Flavonoids in Cardiovascular Diseases

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Flavonoids are metabolites of plants and fungus. Flavonoid research has been paid special attention to in recent times after the observation of their beneficial effects on the cardiovascular system. These favorable effects are exerted by flavonoids mainly due to their antioxidant properties, which result from the ability to decrease the oxidation of low-density lipoproteins, thus improving the lipid profiles. The other positive effect exerted on the cardiovascular system is the ability of flavonoids to produce vasodilation and regulate the apoptotic processes in the endothelium. Researchers suggested that these effects, including their anti-inflammatory function, are consequences of flavonoids' potent antioxidant properties, but recent studies have shown multiple signaling pathways linked to them, thus suggesting that there are more mechanisms involved in the beneficial effect of the flavonoids on the human body. This review aims to present the latest data on the classification of these substances, their main mechanisms of action in the human body, and the beneficial effects on the physiological and pathological status of the cardiovascular system.

Keywords: flavonoids ; polyphenols ; cardiovascular disease

1. Introduction

Cardiovascular disease (CVD) is the leading cause of global mortality and morbidity. There has been an increase in mortality among women with cardiovascular disease, which in recent years has exceeded the number of deaths from breast cancer [1]. The most commonly cited non-modifiable cardiovascular risk factors are age and gender. The incidence of cardiovascular events increases with age, on the one hand due to the increase in plasma cholesterol, and on the other hand due to increased arterial stiffness and peripheral vascular resistance [2]. The gender-related risk of CVD depends on age, so the incidence of CVD in men aged under 50 is 3–5 times higher than in women. Over the age of 50, there is a significant increase in the incidence of CVD among women. Other risk factors mentioned in the literature are genetic factors, sedentary lifestyle, obesity, smoking, high blood pressure, diabetes, and dyslipidemia [3].

Flavonoids are an important class of natural substances, with polyphenolic structure, characterized by a general structure consisting of two benzene rings (two phenyl rings and a heterocyclic ring). The three components lead to the formation of the basic structure of flavonoids, that is to say, the flavan nucleus [4]. Flavonoids from plants are synthesized from phenylalanine, which via phenylpropanol will be transformed into 4-coumarate coenzyme A. This process leads to the formation of chalcone, which has structure similar to that of flavonoids and represents a precursor for numerous flavonoids [5][6]. Depending on the enzymes that act on chalcone and on the plant it derives from, two large classes of flavonoids will result: 2-phenylchromen or 3-phenylchromen [7]. The first class includes flavones, flavonols, flavanones, flavan-3-ols, and anthocyanidins, and from the second group, isoflavonoids [8][9].

Flavonoids can be found in fruits, vegetables, nuts, seeds, in coffee, wine, or tea, with significant antioxidant effects associated with various pathologies such as cancer, atherosclerosis, Alzheimer's disease, etc. [10][11]. At the plant level, they are responsible for the defense against oxidative stress, they act as UV filters and protect plants from different biotic and abiotic stresses, function as signal molecules, detoxifying agents and antimicrobial defensive compounds, and they are responsible for the color of fruits or flowers and their aroma. Polyphenols are the most abundant antioxidants in the diet [12]. Their intake is 10 times higher than that of vitamin C and 20 times higher than vitamin E or carotenoids. Through their antioxidant, anti-inflammatory, anti-carcinogenic, and antimutagenic action, they find use in various nutritional, pharmaceutical, medicinal, and cosmetic applications [13]. A large variety of flavonoids was identified and grouped based on chemical structure and degree of oxidation [14].

The amount and composition of polyphenols in plants is different depending on the species, age, portion of the plant, method of cultivation, storage, and geographical distribution [15]. Flavonoids play various roles in the biological activities of plants, animals and bacteria. Environmental factors like soil type, exposure to solar light, rainfall, and the number of fruits growing in a tree directly influence the concentration of polyphenols in plants [7].

A quick review of the Web of Science Database using the keywords ″flavonoids AND cardiovascular disease″ retrieves 139 papers for 2020, from which we selected the ones reporting plant names/flavonoid names in the title. We have reviewed these papers and synthesized them into the table below (Table 1), in order to show the recent trends in flavonoid research.

Table 1. Selection of recently published papers discussing the relationship flavonoids–cardiovascular disease.

Plant	Flavonoids	Action on the Cardiovascular System	Targeted Conditions
Polygonum minus (Persicaria minor)	Myricetin, quercetin, methyl-flavonol	Antioxidant, anti-inflammatory	Atherosclerosis, hypertension, ischemic heart disease
Lentil (Lens culinaris Medik.)	Quercetin, kaempferol	Anticoagulant, anti-platelet	Cardiovascular diseases associated with hyperactivation of platelets
Ajuga Iva (L.)	Naringein, apigenin-7-*O*-neohesperidoside	Antioxidant, anti-inflammatory anti-hypercholesterolemia	Atherosclerosis
Cymbopogon citratus (DC) Sapf.	Tannins, luteolin, apigenin	Vasorelaxation, antioxidant, anti-inflammatory	Hypertension
Anchusa italica Retz.	Rutin, hesperidin, quercetin, kaempferol, naringenin	Anti-inflammatory, antioxidant, anticoagulant	Ischemic heart disease, myocardial infarction
Heliotropium taltalense (Phil.)	Naringenin, pinocembrin, quercetin	Anti-inflammatory, antioxidant, vasorelaxation	Hypertension
Equisetum Arvense L. (Horsetail)	Resveratrol, apigenin, quercetin	Antioxidant, anti-inflammatory,	Hypertension, ischemic cardiac disease
Trichosanthes kirilowii	Luteolin	Hypolipidemic, antioxidant, anti-atherosclerotic	Ischemic cardiac disease, hyperlipidemia, hypertension
Thai Perilla frutescens	Cyanidins, luteolin, phenolic acids	Anti-inflammatory, antioxidant	Ischemic heart disease, hypertension
Abelmoschus esculentus	Quercetin	Anti-inflammatory, antioxidant, hypolipidemic,	Atherosclerosis, stroke, hypertension
Dracocephalum moldavica L.	Tallianine, luteolin, apigenin, diosmetin	Antioxidant	Ischemic heart disease
Moringa oleifera Lam.	Catechin, epicatechin, kaempferol, quercetin	Antioxidant, anti-inflammatory	Hypertension, ischemic cardiac disease

Ephedra herb	Epiafzelechin (flavanol), quercetin, gallocatechin, apigenin, luteolin	Diuretic, anti-inflammatory, hypotensive, antioxidant	Hypertension
Corchorus olitorius Leaf and *Corchorus capsularis*	Luteolin	Antioxidant, hypotensive, diuretic	Hypertension, ischemic cardiac disease

The phenols bioavailability depends on numerous parameters such as the source from which they are administered, whether they are pharmaceutical or nutritional products, digestion, the degree of functionality of the intestinal microflora, absorption, and metabolism [16]. Most polyphenols are present in the form of glycosides. In order to be absorbed, glycosides must be subjected to the action of intestinal hydrolases, as they are hydrophilic and cannot be absorbed by passive diffusion. In contrast, aglycone is absorbed much more easily by passive transport as they are highly hydrophobic [17]. After being modified by different pathways, the rapidly absorbed flavonoids move past enterocytes and reach the liver, where they will be subjected to other metabolic processes, such as glucuronidation, methylation etc. [18] From the liver, part of the metabolites will be distributed in the blood and the other part will be secreted into the bile to participate in the enterohepatic circuit [19].

Certain polyphenols such as soy isoflavone are well absorbed through the intestinal membrane, while others, such as proanthocyanidin found in wine and cocoa or thearubigin, the main polyphenol in black tea, are poorly absorbed [20][21].

In recent years, flavonoids have received a great deal of attention from specialists for the variety of potential benefits they offer. It is a complex and long-term study due to the heterogeneity of molecular structures, but numerous studies have suggested that dietary polyphenols may be beneficial as adjunctive treatment for the prevention and treatment of chronic inflammatory diseases [22][23]. Even though nowadays there are many plants known to possess a high concentration of flavonoids, maybe the best known are the vegetables and fruits extensively used as daily food. The table below presents a series of beneficial effects and composition of foods rich in flavonoids (Table 2) [23][24][25][26][27].

Table 2. Composition and beneficial effects of certain foods rich in flavonoids [23][24][25][26][27].

Food	**Bioactive Compounds**	**Beneficial Effects on Preventing Cardiovascular Diseases**	**Primary Effects**
Tomatoes	Phenols: phenolic acid, flavonoids, carotenoids	Improve metabolic profile (lipid, carbohydrate metabolism), increase bioavailability of nitric oxide and vascular pressure	Antioxidant, anti-inflammatory, antiplatelet, anti-atherosclerosis, anti-hypertensive, antiapoptotic
Garlic	Allicin	Lowers LDL-cholesterol levels, blood pressure, inflammatory response, oxidative stress	Antioxidant, anti-inflammatory, anti-carcinogenic, antibacterial, antiviral, antifungal, antimicrobial
Edible wild fruits	Polyphenols: procyanidin, quercetin, phenolic acid, anthocyanin, carotenoids	Lower LDL-C levels, blood pressure, body mass index, glycosylated hemoglobin and hemoglobin levels, decrease inflammatory response and oxidative stress, improve endothelial function	Antioxidant, Anti-inflammatory, anti-obesity, anti-diabetic

Apples	Lutein, carotenoids, Antioxidant: phlorizin, quercetin, catechin, procyanidin, epicatechin	Improve lipid profile, lower blood pressure, pro-inflammatory cytokines, lipid oxidation, oxidative stress, blood glucose, increase nitric oxide	Antioxidant, antifungal, antioxidant, antifungal, anti-proliferative
Broccoli	Lutein, zeaxanthin, B-carotene, flavonoids	Improves lipid and carbohydrate profile, reduces pro-inflammatory cytokines and markers of oxidative stress	Antioxidant, anti-inflammatory, anti-carcinogenic
Cocoa	Phytochemicals: methylxanthine, proantho-cyanidin, theobromine	Improves insulin sensitivity, lipid profile, reduces blood pressure, inflammatory response and oxidative stress, improves endothelial function	Antioxidant, anti-inflammatory, hypoglycemic, antiplatelet, anti-hypertensive
Grapes	Polyphenols: resveratrol, carotenoids, flavonoids	Improve lipid profile and carbohydrate metabolism, reduce pro-inflammatory cytokines and oxidative stress, increase nitric oxide	Antioxidant, anti-inflammatory, antihypertensive, anti-diabetic
Olives	Phenolic compounds, hydroxy-tyrosol, oleuropein, polyphenols, flavonoids, theanine, quercetin	Improve lipid profile, lower blood pressure, body mass index, inflammatory response and oxidative stress	Antioxidant, anti-inflammatory, anti-hypertensive, anti-obesity

2. Classification of Flavonoids

Natural polyphenolic compound flavonoids are classified into six main subgroups, namely: flavones, flavanones, flavan-3-ols, flavanols, anthocyanidins, and isoflavones [28][29].

2.1. Flavones

Flavones are found in foods such as celery, garlic and chamomile tea, being rich in luteolin [30]. Among the beneficial effects of luteolin, observed in various studies, are the ability to lower blood pressure in hypertensive rats, improve vasodilation in aortic rings, increase the accumulation of cAMP by inhibiting cAMP-specific phosphodiesterase [31]. By activating the cAMP/PKA cascade, nitric oxide levels increase in endothelial cells by activating endothelial nitric oxide synthase. This induces vascular relaxation through nitric oxide, a mechanism regulated by calcium and potassium channels [32].

2.2. Flavonols

Flavonols are found in onions, broccoli, tea and fruit, and are represented by glycosides, namely quercetin and kaempferol [4].

2.2.1. Quercetin

Quercetin exerts its antihypertensive effect by the ability to improve endothelial function, to modulate the renin-angiotensin-aldosterone system (by modulating the mechanism of contraction of smooth muscles in blood vessels) [33], produces vasodilation at renal level that is protein kinase C-dependent, and lowers blood pressure in patients with diabetes or metabolic syndrome [34][35]. Quercetin also decreases oxidative stress in the heart and kidneys [36].

2.2.2. Kaempferol

Kaempferol, a compound of foods such as broccoli, green tea, strawberries, and beans [30], has antihypertensive properties, effects manifested by the action of endothelial nitric oxide [37]. Besides the antihypertensive effect, kaempferol has the ability to reduce albuminuria and proteinuria, being considered a potential candidate in the improvement of these two situations [38].

2.3. Flavan-3-ols

Flavan-3-ols include monomers such as catechin, gallocatechin, epicatechin, and oligomers (proanthocyanidin) [30]. Catechin monomers are found in the form of aglycones (part of a glycoside without carbohydrate content) in apples, pears, cocoa, tea, and grape-based products. It has been shown that catechins have beneficial effects on vascular function and have a cardioprotective effect. Moreover, studies have shown that they have the ability to reduce both systolic and diastolic blood pressure [39][40].

2.3.1. Epicatechin

Epicatechin presents antihypertensive action. Eating epicatechin-rich chocolate helps decrease systolic blood pressure by 4.2 mmHg and diastolic blood pressure by 2.1 mmHg. It has recently been shown to reduce myocardial rigidity in rats with hypertrophic cardiomyopathy [41].

2.3.2. Epigallocatechin-3-gallate

Epigallocatechin-3-gallate abundant in green tea, has anti-inflammatory, antioxidant, and anti-atherogenic action [42].

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