the heart and blood vessels. CVDs are the leading cause of death worldwide and represent a serious public health problem [1]. Several lines of evidence suggest that pro-inflammatory cytokines may play an important role in the development and progression of CVDs [2–4]. Chronic inflammation is a condition that predisposes to an imbalance between oxidants and antioxidants (oxidative stress) [5]. Reactive oxygen species (ROS) such as hydroxyl radicals, superoxide anion radicals, and non-radical species such as singlet oxygen and hydrogen peroxide, which are important in cellular metabolism, are overproduced during oxidative events. ROS can induce oxidative damage to cardiac and vascular cells, resulting in the overexpression of oncogenes or mutagens, leading to pathological conditions [6]. In addition, ROS can induce endothelial dysfunction, which is associated with the progression of CVDs [7].

Medicinal plants have been used as remedies for human diseases since ancient times. Some cardioprotective effects of medicinal plants may be due to their antioxidant potential [8]. Phytochemicals with antioxidant activities have therapeutic potential to reduce oxidative stress and ameliorate various oxidative stress-related diseases [9]. There are several classes of antioxidant compounds in the plant kingdom, but generally they can be

classified into enzymatic or non-enzymatic (low-molecular-weight) and high-molecular-weight antioxidants. Hundreds of bioactive antioxidants have been identified in plants. On this basis, this review summarizes the cardiovascular effects of some carotenoids (a/β-carotene, lycopene, and lutein) and polyphenols such as phenolic acids (caffeic, p-coumaric, ferulic, and chlorogenic acids), flavonoids (quercetin, kaempferol, epigallocatechin gallate), and hydroxytyrosol on cardiovascular research models. In this context, carotenoids, phenolic acids, and flavonoids have been the subject of numerous preclinical or clinical studies aimed at elucidating their role in the prevention and treatment of CVDs. Carotenoids, for example, not only act as ROS scavengers but also modulate cell signaling pathways that may influence cardiovascular health. Phenolic acids and flavonoids, found in fruits, vegetables, grains, and other plant foods, have also demonstrated antioxidant and anti-inflammatory properties that may contribute to cardiovascular risk reduction [10].

Despite these advances, several unknowns and challenges remain in the study of plant antioxidants and their clinical application. The bioavailability and metabolism of these compounds can vary widely among individuals, affecting their therapeutic efficacy. In addition, the interaction of antioxidants with other dietary components and drugs, as well as their potential side effects, are critical issues that must be addressed to ensure their safety and efficacy in clinical practice. It is hoped that a better understanding of these natural compounds and their potential benefits will provide a clearer and more informed perspective on their potential inclusion in comprehensive cardiovascular health strategies.

2. Cardiovascular Diseases

Rheumatic heart disease, ischemic heart disease, ischemic stroke, intracerebral and subarachnoid hemorrhage, hypertensive heart disease, aortic valve disease, myocarditis, alcoholic cardiomyopathy, pulmonary arterial hypertension, atrial fibrillation, aortic aneurysm, endocarditis, and others are clinical conditions of this class of pathologies with a high mortality index. A common fact for CVDs is that their incidence increases with age [1].

Ischemic heart disease results from an imbalance between oxygen supply and demand to the myocardium caused by atherosclerosis of the coronary arteries [11]. Cerebrovascular disease includes conditions that affect the blood supply to the brain and can lead to overt stroke [12]. Hypertensive heart disease encompasses a broad spectrum of abnormalities that represent the accumulation of functional and structural adaptations to increased blood pressure load such as increased left ventricular mass, left ventricular systolic and diastolic dysfunction, impairment of coronary reserve, arrhythmias, and left atrial and aortic root enlargement [13,14]. Cardiomyopathies result from abnormal heart muscle function that causes myocardial dysfunction in the absence of coronary artery disease (CAD), hypertension, valvular, and congenital heart disease. These can be familial (genetic mutations) or non-familial [15]. Rheumatic heart disease is the result of valvular damage caused by an abnormal immune response to group A streptococcal infection, usually during childhood [16]. Atrial fibrillation is the most common sustained arrhythmia [17]. An aortic aneurysm is a localized dilation that predisposes the artery to sudden rupture [18]. Endocarditis is defined as inflammation of the endocardial surface of the heart. In most cases, the inflammation is associated with a bacterial or fungal infection [19]. Pulmonary arterial hypertension is identified as a rare and severe condition characterized by remodeling and obstruction of the pulmonary microvasculature, resulting in increased pulmonary vascular resistance, elevated pulmonary arterial pressures and right ventricular failure [20].

Oxidative Stress: A Key Player in Cardiovascular Diseases

Oxygen/nitrogen free radicals, also known as reactive oxygen species (ROS, RNS), are molecules containing one or more unpaired electrons and singlet oxygen. Several types of ROS/RNS have been described, including superoxide anion (O_2^-), hydroxyl radical (HO), lipid radical (ROO^-), peroxynitrite ($OONO^-$) and nitric oxide (NO). Other ROS, such as

hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl), are not free radicals but have oxidative effects [21,22].

ROS/RNS are generated in cardiovascular cells such as vascular smooth muscle cells (VSMCs) and endothelial cells, cardiac fibroblasts and cardiomyocytes [23] through the action of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), the major enzymatic system that generates ROS. The isoenzymes NOX1, NOX2, NOX4 and NOX5 have been identified. NOX2 and NOX4 generate ROS/RNS in cardiomyocytes and cardiac fibroblasts, whereas NOX1, NOX4 and NOX5 generate ROS/RNS in vascular smooth muscle cells. All NOX isozymes lead to the generation of O_2^- except NOX4, which generates H_2O_2 [24,25] (see Figure 1).

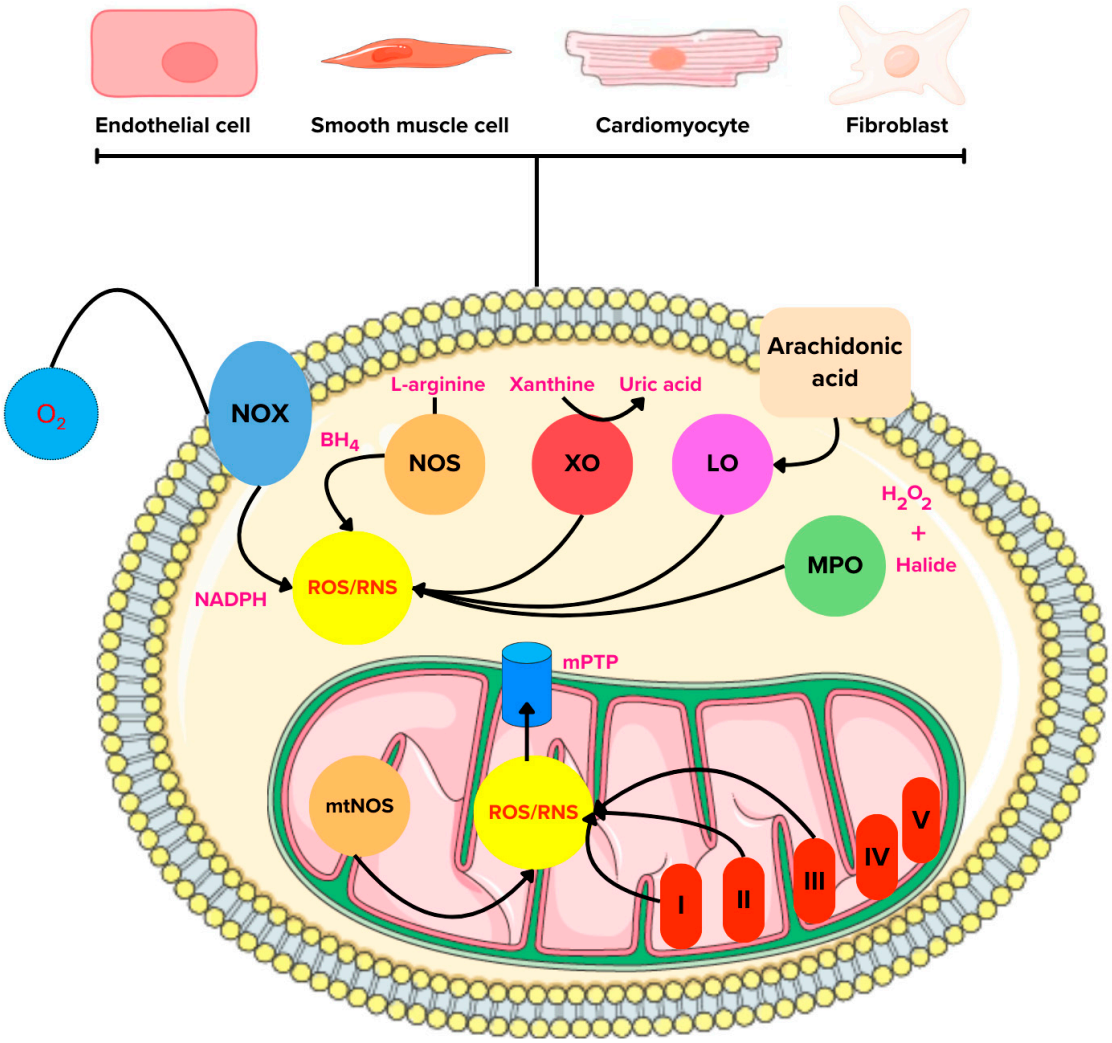

Figure 1. Schematic representation of oxygen/nitrogen free radical (ROS/RNS) generation in cardiac cells. NOX: nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; NOS: nitric oxide synthase; XO: xanthine oxidase; LO: lipoxygenases; MPO: myeloperoxidase; BH_4: 2-amino-6-(1,2-dihydroxypropyl)-5,6,7,8-tetrahydro-1H-pteridin-4-one; mPTP: mitochondrial permeability transition pore; H_2O_2: hydrogen peroxide; mtNOS: mitochondrial NOS; Mitochondrial complexes: I, II, III, IV, V.

However, other enzymatic systems such as nitric oxide synthases (NOS), xanthine oxidase (XO), lipoxygenases (LO) and myeloperoxidases (MPO) also contribute to the production of ROS/RNS. For example, NO is synthesized from L-arginine by NOS. Although the expression of these enzymes is not tissue-specific, there are three types of NOS, named neuronal (nNOS or NOS I), inducible (iNOS or NOS II) and endothelial (eNOS or NOS III). In addition, a mitochondrial NOS (mtNOS) similar to nNOS has been de-

scribed. Under dysfunctional conditions, NOS is probably uncoupled by a reduction in 2-amino-6-(1,2-dihydroxypropyl)-5,6,7,8-tetrahydro-1H-pteridin-4-one (BH_4), producing O_2^- instead of NO. The small amount of NO produced reacts with h to form $OONO^-$ [26]. On the other hand, XO produces O_2^- and H_2O_2 as a metabolic product of the conversion of xanthine to uric acid, LO generates H_2O_2 from arachidonic acid and MPO mediates the coupling of H_2O_2 with halide or semihalide ions resulting in the production of HOCl. The major source of ROS in the cell is the electron transport chain in the inner mitochondrial membrane, particularly in complexes I, II and III, where an incomplete reduction of oxygen can form O_2^-. In addition, uncoupling of oxidative phosphorylation, which occurs when the proton gradient is not efficiently used for adenosine triphosphate (ATP) synthesis, can increase electron leakage and ROS production [27]. Once generated, ROS/RNS exit the mitochondria through the permeability transition pore (mPTP) (Figure 1) [28,29].

Animals and plants have evolved mechanisms to neutralize the effects of ROS/RSN, known as antioxidants. These compounds prevent the deleterious effects of ROS/RSN by scavenging species that initiate peroxidation, chelating metal ions, preventing the formation of peroxides, breaking the auto-oxidative chain reaction and/or reducing O_2 concentrations. Antioxidants can be classified into several classes (natural, synthetic, endogenous or exogenous), but they can be grouped into three lines of defense (Figure 2): (1) enzyme antioxidants, which eliminate superoxide radicals and break down hydrogen peroxides and hydroperoxides into harmless molecules; (2) scavenging antioxidants, which neutralize free radicals by donating electrons to them; and (3) enzymes, which repair or eliminate damaged DNA and proteins to prevent their accumulation and toxic effects [30–32]. However, when ROS are generated in higher concentrations than antioxidants, a condition called oxidative stress is established, which causes physiological changes mediated by the oxidation of essential biomolecules [33].

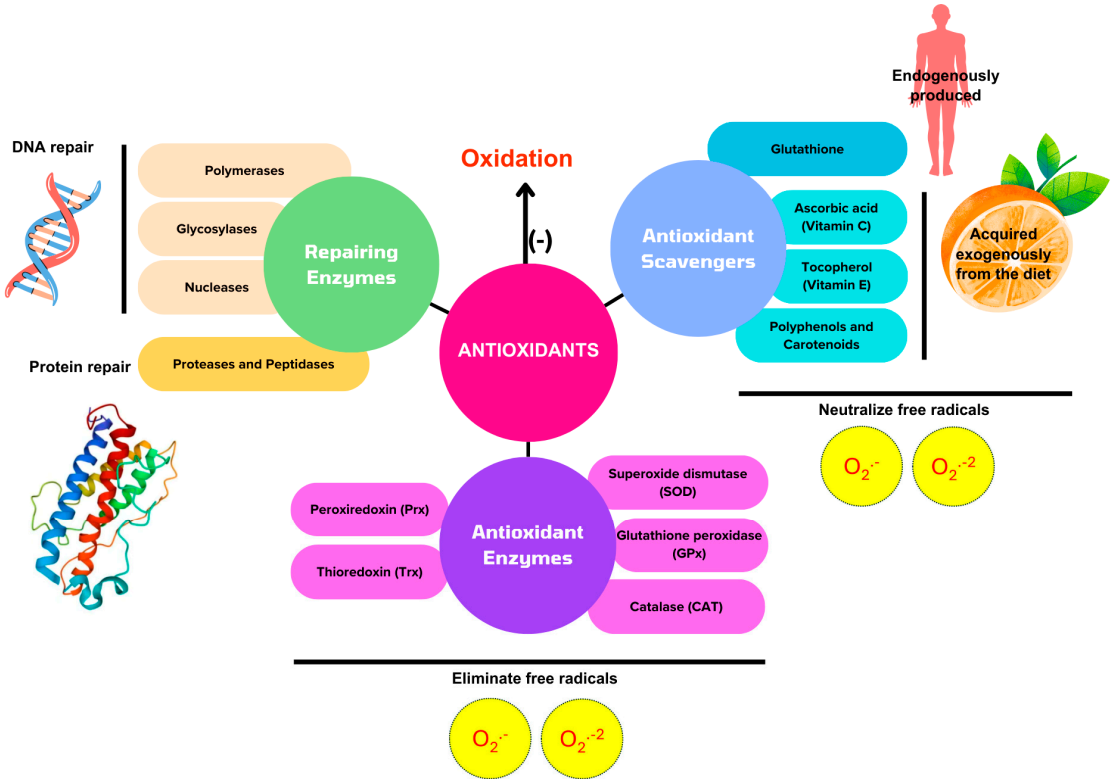

Figure 2. Types of antioxidants and their main function. When the production of these antioxidants is exceeded by the generation of free radicals, oxidative stress occurs. O_2^-: superoxide; O_2^{-2}: peroxides.

In cardiovascular tissues, oxidative stress leads to endothelial dysfunction, inflammation and lipid peroxidation [34]. A common fact in oxidative stress-induced CVDs is the formation of atherosclerotic plaques via the oxidation of low-density lipoproteins (LDLs) [35]. In addition, ROS/RNS can modulate the activity of several signaling pathways or genes involved in cell proliferation and transformation that regulate cardiac and vascular function [36] (see Figure 3). All of the above responses contribute to the etiology and progression of CVDs. There is increasing evidence that antioxidants protect against oxidative stress-induced cardiovascular dysfunction. Indeed, antioxidant treatment has beneficial health effects in patients or animals with cardiovascular dysfunction [37,38].

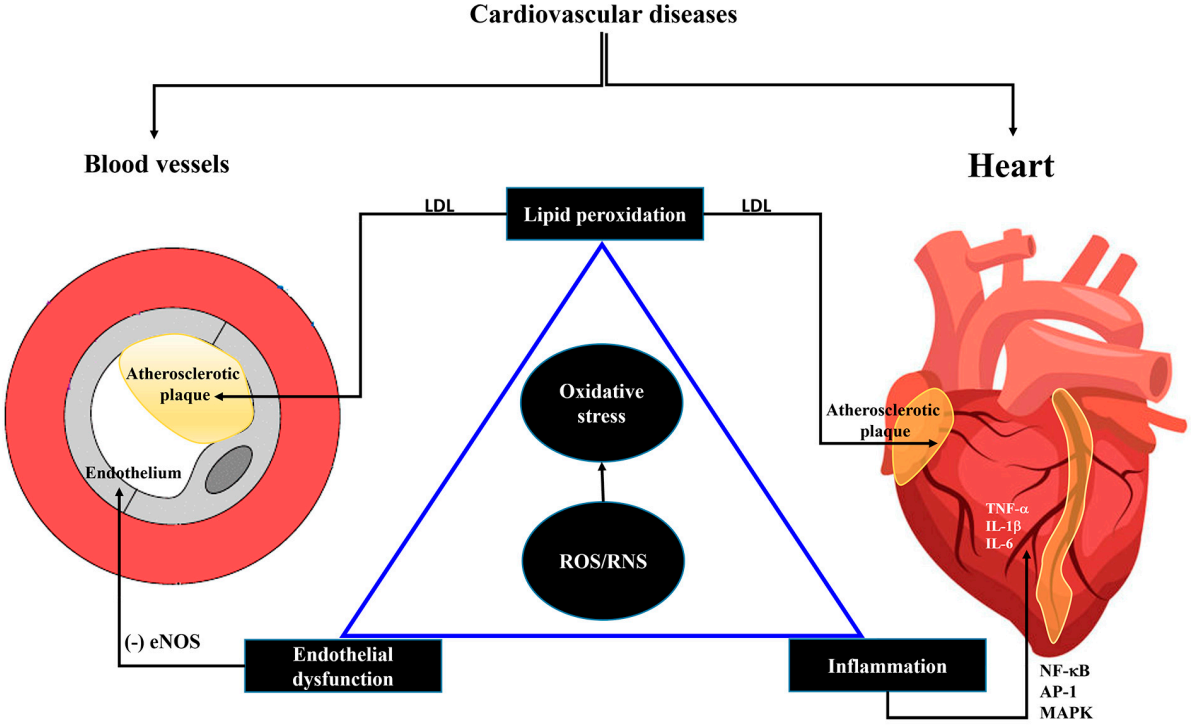

Figure 3. Schematic representation of the triad involved in the progression of cardiovascular diseases. ROS: reactive oxygen species; RNS: reactive nitrogen species; LDL: low-density lipoprotein; eNOS: endothelial nitric oxide synthase; NF-κB: nuclear factor-kappa B; AP-1: activator protein-1; MAPK: mitogen-activated protein kinase; TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; IL-6: interleukin-6.

3. Plant Antioxidants

Humans have used plants since ancient times, and even in recent times, about 70–95% of the people in developing countries use them [39]. Plants have powerful enzymatic antioxidants (such as catalase, superoxide dismutase, glutathione peroxidase, NADPH dehydrogenase and peroxiredoxin) and low-molecular-weight scavenging antioxidants (such as glutathione, ascorbic acid, tocopherols, proline, carotenoids, phenolic compounds) and high-molecular-weight compounds (such as tannins). Carotenoids and phenolic compounds are ubiquitous in fruits, vegetables and other plants, which have certain health benefits due to their anti-inflammatory, anti-carcinogenic, anti-atherogenic, antithrombotic, cardioprotective and vasodilatory effects attributed to their antioxidant activities [8,9,40].

Carotenoids are the most potent antioxidants of the tetraterpene family (C40-based isoprenoids) and are divided into two classes: carotenes (which contain only carbon and hydrogen atoms) and oxocarotenoids (xanthophylls) (which carry at least one oxygen atom). These compounds are responsible for the yellow, orange or red color of fruits, leaves and flowers. The most abundant pigments in the plant kingdom are α/β-carotene, lycopene and lutein (Figure 4) [41,42].

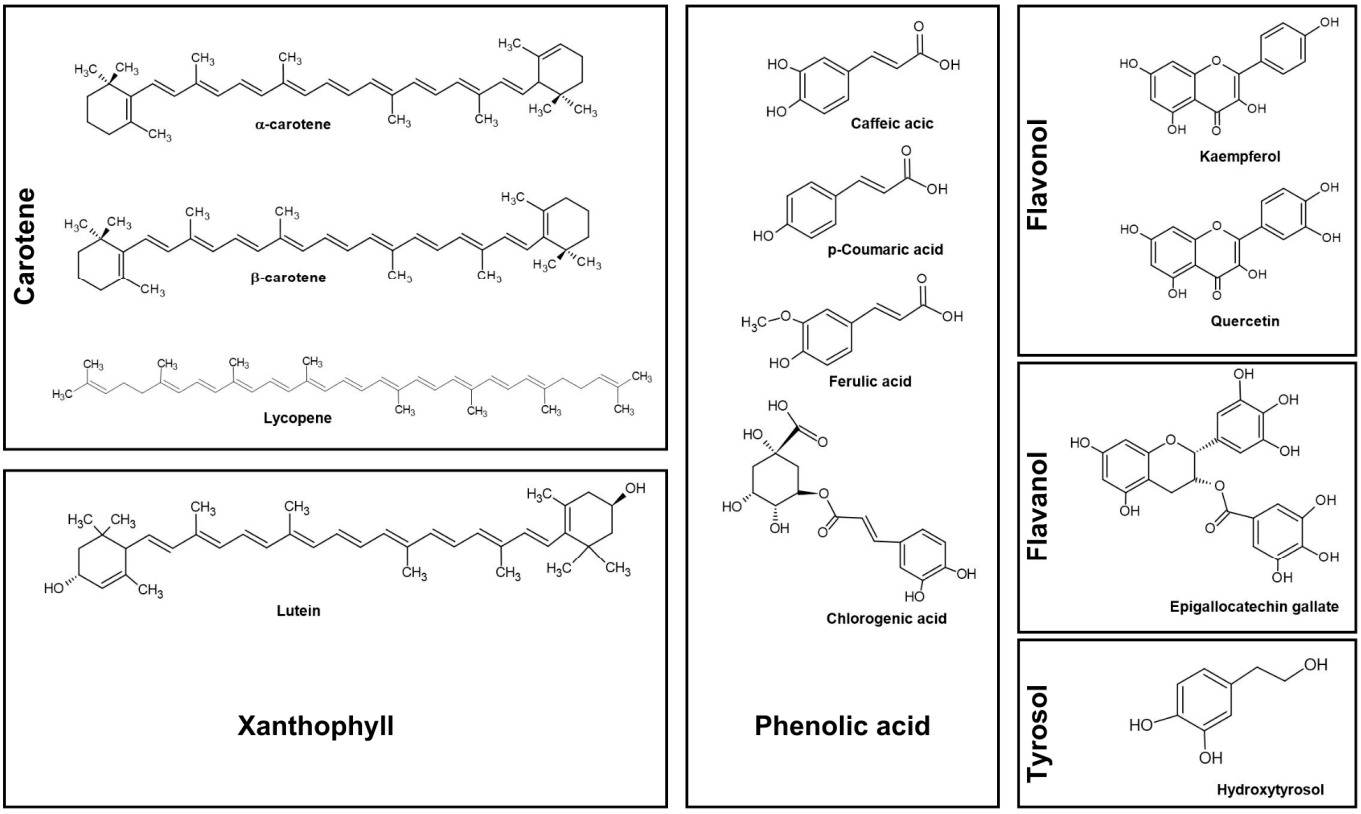

Figure 4. Chemical structure of natural antioxidants belonging to the family of carotenoids and phenolic compounds.

Phenolic compounds have one or more aromatic rings and one or more hydroxyl groups. They are essential for plant reproduction and growth and can be grouped into several classes, but phenolic acids and flavonoids are the most important dietary compounds. Phenolic acids can be divided into two broad categories based on their chemical nature: hydroxybenzoic acid derivatives and hydroxycinnamic acid derivatives. The latter are the most abundant in the plant kingdom, and the most common are caffeic, p-coumaric, ferulic and chlorogenic acids, which exhibit potent antioxidant properties. On the other hand, flavonoids are a group of polyphenolic compounds that can be classified into flavones, flavonols, flavanones, flavanols, anthocyanidins, chalcones, isoflavones, flavanonols and aurones. However, flavonols such as quercetin and kaempferol are the major groups of flavonoids found in plants. A flavanol and tyrosol known such as epigallocatechin gallate and hydroxytyrosol, respectively, are the most potent antioxidants found in nature. In addition to their antioxidant effects, all of them (Figure 4) interfere with several biochemical signaling pathways and thus physiological and pathological processes [43–45].

4. Therapeutic Potential of Plant Antioxidants for Cardiovascular Diseases

Plant antioxidants could be co-adjuvants for the treatment of CVDs. The biological actions of plant antioxidants (extracts, dietary supplements or purified metabolites) have been evaluated in humans with CVDs, in animal models or in cellular models to elucidate their benefits or toxic consequences. Several classes of plant antioxidants have been identified. Among them, carotenoids and polyphenols are the most potent antioxidants in the plant kingdom.

4.1. Carotenoids

Carotenoids are compounds with long and linear structures containing multiple conjugated double bonds. This conjugation is responsible for their antioxidant properties and their ability to absorb light in the visible spectrum, giving them their characteristic

color [46,47]. In this section, we will review the most potent compounds in both categories (Figure 4, Table 1).

Table 1. Cardiovascular effects mediated by α/β-carotene, lycopene and lutein.

Compound	Specie	Dose/Concentration	Effect	Mechanism	References
α-Carotene	Human	-	Reduced serum levels in coronary artery disease	-	[48]
β-Carotene	Mouse	800 mg/kg from dietary sources	Anti-atherosclerotic	(−) macrophage infiltration (−) ICAMs, (−) VCAMs (−) PPAR γ (−) MCP-1	[49]
	Rat	30 mg/kg/day for 4 weeks	Reduction of the infarct area	(+) HO-1	[50]
	Rat	20 mg/kg for 3 weeks	Hypotensive	(−) MDA	[51]
	Human	0.75 mL	Hypotensive	(−) oxLDL	[52]
Lycopene	Rat	30–50 mg/kg for 6–8 weeks	Anti-atherosclerotic	(−) LDL	[53]
	Mouse	10 mg/kg for 4 weeks	Anti-inflammatory	(−) TGF-β1 (−) TNF-α (−) IL-1β (−) NF-κB (−) Caspase 3, 8 and 9 (−) Collagen I (−) Collagen III	[54]
	Mouse	1 μM	Reduction of the infarct area	(−) MDA (−) JNK	[55]
	Rat	1.5 mg/kg	Reduction of the infarct area	(−) MDA (−) LDL (+) Antioxidant enzymes	[56]
Lutein	Human	20 mg/day for 12 months	Anti-atherosclerotic	(−) IL-6 (−) MCP-1 (−) LDL	[57]
	ApoE KO mouse	25–100 mg/kg	Anti-atherosclerotic	(−) NOX (−) PPAR	[58]
	Rat	0.2 mg/kg	Antioxidant	(+) SOD (+) GPx (+) GSH (+) Catalase (−) MDA (−) COX-2	[59,60]
	Rat	2 mg/kg	Hypotensive	(−) MDA (+) GSH	[61]

4.1.1. α-Carotene

α-Carotene is found in yellow-orange and dark green vegetables such as carrots, sweet potatoes, squash and broccoli. The serum concentration in healthy people is about 0.12 μM [62]. However, serum levels are reduced in patients with coronary artery disease [48].

4.1.2. β-Carotene

Atherosclerosis is the narrowing of the arteries due to the buildup of cholesterol in the artery walls. It can lead to life-threatening complications such as stroke and heart attack. Experimental evidence suggests that treatment with β-carotene (800 mg/kg diet) for 60 days prevents atherosclerotic plaque formation in rodents with angiotensin-induced aneurysm by reducing macrophage infiltration, expression of adhesion molecules such as intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecules (VCAMs) and inflammatory genes such as the peroxisome proliferator-activated receptor gamma (PPAR-γ) and monocyte chemoattractant protein-1 (MCP-1) [49]. In fact, low serum β-carotene levels increase the risk of developing congestive heart failure [63], myocardial infarction [64], atherosclerosis and stroke in humans [63,65].

Ischemic events cause irreversible damage to myocardial cells, resulting in necrosis. Cardiomyocytes in the subendocardium are most susceptible to ischemia. Repair of infarcted myocardium follows a well-characterized sequence of necrosis, inflammation, remodeling and scar formation. Interestingly, 4-week administration of a low dose of β-carotene (30 mg/kg/day), but not a high dose (150 mg/kg/day), reduces infarcted heart size and increases heme oxygenase-1 (HO-1) expression in rats [50].

High blood pressure, or hypertension, is a serious condition that over time can damage blood vessel walls and increase the risk of CVDs, including heart attack, stroke and other diseases. Treatment with β-carotene (20 mg/day) for three weeks reduces high blood pressure in hypertensive rats probably by reducing serum malondialdehyde (MDA) levels [51]. Similar results were observed in humans treated for one month with β-carotene capsules from sea buckthorn seed oil (0.75 mL), in which case a reduction in oxidized LDL was observed [52].

4.1.3. Lycopene

Lycopene is a polyunsaturated hydrocarbon phytochemical found in red fruits and vegetables (papayas, tomatoes, red peppers, watermelons, etc.). Experimental evidence suggests that treatment with lycopene (30–50 mg/kg/day) for 6–8 weeks prevents the formation of atherosclerotic plaques in rodents by reducing LDL [53].

In atherosclerosis, VSMC proliferation and endothelial dysfunction contribute to vessel wall inflammation and lipoprotein retention, as well as to the formation of the fibrous cap that provides plaque stability. Consistent with this, 2 months of oral lycopene supplementation improves endothelial function in patients with CVDs [66]. In a murine model of myocardial infarction, lycopene (10 mg/kg, for 4 weeks) reduced the mRNA expression of inflammatory mediators such as transforming growth factor beta 1 (TGF-β1), collagen I and III, tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), caspases (3, 8 and 9) and inhibited the NF-κB pathway, thereby reducing the inflammatory response and cardiomyocyte apoptosis, which may be a key mechanism of lycopene in attenuating ventricular remodeling [54]. Administration of lycopene, 1 μM; i.v. or 1.5 mg/kg; p.o., protects against myocardial damage induced by ischemia/reperfusion [55] or isoproterenol-induced myocardial injury [56]. These cardioprotective effects involve the inhibition of fatty acid oxidation and the inhibition of c-Jun N-terminal kinase (JNK) signaling. In addition, the cardioprotective effects of carotenoids include the prevention of endogenous antioxidant depletion and mitochondrial damage and the alleviation of endoplasmic reticulum stress, which is critical for cardiomyocyte function and survival [67,68]. Lycopene supplementation for 30 days reduces inflammatory markers in women with heart failure [69].

4.1.4. Lutein

The xanthophyll lutein (β,ε-carotene-3,3′-diol) is abundant in green leafy vegetables such as kale and spinach, where its yellow-orange color is masked by the dominant green color of chlorophyll [70].

In patients with atherosclerosis, lutein (20 mg/day) taken orally for 12 months reduces carotid artery thickness [71] by reducing cytokines, such as interleukin-6 (IL-6) and MCP-1,

and lipoproteins, such as LDL [57]. Moreover, in peripheral blood mononuclear cells (PBMCs) isolated from patients with coronary artery disease, lutein prevented the secretion of IL-1β, IL-6 and TNF-α [72]. Similarly, 24 weeks of treatment with lutein in mice showed anti-atherosclerotic effects via a reduction in NOX and increase in PPAR expression [58]. On the other hand, in rodent models of ischemia-induced injury, lutein (0.2 mg/kg, i.p.) increases superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase and glutathione (GSH) [60] and decreases MDA and cyclooxygenase-2 (COX-2) [59]. Treatment with lutein (2 mg/kg) for three weeks reduces blood pressure in hypertensive rats [61].

4.2. Polyphenols

Polyphenols are bioactive compounds found in many plants. They are known for their antioxidant and anti-inflammatory properties, which contribute to many health benefits, especially cardiovascular health [73]. Several thousand polyphenols have been identified, and their classification is closely related to their chemical structure (phenol ring). At least five major groups such as phenolic acids, stilbenes, lignans, flavonoids and tannins have been identified [74,75]. In this manuscript, we will discuss some of the phenolic acids and flavonoid compounds with the greatest therapeutic potential in cardiovascular disease and one compound of great interest belonging to the tyrosol subclass (Table 2).

Table 2. Cardiovascular effects mediated by caffeic, p-coumaric, ferulic and chlorogenic acids, kaempferol, quercetin, epigallocatechin gallate and hydroxytyrosol.

Compound	Specie	Dose/Concentration	Effect	Mechanism	Reference
Caffeic acid	Rat	10–50 mg/kg	Protection of cerebral vessels	(−) 5-LO	[76]
	Rat	1 mg/kg	Cardioprotector against ischemia	(−) Troponin (−) ROS	[77]
	H9c2 rat cells	75 μg/mL	Inhibits apoptosis of cardiac cells	(−) Caspases (−) Bax (+) Bcl2	[78]
	Mouse	1–5 mg/kg	Protection of cerebral vessels	(−) TNF-α (−) IL-1β (−) MCP-1	[79]
	Rat	250–1000 mg/kg	Hypotensive	(−) ACE (+) NO	[80–84]
p-Coumaric acid	Vascular cells	1 mM	Anti-angiogenic	(−) AKT (−) ERK	[85,86]
	Rat	8–100 mg/kg	Cardioprotector against cardiac injury	(+) NO (−) LDH (−) LDL	[87–89]
	Rat	10–50 μg/mL	Hypotensive	(−) Calcium channels	[90]
Ferulic acid	Rat	10–40 mg/kg	Antithrombotic	(−) p38 MAPK (−) ERK (+) PKA (−) AKT (−) $\alpha_{IIb}\beta_3$/ (FIB)/AKT	[91,92]
	Rat	20 mg/kg	Prevents cardiac hypertrophy	(+) SOD (−) CK-MB	[93]
	Rat	20 mg/kg	Hypotensive	(+) NO	[94]
Chlorogenic acid	Rat aorta	1 mg/mL	Hypotensive	(−) Calcium channels (−) ACE (+) NO	[81,90,95,96]

Table 2. *Cont.*

Compound	Specie	Dose/Concentration	Effect	Mechanism	Reference
	Rat	40 mg/kg	Prevents cardiac hypertrophy	(−) LDH	[97]
	Rat	10–20 mg/kg	Anti-inflammatory	(−) mtROS (−) MKP-1 (−) TNF-α	[98,99]
Kaempferol	Rat	5–20 mg/kg	Prevents cardiac hypertrophy	(−) LDH (−) CK-MB (−) TNF-α (−) IL-6 (−) p38 MPAK (−) JNK (+) GSH (+) SOD (+) Catalase (+) GSK-3β (+) SIRT1	[100–103]
	Vascular cells	50–100 μM	Antioxidant	(+) GSH (+) SOD (−) MDA (−) NF-κB (−) CRP (−) VEGF (−) JNK (−) p38 MAPK	[104–107]
Quercetin	Human	120 mg/kg	Anti-atherosclerotic	(+) SIRT1 (−) NOX (−) NF-κB	[108–111]
	Rat	50 mg/kg	Cardioprotector against myocardial injury	(−) TNF-α (−) IL-6 (−) IL-10 (+) SOD (+) GSH (+) Catalase (+) GSK-3α/β	[112,113]
	Human	500 mg/day	Hypotensive	(+) NO (−) NOX (−) MLCK (+) HSP 70/ ERK/ PPAR γ	[114–118]
Epigallocatechin gallate	Human	150–1200 mg/day	Hypotensive	(+) eNOS (−) NOX	[119,120]
	Rat	20–100 mg/kg	Antithrombotic	(−) ROS	[121,122]
	Mouse	10–40 mg/kg	Anti-atherosclerotic	(+) TTC39B gene (+) LDLR (−) Cytokines	[123–125]
Hydroxytyrosol	Human vascular cells	5–10 μM	Protects vascular cells	(−) ROS	[126,127]
	Rat	20–200 mg/kg	Prevents cardiac hypertrophy	(−) GRP78 (−) CHOP (−) mPTP (−) AKT/GSK-3β	[128–130]

4.2.1. Phenolic Acids

Phenolic acids are a class of organic compounds that belong to the polyphenol family. They are characterized by a structure that includes at least one phenolic ring (a benzene ring with one or more hydroxyl groups) attached to a carboxyl group. They fall into two major subclasses: hydroxybenzoic acid and hydroxycinnamic acid [74,75]. These compounds are widely distributed in plants and are important for both plant metabolism and human health. Here, we review key findings on the more relevant compounds of the hydroxycinnamic acid subclass (Figure 4).

Caffeic Acid

Ischemic heart disease is a complex condition. The first step is a myocardial infarction, which suddenly deprives the heart muscle of oxygen and nutrients. To survive this damaging insult, cardiac myocytes undergo extensive remodeling. Prolonged ischemia causes permanent damage to heart cells. Effective restoration of coronary blood flow is the best approach for rescuing myocardium from ischemia. This is known as reperfusion. However, reperfusion itself causes significant cardiac damage in addition to ischemia. The overproduction of free radicals during ischemia/reperfusion (I/R) injury highlights the interest in the use of antioxidant therapy. Furthermore, caffeic acid has a significant protective effect on global cerebral ischemia-reperfusion injury in rats. Its neuroprotective effects are probably mediated by the inhibition of 5-lipoxygenase (5-LO) [76]. The antioxidant properties of phenolic acids could be used as pharmacological tools in ischemic heart disease. In this sense, caffeic acid has been shown to attenuate free radical-induced lipid peroxidation and reduce plasma levels of troponin, a biochemical marker of myocardial damage, in rats subjected to ischemia/reperfusion protocols. This compound improves cardiomyocyte viability and reduces intracellular ROS levels [77]. Caffeic acid from *Boerhavia diffusa* L. inhibits the apoptosis of cardiac cells by inhibiting caspases and Bax and by stimulating Bcl2 [78]. Caffeic acid derivatives also prevent isoproterenol-induced myocardial damage in hypertensive rats by inhibiting lipid peroxidation and inducing antioxidant enzymes (SOD, GPx, catalase) [131].

A stroke can occur when the blood supply to the brain's blood vessels is inadequate. Ischemic stroke is caused by a blockage or narrowing of the cerebral arteries, so treatment focuses on restoring adequate blood flow to the brain. Because the infiltration and activation of inflammatory cells and the secretion of cytokines exacerbate brain damage, it has been suggested that inflammation plays an important role in the pathogenesis of ischemic stroke and other forms of ischemic brain injury. In a sophisticated model of permanent focal ischemia induced by cranial irradiation with a cold light laser combined with a systemic administration of rose bengal to the medial frontal and somatosensory cortices of mice, intraperitoneal injection of a caffeic acid derivative reduces the expression of inflammatory cytokines (TNF-α and IL-1β) and MCP-1, a chemokine that regulates the migration and infiltration of monocytes and macrophages [79].

Cardiac fibrosis is an event involved in cardiac remodeling. The caffeic acid derivative inhibits cardiac fibrosis by modulating TGF-β superfamily signaling, which plays a critical role in regulating cell growth, differentiation and development in a variety of biological systems [132]. Interestingly, the caffeic acid derivative has been shown to prevent vascular dysfunction in a rat model of metabolic syndrome [133]. Indeed, the caffeic acid derivative counteracts the atherosclerotic changes associated with diabetes by ameliorating the significant functional and structural alterations in the vessels in addition to its anti-hyperinsulinemic effects [134].

Recently, caffeic acid and its derivative have been shown to be hypotensive in the rat [80,82,83]. Experimental evidence suggests that caffeic acid may inhibit angiotensin converting enzyme (ACE) [81]. Importantly, caffeic acid and its derivatives had no toxic effects in WI-38 cells compared to the clinically used drug captopril, an ACE inhibitor [135]. At very low doses, similar to those observed after moderate white wine consumption, caffeic acid may exert a protective effect on endothelial cell function by modulating NO

release independently of eNOS expression and phosphorylation. Caffeic acid-induced NO modulation may limit the progression of cardiovascular and renal diseases associated with oxidative stress-mediated endothelial injury [84].

p-Coumaric Acid

Atherosclerotic plaques can be associated with the formation of new blood vessels (angiogenesis) within the plaque. However, angiogenesis can contribute to plaque destabilization and rupture, resulting in intra-arterial occlusion. In the case of coronary arteries, this sudden and catastrophic restriction of blood supply to the heart causes an acute coronary syndrome, often leading to a fatal loss of cardiac function [136]. Thus, anti-angiogenic compounds may be useful in the treatment of CVDs. In this sense, p-coumaric acid has been shown to inhibit smooth muscle cell proliferation, endothelial cell sprouting in rat aortic rings and endothelial cell migration. In addition, p-coumaric acid downregulates the mRNA expression levels of angiogenic, vascular endothelial growth and fibroblast growth factors and inhibits the serine/threonine kinase (AKT) and extracellular signal-regulated kinase (ERK) signaling pathways, which are known to be critical for angiogenesis [85,86].

p-Coumaric acid isolated from the stems of silver fir (*Abies alba*) showed a weak cardioprotective effect on rat hearts damaged by ischemia/reperfusion [87], but a better cardioprotective effect on cardiac damage induced by isoproterenol, probably due to its antihypertrophic, antilipidemic, antioxidant and antiapoptotic properties [88,89]. These findings suggest that the efficacy of plant-derived antioxidants may be altered by the etiology of CVDs. It also shows hypotensive effects [90].

Ferulic Acid

Thrombosis has a significant impact on the pathogenesis and progression of atherosclerosis and cardiovascular disease. Ferulic acid exhibits antithrombotic effects due to its antiplatelet, but not anticoagulant, property. The above response may be mediated by the inhibition of p38 mitogen-activated protein kinase (MAPK) and ERK2 phosphorylation through the activation of protein kinase A (PKA) [91] and via the downregulation of the expression of $\alpha_{IIb}\beta_3$ integrin/fibrinogen (FIB)/AKT signaling [92]. It also inhibits oxidative stress and apoptosis in aortic VSMCs by inhibiting NOX, MDA, inflammatory cytokines (Il-6, Il-1β and TNF-α) and NF-κB and promoting the activation of SOD, GSH and catalase [137].

Thirty-five-day treatment with ferulic acid shows cardioprotective effects in rat cardiac hypertrophy through the inhibition of lipid peroxidation, restoration of antioxidant status and myocardial marker enzyme creatine kinase-MB (CK-MB) activity, as well as its potential antihypertensive activity [93]. In a rodent model of metabolic syndrome, treatment with ferulic acid for 6 weeks improved cardiovascular function in hypertensive rats, probably by improving endothelial function [94].

Chlorogenic Acid

Hakkou and colleagues showed that chlorogenic acid isolated from *Inula viscosa* lowered arterial blood pressure in hypertensive rats [96], probably through a blockade of calcium channels [90] and ACE [81,95] as well as endothelium-dependent mechanisms [96]. Chlorogenic acid was able to protect against HOCl-induced endothelial dysfunction in isolated mouse aortic rings and to improve endothelial cell survival via NO production by eNOS and HO-1 expression in human aortic endothelial cells [138]. In addition, chlorogenic acid attenuates oxLDL-induced oxidative stress and proapoptotic responses by modulating the sirtuin 1 (SIRT1)/adenosine monophosphate-activated protein kinase (AMPK)/ PPAR γ coactivator 1 alpha(PGC-1α) pathway and preserving mitochondrial membrane potential and mitochondrial biogenesis in human endothelial cells [139].

Chlorogenic acid exerts cardioprotective effects in isoproterenol-induced myocardial injury in rats by normalizing electrocardiographic changes, restoring mitochondrial and lysosomal enzyme activities, and reducing lactate dehydrogenase (LDH 1 and LDH 2)

expressions to near normal levels [97]. Pretreatment with chlorogenic acid, especially at the concentration of 100 μM, can effectively block isoproterenol-induced damage to VSMCs by abolishing the increase in protein expression levels of histones (γ-H2AX), protein kinase ataxia telangiectasia mutated and Rad3 related (ATM and ATR), tumor suppressor gene (BRCA1) and serine/threonine kinase Chk2 and further preventing ROS formation [140]. Amelioration of a chlorogenic acid-phospholipid complex post-infarction inflammatory response in the aging heart is associated with mtROS and (2) plays a critical role in mitogen-activated protein kinase phosphatase-1 (MKP-1) suppression; hence, the controlled activation of JNK may mediate mitochondrial redox stress and subsequent inflammatory injury in the aging heart [98]. Interestingly, TNF-α-induced inflammation in human EA.hy926 endothelial cells is prevented by yerba mate and green coffee extracts, their major hydroxycinnamic acids and microbial metabolites [99], supporting the anti-inflammatory effect of chlorogenic acid.

4.2.2. Flavonoids

Flavonoids have a basic chemical structure consisting of a skeleton of carbon atoms organized into at least three rings. Depending on the variations in the ring structure and the substituents on the rings, flavonoids are divided into several subclasses: flavonols, flavones, flavanones, flavanols, isoflavones and anthocyanins [74]. In this review, we will focus only on kaempferol and quercetin (both flavonols) and epigallocatechin gallate (flavanol) (Figure 4).

Kaempferol

Kaempferol exerts cardioprotective effects against ischemia-reperfusion injury by: (1) attenuating inflammation and apoptosis through antioxidant activity, (2) modulating the MAPK pathway [101], (3) inhibiting glycogen synthase kinase-3 beta (GSK-3β) activity [102] and (4) the mitochondrial pathway mediated by SIRT1 [100]. Sympathetic activity is increased in some CVDs, resulting in high plasma catecholamine levels and cardiotoxicity. I.v. or i.p. administration of kaempferol (10–20 mg/kg) prevents isoproterenol-induced myocardial damage in the rat by decreasing pro-inflammatory mediators (TNF-α, IL-6) and increasing anti-inflammatory (IL-10) and antioxidant (SOD, GSH and catalase) mediators [101,103].

A large body of evidence suggests that angiotensin plays a central role in the pathogenesis of hypertension and cardiac hypertrophy by modulating contractile and hypertrophic mechanisms in the heart and blood vessels. In this sense, kaempferol has been shown to prevent and reverse angiotensin-induced ventricular fibrosis and cardiac dysfunction [141]. Treatment with kaempferol protects against cardiac hypertrophy. This cardioprotection may be due to the inhibition of the apoptosis signal-regulating kinase 1 (ASK1)/MAPK pathway and the regulation of oxidative stress [103]. In addition to its cardioprotective effects, kaempferol and its derivatives protect vascular smooth muscle cells from oxidative damage by (1) acting as an antioxidant (inhibiting MDA production and increasing intracellular SOD and GSH expression), (2) modulating the osteopontin-αvβ3 integrin pathway to inhibit NF-κB activation, (3) modulating bone morphogenetic protein (BMP)-mediated miR-21 expression [105,107], (4) by inhibiting inflammatory factors such as C-reactive protein (CRP), vascular endothelial growth factor (VEGF), JNK2 and p38 MAPK [104] and (5) by relaxing coronary arteries via the activation of large conductance $Ca^{(2+)}$-activated $K^{(+)}$ channels [106].

Quercetin

Coronary artery disease is a condition in which a waxy substance builds up inside the coronary arteries. Atherosclerosis is a precipitating condition. Two months of treatment with quercetin (120 mg/kg, p.o.) improves cardiovascular function in patients with coronary artery disease [109]. This beneficial effect of quercetin may be due to (1) anti-atherogenic effects mediated by restoring the balance of triglycerides and cholesterol [111]

via SIRT1, a nicotinamide adenine dinucleotide (NAD^+, NADH)-dependent class III protein deacetylase) and (2) the ability to suppress endothelial oxidative injury by modulating a complex network of antioxidant (AMPK/AKT/eNOS) and oxidant (NOX2) signaling pathways [110] and by inhibiting NF-κB [108].

Oral quercetin (50 mg/kg) prevents isoproterenol-induced myocardial damage by decreasing pro-inflammatory mediators (TNF-α, IL-6) and increasing anti-inflammatory (IL-10) and antioxidant (SOD, GSH and catalase) mediators [112]. However, the cardioprotective effects of flavonols may be dose-dependent or chronic damage-dependent (compensatory mechanisms), based on the report by Riha and colleagues who observed that 10 mg/kg (p.o.) of quercetin did not ameliorate the cardiovascular toxicity induced by acute administration of this sympathomimetic agent in rats [142].

Quercetin therapy may improve the outcome of heat stroke in rats by attenuating both excessive hyperthermia and myocardial injury. The protective effects of quercetin may be attributed to anti-lipid peroxidation and antioxidant and anti-inflammatory properties [143]. In addition, quercetin prevents cardiac hypertrophy associated with proteasome inhibition and GSK-3α/β activation [113]. Pretreatment with quercetin protected against myocardial IR injury by reducing oxidative stress, suppressing the inflammatory cascade, inhibiting apoptosis in vivo and inhibiting the phosphoinositide 3-kinase (PI3K)/AKT pathway [144]. Quercetin is effective in regulating the atherosclerotic inflammatory process by inhibiting oxLDL-induced endothelial leukocyte adhesion through the attenuation of the Toll-like receptor (TLR)/NF-κB signaling pathway in rats [145].

Quercetin induces hypotensive effects in humans [115] through its vasodilatory effect [114] by endothelial mechanisms [146], by inhibiting NOX-mediated superoxide anion production [116], and by reducing oxidative stress through the modulation of heat shock protein 70 (HSP 70)/ERK/PPAR γ pathways [118] and the inhibition of myosin light chain kinase (MLCK) [117].

Epigallocatechin Gallate

Cocoa and green tea are excellent sources of polyphenols. Both contain flavanols such as epicatechin, epigallocatechin, epicatechin gallate and epigallocatechin gallate (EGCG). However, the latter is the most abundant in both plants [74]. EGCG is one of the most potent antioxidant compounds. This antioxidant capacity confers cardioprotective effects. For example, long-term consumption of EGCG has been shown to reduce blood pressure in diabetic [119] and in obese [120] humans at doses of 150 and 1200 mg, respectively. The antihypertensive mechanisms of EGCG may be related to the increase in eNOS and the reduction in NOX2 and consequently in ROS [147]. EGCG (100 mg/kg/14 days, p.o.) improves the luminal layer of rat femoral arteries and veins and prevents thrombus formation [121]. Similar results were obtained in rat vena cava with a lower dose but longer treatment (20 mg/kg/42 days) via the inhibition of ROS, PI3/AKT pathway and inflammatory cytokine secretion [122]. This cardioprotective mechanism may help prevent myocardial infarction and ischemic heart disease. On the other hand, EGCG (40 mg/kg) ameliorates myocardial injury in rodents by inhibiting the AKT/mammalian target of rapamycin (mTOR) [148] and Hippo [149] pathways and by increasing the nuclear factor erythroid 2-related factor (2Nrf2)/HO-1/NAD(P)H quinone oxidoreductase 1 (NQO1) antioxidant pathway [150]. EGCG has an anti-atherosclerotic effect when administered intraperitoneally (10 mg/kg/16 weeks) [123] or intragastrically (40 mg/kg/18 weeks) [124] in mice. This effect is associated with improved lipoprotein balance by increasing the TTC39B gene [124], decreasing inflammatory cytokines [123] and upregulating low-density lipoprotein receptor (LDLR) expression [125]. It is well known that atherosclerosis is a condition that increases the likelihood of developing coronary heart disease, cerebral and myocardial infarction, and peripheral vascular disease.

4.2.3. Hydroxytyrosol

Tyrosols are a class of phenolic compounds found in various foods such as olive oil. Tyrosol is a phenolic alcohol that has the basic chemical structure of a benzene ring with a hydroxyl group (−OH) attached to a side chain of two carbon atoms ending in a hydroxyl group (−CH2CH2OH). The two major compounds in this subclass of polyphenols are tyrosol and hydroxytyrosol [151]. Regulatory agencies such as the European Food Safety Authority (EFSA) have recognized that hydroxytyrosol has cardioprotective effects by inhibiting lipoprotein oxidation [152].

Hydroxytyrosol is found primarily in olive oil. It is another potent natural antioxidant. Pharmacokinetic studies in humans [153] and rodents [154] have confirmed that the half-life of hydroxytyrosol is approximately 150 to 166 min. In a study of patients with CAD, supplementation with hydroxytyrosol-enriched olive oil improved endothelial and arterial function by inhibiting markers of oxidative stress such as MDA and inflammatory mediators such as IL-6 [155]. Consistent with these findings, hydroxytyrosol (10 μM) abolished SIRT1-mediated ROS production in human umbilical vein endothelial cells (HUVECs) [127] and AKT/eNOS in human aortic endothelial cells (HAECs) [126]. Hydroxytyrosol (5 μM) enhances angiogenesis and migration in HUVECs, which represents an important potential for the treatment of ischemic heart disease. This cardioprotective activity is related to the vascular endothelial growth factor receptor (VEGF-R2) and PI3K/AKT/eNOS pathways [156]. Hydroxytryrosol (40 μM) also prevents the apoptosis of myoblastic cells. In addition, olive oil extract at 200 mg/kg/day (for one month) reverses isoproterenol-induced myocardial damage in the rat via the inhibition of endoplasmic reticulum stress markers such as glucose-regulated protein 78 (GRP78) and C/-EBP homologous protein (CHOP) [128]. In an in vivo rodent model of ischemia followed by reperfusion, even low doses (20 mg/kg) reduce the infarcted area by optimizing the Akt/GSK-3β pathway [130]. In isolated hearts, hydroxytyrosol (1000 μM) prevents ischemia/reperfusion-induced damage by closing mPTP [129].

5. Limitations and Challenges of Plant Antioxidants for Therapeutic Use

Extraction and purification of plant antioxidants can be costly and complex, and yields are typically low, increasing production costs. Traditional methods using organic solvents to obtain antioxidants (e.g., kaempferol) are time-consuming and have poor yield [157]. Therefore, the cost, yield and time required to obtain antioxidants can be a barrier to the development and commercialization of affordable therapeutic products. One way to increase the yield of compounds of interest is to express plant genes related to their biosynthetic pathways in biological matrices such as yeast and bacteria [157–159]. Although the cost of these bioprocesses can be high, the cost/yield ratio is favorable, making them more cost-effective processes for the production of plant antioxidants.

Once you have the active ingredient, another element to consider is that these compounds can be unstable during storage and processing, reducing their effectiveness. Exposure to light, heat, oxygen and changes in pH can degrade these compounds and reduce their antioxidant activity. To cite the case of lutein, when exposed to these environmental conditions, its conjugated double bonds are destroyed, resulting in the loss of its biological properties. Interestingly, the combination with phenolic acids such as ferulic, caffeic and chlorogenic acids increases the stability of the molecule [160]. Therefore, the choice of the best dosage form and excipients is a major challenge.

Many botanical antioxidants have limited bioavailability, meaning that their absorption, distribution, metabolism and excretion in the body are not optimal. Factors such as water and fat solubility, stability in the gastrointestinal tract and the ability to cross biological barriers affect their therapeutic efficacy. One of the ideal compounds to illustrate this limitation is quercetin. Quercetin is a molecule with high potential as a cardioprotective agent; however, this molecule is insoluble in water, which hinders its absorption in the gastrointestinal system [161], has an accelerated metabolic rate leading to the formation of inactive metabolites and rapid clearance [162], resulting in low bioavailability in the body.

In addition, quercetin is metabolized by the microbiota in the colon, further reducing its concentration. Different delivery strategies such as liposomes, nanoparticles, nanoemulsions and micelles improve its absorption and prevent its metabolism in the digestive system [163].

Determining the optimal dose of phytonutrients is challenging. At high doses, some polyphenols (ferulic and caffeic acids) may cause side effects such as liver damage, nausea and vomiting [164]. Herbal antioxidants may interact with conventional drugs by altering their absorption, metabolism, or effectiveness. These interactions may result in unwanted side effects or improved therapeutic effects of the combined treatment. For example, the combination of quercetin with ritonavir causes severe gastrointestinal toxicity [165], while EGCG decreases the reuptake of rosuvastatin, resulting in a better reduction in blood cholesterol [166]. For this reason, more emphasis should be placed on identifying interactions with drugs used to treat cardiovascular disease as early as possible. In addition, the long-term safety of supplementation with high levels of antioxidants is not fully established. Although there is preliminary evidence for the benefits of plant antioxidants, more clinical research is needed to confirm their efficacy and safety in specific therapeutic applications. Many current studies are preclinical or have experimental designs that limit the generalizability of the results.

Finally, the regulation and standardization of botanical antioxidant supplements varies from country to country. In the European Union (EU), EFSA must approve health claims, and ingredients must meet safety standards before they can be marketed. In the United States (US), the Food and Drug Administration (FDA) does not require prior approval of dietary supplements, except for new ingredients. Standardization is more rigorous in the EU, where dietary supplements must meet strict guidelines and provide sound scientific evidence to support their health claims. In the US, manufacturers have more freedom to market products as long as they are not misleading and meet safety and labeling standards. In both markets, manufacturers are responsible for ensuring the safety and efficacy of their products, but the level of oversight differs. In the EU, there is greater pre-market regulatory responsibility, whereas in the US, oversight is more focused on post-market compliance [165,167]. In addition, the nature of the raw material used to produce these antioxidant supplements, whose chemical content and biological properties vary significantly depending on the purification method used, makes it difficult to standardize this type of product. To date, only hydroxytyrosol obtained from extra virgin olive oil has an EFSA health claim [168,169].

6. Conclusions

Cardiovascular diseases (CVDs) are the leading cause of death worldwide and include a variety of pathologies such as ischemic heart disease, ischemic stroke, arterial hypertension and others. The incidence of these diseases increases with age, highlighting the need for effective preventive and therapeutic strategies.

Oxidative stress, generated by an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant capacity, plays a central role in the progression of cardiovascular disease. This phenomenon contributes to endothelial dysfunction, inflammation and lipid peroxidation, promoting atherosclerotic plaque formation and tissue damage. Excessive generation of ROS in cardiovascular cells, mediated mainly by enzyme systems such as NOX and other enzymes such as nitric oxide synthase (NOS) and xanthine oxidase (XO), exacerbates oxidative damage in cardiac and vascular tissues.

Plant antioxidants, found in a variety of fruits, vegetables and other plants, have been shown to have significant cardioprotective properties. These compounds can be classified into several groups, including carotenoids, phenolic acids and flavonoids, each with specific mechanisms of action that contribute to their antioxidant effects. Plant antioxidants act by neutralizing ROS, enhancing endogenous antioxidant capacity and modulating various cellular signaling pathways. These mechanisms include regulating the expression of inflammatory mediators and modulating pathways involved in apoptosis and cell prolif-

eration. By reducing oxidative stress and inflammation, plant antioxidants not only prevent cardiovascular damage but also promote tissue repair and functional recovery.

A growing body of evidence suggests that plant antioxidants may be effective adjuncts in the treatment of cardiovascular diseases. Their inclusion in the diet or as supplements may offer a complementary strategy to improve cardiovascular health and reduce the incidence of adverse events. However, it is essential to conduct research focused on optimizing the doses and combinations of these compounds to maximize their therapeutic benefits; conducting clinical trials to support the efficacy of these compounds in humans; evaluating the bioavailability, metabolism and specific effects of each antioxidant in the human body; analyzing the interactions of plant antioxidants with other drugs or treatments; identifying the side effects that could result from their consumption at high doses; and identifying the potential side effects of their use in the treatment of cardiovascular diseases.

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