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# Cardiovascular Disease and Nutrition

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## Abstract

Many studies have been published on the relationship between the risk of cardiovascular disease and various nutrients, foods, and eating patterns. Despite the well-accepted concept that diet has a significant influence on the development and prevention of cardiovascular disease, foods considered healthy or harmful have varied over the years. Cardiovascular diseases are one of the main causes of illness and death in Western countries, and cardiovascular drugs are the most commonly used medications. There are two types of factors involved in the development of cardiovascular disease. Some factor can be modified, like lifestyle, diet, environment, or smoking. Others such as genetic factors, gender, history, or age cannot be modified. In this chapter, some food, nutrients, and bioactive compounds that are susceptible to exert beneficial or harmful properties on cardiovascular disease are presented.

**Keywords:** nutrition, cardiovascular diseases, CVR, omega-3

## 1. Introduction

Diet and healthy lifestyle are the best tools to have good cardiovascular health. This relationship is so direct because the majority of cardiovascular diseases have their origin atherosclerotic plaque, hypertension, and obesity. These three cardiovascular risk factors are directly related to dietary habits and lifestyle. It is widely demonstrated from the scientific point of view that dietary habits influence cardiovascular health. There are diets such as the Dietary Approaches to Stop Hypertension (DASH) as the Mediterranean diet, which are clear examples of heart-healthy diets. However, there are discrepancies with regard to what are the components of a heart-healthy diet. There are foods that are considered healthy for the heart in all editions of food guides and recommendations, among which we can find fruits, vegetables, and whole grains, which have always been considered fundamental for health, and there are other foods that can currently be considered heart-healthy, since there are numerous studies that this is supported, such as virgin olive oil, pulses, fish, and nuts (especially nuts). This chapter focuses on the most recent food evidence (e.g., fruits and vegetables) and nutrients (such as fiber and omega-3) considered to be cardio-healthy today and as a counterpoint, the scientific clairvoyance that exists on those foods considered less heart-healthy because they are considered to increase cardiovascular risk (eggs, dairy products, meats, and salt).

## **2. Cardiovascular disease and its association with dietary patterns and nutrients**

### **2.1 Meta-analysis related to dietary patterns and cardiovascular disease**

Nowadays, most of the evidence supporting the beneficial and harmful effects of food and nutrients is based on observational epidemiological studies. The information of the present section aims to elucidate the current knowledge about dietary patterns and cardiovascular problems. The information is divided in food groups, in order to clarify as most as possible.

Fruits and vegetables have traditionally been considered promoting health foods. This is due to the association between the greater consumption of these products and the reduction of the risk of suffering chronic diseases, such as cardiovascular disease (CVD). Consequently, the current dietary guidelines recommend an increase in the consumption of fruits and vegetables up to five servings a day [1].

Current evidence is largely based on prospective cohort studies showing uniform associations between increased consumption of fruits and vegetables and reduced risk of both coronary artery disease (CAD) and stroke. However, these studies do not have the highest level of scientific evidence. In contrast, the number of controlled intervention trials (which provide a higher level of scientific evidence) in which the relationship between fruit and vegetable consumption and clinical endpoints has been investigated is unusual. However, the results of these studies show associations between increased consumption of fruits and vegetables and improvement of blood pressure and microvascular function. Meanwhile, associations with plasma lipid concentrations, risk of diabetes mellitus (DM), and body weight have not yet been definitely recognized [2].

The dietary habits of English population between 2001 and 2013 have been studied and reported in a recent study. It was observed that the consumption (seven daily servings of fruits and vegetables) reduces the specific risks of death from cancer and heart disease in 25 and 31%, respectively [3]. This report also showed that vegetables have a significantly greater beneficial health effect than fruits. It is important to emphasize that, whatever the starting point, the data indicate that the highest consumption of fruits and vegetables always provides a benefit. In addition, many confounding factors, such as poor access to fresh fruits and vegetables for people with preexisting health conditions or complicated lifestyles or those living in disadvantaged areas, affect the experimental approach used by these researchers. In conclusion, as reported by Berciano and Ordovás [2], the evidence indicating consumption of fruits and vegetables as dismissal of the risk of CVD is largely limited to observational epidemiology. Therefore, new intervention studies will be necessary to establish the existing real relationship.

Fruits and vegetables are very rich in both soluble and insoluble fibers, which structural and functional characteristics may vary greatly. Insoluble fibers, such as cellulose and lignin, are non-hydrolyzable and hardly undergo fermentation, while soluble fibers, such as pectin or inulin, are not hydrolyzed in the stomach but can be fermented by the gut microbiota. The main physiological effect associated with the consumption of insoluble fibers is the reduction of intestinal transit time which allows water retention, promotes an increase in fecal mass, and facilitates the movement of food through the intestine, due to mechanical stimulation of the intestinal walls. The distension caused also increases the feeling of fullness and can contribute to reducing caloric intake [4].

On the other hand, the main physicochemical properties of the soluble fibers that characterize their effects are viscosity, the ability to form gels, and fermentability. The increase in viscosity slows gastric emptying (which contributes to satiety)

and increases transit time. This helps to produce the stabilization of the glucose and insulin response and reduces the absorption of dietary cholesterol [4].

Regarding CVD, the most important property of dietary fiber is fermentability that reduces the concentration of low-density lipoproteins (LDL) in the blood. The mechanism is mediated by short-chain fatty acids produced by colon bacteria. Apart from this effect, there are other important considerations related to the lymphocyte activation, the inhibition of cell proliferation and the anti-inflammatory effects and the bile acid binding activity exerted by the dietary fiber, which act as a kidnapper [5]. Despite knowing the different properties and effects on health that may have the various types and origins of fiber, most studies have provided insufficient data, which prevents an independent assessment of the associated risks of disease. However, total fiber intake is uniformly associated with a small reduction in the risk of CVD, coronary disease (CD), and stroke [6].

All existing reviews conclude that diets rich in fiber are significantly associated with lower risk of stroke, CVD, and CD. This inverse association reinforces what is indicated in the current guidelines, which recommend an increase in fiber consumption, although studies that have described results related to fractions of fiber are too scarce to establish specific recommendations on soluble/insoluble fiber and the types of origins of those fibers. Dose-response analyses have identified cutoff values that have not been validated and appear to show wide differences between different types of fiber. The broader study on this topic indicates that the existence of a threshold effect has not been verified and that the message to be retained must be rather than the greater the consumption of fiber, the greater the protection [2, 5, 6].

In the last years, coffee has been relegated to the background with the boom in tea consumption. Green tea is considered a healthy drink and consumed worldwide and has been attributed various beneficial effects to its regular intake, such as reducing the risk of suffering from diseases ranging from certain cancers to dementia and obesity. With regard to CVD, regular consumption of green tea has been associated with small reductions in CVD risk factors, such as LDL and blood pressure, which may have clinical relevance [7]. However, the number of studies reviewed is too low to be able to draw definitive conclusions, and there is a significant lack of long-term follow-up data and cardiovascular events to assess the long-term effects of green tea consumption.

Similar to green tea, wine and coffee are two beverages containing a wide variety of phytochemical substances that have been associated with a protective effect against heart disease. Although these compounds, mostly polyphenols, have been intensively studied over the past two decades, the main effects of wine (or alcoholic beverages in general) and coffee consumption continue to be attributed to ethanol and caffeine, respectively [8]. Recent reviews indicate that beer and especially red wine [7, 8] are associated with a greater reduction in the risk of CVD due to its high polyphenol content [9, 10]. The protective effects of coffee against CVD are not well established. In fact, a moderate consumption of coffee (two to four cups a day) has not shown any adverse effects in the long term [2]. However, it is well known that an excessive consumption of caffeine leads to hypertension, and in particular unfiltered coffee contributes to elevate the serum concentration of LDL, total cholesterol, and triglycerides [11]. It is important to note that the mentioned effects are subject to interpersonal differences, since there are many genetic polymorphisms that are known to affect different enzymes that are involved in their metabolism [2].

Regarding animal food, blue fish (like other many high-fat foods), such as olive oil, was on the list of “unhealthy” foods because of its high-fat content. However, from the earliest 1970s, omega-3 fats from blue fish were reported as beneficial to health and especially to health related to CVD [12]. However, there are still wide discrepancies regarding their effects on optimal doses, as well as their relationship



with omega-6 fatty acids or other components of the diet. In fact, the results of the published randomized clinical trials (a total of 48 studies that included 36,913 individuals) have not shown a reduction in the risk of total mortality or the set of cardiovascular events in people who take supplementary omega-3 fats [2]. Consequently, despite the known effect of omega-3 fat on plasma triglyceride concentrations, there is no unequivocal evidence that omega-3 fats in the diet or supplements modify total mortality or the set of cardiovascular events. In fact, a recent study [13] raises certain doubts about the validity of the premises used to support the initial hypothesis on omega-3 and CVD [14].

Continuing with foods of animal origin, one of the most ancient are eggs, which were introduced in the diet prior to the appearance in the evolution of *Homo sapiens*. It is not surprising that eggs are an important source of nutrients such as proteins, unsaturated fats, fat-soluble vitamins, folate, choline, and minerals. The possible counterpoint derives from the fact that, on average, an egg contains 200 mg of cholesterol, one-third of the recommended daily amount. The rationale for this recommendation continues to be linked to the diet-heart hypothesis. In contrast, epidemiological evidence has consistently shown that it is unlikely that the consumption of one egg a day has any significant impact on the risk of CVD in healthy people.

Similarly, the relationship between egg consumption and the clinically relevant elevation of plasma cholesterol concentrations is too old. Newer studies revealed the actual hypothesis about egg consumption. One of the most recent studies is the HELENA study, showing that egg consumption was not associated with the lipid profile, adiposity, insulin resistance, blood pressure, good cardiorespiratory function, or the integrated CVD risk score [15]. In general, current evidence supports that egg consumption is not associated with risk of CVD, CD, or cardiac death in the general population and may even have a protective value against hemorrhagic stroke [16].

In contrast, egg consumption may be associated with an increase in the incidence of type 2 diabetes mellitus in the general population and the comorbidity of CVD in diabetic patients [17]. Consequently, it seems that the most recent results exonerate the eggs from their intended role of significant dietary factor of the CVD epidemic. In this regard, it is important to bear in mind that the absorption of cholesterol has great interindividual differences, and only a fifth of the population can respond with increases in plasma cholesterol to the presence of cholesterol in the diet [17]. Therefore, it is important to identify the genetic determinants of this variability.

Regarding meat, scientific literature has been focused on the relationship between diet meat, CVD, and total mortality, which have led to a situation less clear than in the case of egg consumption. What seems to be clear is the association between red meat consumption and total mortality related to CVD, as well as the risk of CVD, ischemic stroke, and type 2 diabetes mellitus.

However, this association can often be caused by the consumption of processed meats and not always by fresh red meat. In fact, it has been pointed out that the harmful effects observed by processed meat may be related to other components, such as sodium, nitrites, heme iron, and L-carnitine. For example, the effects of elevating blood pressure associated with the high sodium content of processed foods could explain the increased risk of people sensitive to salt. There is recent evidence reporting that trimethylamine, phosphatidylcholine, choline, and L-carnitine in processed and red meat can promote CVD [18]. The scientific literature indicates that the consumption of unprocessed red meat and processed red meat is not beneficial for cardiometabolic health. In fact, it can be observed that clinical and public health guidelines prioritize above all the reduction of consumption of processed meat.

Finally, other foods demonized in recent years are dairy products, in part due to their relatively high content of saturated fats and cholesterol. Consequently, after having occupied for decades a prominent place among recommended foods, dairy products also suffered the consequences of the “non-healthy anti-saturated fat fever.” However, this group of foods had a relatively easy way out, and the dairy industry started to produce a whole range of low-fat products. As observed by Berciano and Ordovás [2], these products already have enough time on the market to evaluate them regarding the intrinsic benefits in terms of CVD compared to more traditional varieties.

The comparison between fatty and non-fatty dairy products is important because the relationship between CVD and saturated fats may not be as simple as initially thought. That fact can be due to multiple reasons.

First, not all fats would be the same and were, in origin, classified as good (unsaturated) and bad (saturated). However, actual knowledge seems to discuss that theory. In fact, it was appreciated that “healthy” fats as polyunsaturated fats omega-6 could not be as good as thought. Contrariwise, some of the “bad fats” could be healthy (the case of fats saturated from dairy foods) [19].

Second, the replacement of saturated fats in the diet with simple carbohydrates has led to an increase in obesity and health complications. Therefore, it is probable that some of the adverse effects associated with saturated fats in the past must be factors other than saturated fats. Thus, in recent times the relationship between dairy foods and the risk of CVD has been revisited on multiple occasions [19]. In an interesting study, Huth and Park [20] reviewed the published evidence on milk products with milk fat content and cardiovascular health. The results of this review indicate that most of the observational studies found no association between the consumption of dairy products and increased risk of CVD, CD, and stroke, regardless of the concentration of fat in the milk.

In general, it can be concluded that the consumption of dairy products provides protection against CVD or, at least, has no adverse effects. Consequently, the existing data support the concept that milk and low-fat milk products contribute to the prevention of hypertension and reduce the risk of stroke and, potentially, other CVD events. Another review revised the scientific literature related to observational studies on the relationship between the fat of dairy products and high-fat dairy foods, obesity, and cardiometabolic disease [21]. Of a total of 16 studies, in 68% there was an inverse association between the consumption of high-fat dairy products and the parameters of assessment of adiposity. In fact, studies conducted to examine the relationship between the consumption of high-fat dairy products and metabolic health has described an inverse association or no association [21]. Consequently, these results indicate that milk fat or high-fat dairy foods do not contribute to obesity or cardiometabolic risk and imply that the consumption of high-fat dairy products within the usual dietary patterns has an inverse association with the obesity risk.

### **3. Oxidative stress and antioxidants**

It is commonly accepted by scientific community that oxidative stress is within the base of the etiology of cardiovascular diseases. However, the understanding of the role of reactive oxygen and nitrogen species (RONS) has evolved somewhat. They are not further seen in a whole negative perspective, but current knowledge supports that they are generated as part of normal metabolism, as well as a defense mechanism of cells from immune system to combat against infections; besides, they are implicated in intracellular signaling pathways [22]. Hence, low concentrations seem protective by triggering defense mechanisms that prevent cellular damage [23].

The levels of RONS are counteracted by cellular defenses in the form of antioxidants, to maintain an adequate balanced oxidative status. However, when an imbalance in the production/elimination of these reactive species occurs, a specific cellular function can be altered [24].

The excess of free radicals attacks macromolecules, mainly polyunsaturated fatty acids (PUFA) of cell membranes [25] that leads to cell death and conducts to different pathological conditions, as vascular diseases. Oxidation of PUFA generates fatty acid radicals, which adds oxygen to form fatty acid peroxy radicals. These radicals can further oxidize PUFA molecules and initiate new chain reactions, producing lipid hydroperoxides that can produce more radical species [25].

Oxidative stress contributes markedly to endothelial dysfunction, with a reduced activity of nitric oxide (NO). NO induces vasodilation, inhibits platelet aggregation, prevents LDL oxidation, and decreases production of proinflammatory cytokines. Free radicals oxidize and inactivate NO impeding its protective action. Besides, vascular cells generate reactive species principally by NADPH oxidase pathway [26]. The increased NADPH oxidase activity and the decrease in antioxidant enzyme defenses and cysteine/cystine redox potential increase the risk of cardiovascular disease [22].

Free radicals induce the expression of adhesion molecules in vascular wall, as intercellular adhesion molecule 1 (ICAM-1), what activates the migration of monocytes and T cells to the vessel [27] and helps to their attachment to the endothelial surface. The oxidation of low-density lipoproteins (LDL) by free radicals is followed by their uptake by macrophages. Macrophage cells are converted into foam cells, accumulating in the wall and further activating cells from the immune system, perpetuating the damage. This is the hallmark of initiation of the process of atherosclerosis.

These oxidative changes can be prevented/ameliorated or mitigated by antioxidants. From a chemical point of view, antioxidants are molecules able to react with oxidative species, as free radicals, thus preventing oxidation of a third molecule. Based on their nature, antioxidants have been classified as enzymatic and nonenzymatic forms. Enzymes that break down and remove free radicals include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). SOD converts the superoxide radical  $O_2^{\cdot-}$  into  $O_2$  and  $H_2O_2$  in the presence of metal ion cofactors as copper, zinc, or manganese. CAT converts  $H_2O_2$  in  $H_2O$  and  $O_2$ , and GPx converts  $H_2O_2$  to  $H_2O$  and fatty acid hydroperoxides to their corresponding alcohol forms. All of them show synergistic effect and play the major role in prevention of oxidative damage [25].

Low molecular weight antioxidants react due to one-electron reactions with free radicals and possess a chemical structure able to delocalize the one electron that resulted. They form relative stable radicals by delocalization of the unpaired electron within their structure. The term includes both endogenous (glutathione, uric acid, bilirubin) and exogenous antioxidants from dietary origin (ascorbic acid,  $\alpha$ -tocopherol, carotenoids, and polyphenols, among others).

$\alpha$ -Tocopherol is the main antioxidant in lipid environment, as it scavenges lipid peroxides in cell membranes and lipid particles, including low-density lipoprotein (LDL), forming an  $\alpha$ -tocopheroxyl radical. It intercepts lipid peroxy radicals and terminates lipid peroxidation reactions [25].

Vitamin C has been considered the most important water-soluble antioxidant in extracellular environment. It scavenges various RONS and regenerates the  $\alpha$ -tocopheroxyl radical back to tocopherol [28]. It forms ascorbyl radical, and two molecules react rapidly to produce one molecule of ascorbate and one molecule of dehydroascorbate.

Dietary polyphenols behave as scavenging antioxidants due to their chemical structure of benzo- $\gamma$ -pyrene cycle. They are able to delocalize the unpaired electron formed after the reaction with free radicals, as they possess an ortho-dihydroxy



structure in the B-ring and a [2, 3] double bond in conjugation, as well as the 4-hydroxyl function in C ring. Besides, they can chelate metal ions implicated in the generation of free radicals [29].

Epidemiological studies have shown that a regular intake of fruits and vegetables, rich in antioxidants, reduces the risk of degenerative diseases and cancer [30]. Animal models and in vitro studies performed with particular antioxidants have supported this point of view. There is a generalized and accepted idea that the excessive production of free radicals causes damage and that the scavenging of these radicals is health protective. Hence, a number of human clinical trials on different populations with antioxidant supplementation were performed some decades ago. However, they showed non-antioxidant effects or even negative outcomes [31]. A meta-analysis of more than 300,000 individuals showed no prevention of cardiovascular disease after supplementation with vitamins E, C, and A and an increased risk of cancer in smokers with  $\beta$ -carotene supplementation [32]. Antioxidants have failed to prevent or delay the development of atherosclerosis [33, 34].

It must be pointed out that most in vitro and animal models used pharmacological doses of antioxidants in imposed oxidative stress conditions, far from the real physiological situation [35].

The contradictory results obtained in the human intervention studies prompted the investigators to undertake a better understanding toward the mechanisms of antioxidants to maintain a balanced redox status.

The classic perception of antioxidants as free radical scavengers has evolved to their action on cell signaling to stimulate enzymatic antioxidant protection. In fact, most free radicals and electrophile species are removed through enzymatic reactions using reducing power in the form of NADPH, GSH, and reduced thioredoxin [36]. Moreover, free radicals are extremely reactive within the cell, and the most effective protection mechanism is to prevent their formation, by enzyme-catalyzed reactions, rather than trying to scavenge them once formed. Catalase dismutates  $H_2O_2$  to  $H_2O$  and  $O_2$ , and peroxidase reduces hydroperoxides using GSH. The only possible biologically relevant antioxidant able to react with hydroxyperoxyl radicals is  $\alpha$ -tocopherol [37]. Its subsequent radical formed, and the  $\alpha$ -tocopheroxyl radical is reduced back by ascorbic acid [25].

Cells are able to adapt its redox potential increasing antioxidant enzymes, leading to transcription factors that act as redox sensors. Some antioxidants possess hormetic actions by upregulating the expression and activity of antioxidant defense enzymes, as well as by activating endothelial nitric oxide synthase (eNOS) that increases NO production and hence ameliorates vascular tone. The reaction of phytochemical antioxidants with free radicals gives oxidized products that are involved in signal transduction pathways. The last consequence is the activation of enzyme antioxidant activity and repair systems. Enzyme-catalyzed reactions occur at higher reaction rates than free radical scavenging by exogenous antioxidants.

One of the main pathways involved is nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 is linked to the protein Keap 1 and remains inactive in the cytosol until Keap1 is oxidized. Nrf2 then translocates to nucleus where it activates ARE genes. The activation of the Nrf2 transcription factor and the antioxidant response element (ARE) to which Nrf2 binds conducts to the transcription of genes encoding phase II detoxification enzymes.

Reports about the activation of this signaling pathway by compounds within the diet are increasing recently. Dietary soy has shown to inhibit atherosclerotic lesion progression by a mechanism that involves this Nrf2 gene transcription. Other phytochemicals include curcumin from turmeric [38], diallyl sulfide from garlic [39], isothiocyanates as sulforaphane from broccoli [40], and polyphenols from apple [41].



These mechanistic studies have been performed with pure compounds, and it is conceivable that supplementation with antioxidants in concentrations that saturate this system can exert none or even harmful effects [24]. Hence, it is advisable to provide an adequate level of antioxidants by nutritional intake to regulate the antioxidant system in a physiological basis.

#### **4. Bioactive compounds**

“Bioactive compounds” are extranutritional constituents that typically occur in small quantities in foods. Epidemiological studies have demonstrated that nutritional habits, like those based on high consumption of foods rich in bioactive substances (natural products derived from plants, marine organisms, and animals), have been associated with a longer life expectancy and a significant decrease in the incidence and prevalence of several chronic diseases with inflammatory basis, such as CVD [42].

These bioactive compounds possess a wide range of biological activities including antitumor, anti-inflammatory, anticarcinogenic, antiviral, antimicrobial, antidiarrheal, antioxidant, and other activities [43].

Dietary supplementation with bioactive natural compounds demonstrated that lipid-lowering effects (cholesterol synthesis inhibitors, intestinal cholesterol absorption inhibitors, and LDL-C excretion stimulants) are currently supported by the international guidelines for CVD prevention and some international expert panels [44].

##### **4.1 Omega-3**

The functions of the fatty acids are diverse. In addition to their energetic value, they are also part of the phospholipids found in the membranes of the body's cells and determine in a greater or lesser extent the structure and functionality of the cell. Such functionality refers to aspects like fluidity and permeability, lipid peroxidation, etc. [45]. Experimental, epidemiological, and interventional studies have demonstrated the beneficial cardiovascular effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have anti-atherosclerotic, antithrombotic, antiarrhythmic, and anti-inflammatory effects.

Food contains omega-3 fatty acids in three main active forms: eicosapentaenoic acid (20: 5 omega 3, EPA), docosahexaenoic acid (22: 6 omega-3, DHA) and alpha-linolenic acid (18: 3 omega-3,  $\alpha$ -ALA). EPA and DHA forms can be found in fish oils, fish that mainly live in cold waters such as salmon, tuna, and sardines, among other varieties. EPA, DHA, and ALA are essential fatty acids, and they need to be ingested in the diet, since the body cannot synthesize them [46].

In a study, it was showed that the intake of EPA and DHA is inversely related to cardiovascular risk in a dose-dependent manner up to about 250 mg/day in healthy populations, and the intake of 1 g/day is associated with a marked protection from a sudden cardiac death [47]. The daily recommended intake of omega-3 fatty acids varies from 250 mg to 1 g of EPA and DHA.

##### **4.2 Polyphenols**

Polyphenols are bioactive compounds that can be found mostly in foods like fruits, cereals, vegetables, dry legumes, and chocolate and beverages such as coffee, tea, and wine. They are extensively used in the prevention and treatment of cardiovascular disease (CVD) providing protection against many chronic illnesses [48].

Polyphenols can regulate cellular lipid metabolism, vascular and endothelial function, hemostasis, as well as platelet function, which represent primary

conditions for atherosclerotic plaque formation and development. The cardioprotective effects of polyphenols have been linked mainly to its antioxidant properties; however, recent findings attribute its anti-atherosclerotic potential to modulate simultaneous signaling and mechanistic pathways [42]. Recently, the PREDIMED study reported that dietary polyphenols intake such as extra-virgin olive oil and nuts were associated with improved CVD risk factors and decreased inflammatory biomarker levels in high-CVD-risk participants [49].

Moreover, polyphenols alter hepatic cholesterol absorption, triglyceride biosynthesis and lipoprotein secretion, the processing of lipoproteins in plasma, and inflammation [48]. A recent study showed that polyphenols intake decreased blood pressure (BP), increased plasma high-density lipoprotein (HDL) and decreased the inflammatory biomarkers of CVD, including vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), IL-6, TNF- $\alpha$  as well as MCP-1. Treatment with quercetin ameliorated the high-fat diet-induced MetS such as abdominal obesity, cardiovascular remodeling, and liver complications in rats by increasing the expression of Nrf2, HO-1, and carnitine palmitoyltransferase 1 (CPT1) and decreasing NF- $\kappa$ B [50].

Finally, it has been reported that the effects of polyphenols on human health depend on the amount consumed and on their bioavailability.

### 4.3 Phytosterols

Phytosterols are bioactive compounds found in foods of plant origin, which can be divided into plant sterols and plant stanols. Food sources of phytosterols include vegetable oils, mainly corn (909 mg/100 mL), sunflower (411 mg/100 mL), soybean (320 mg/100 mL), and olive (300 mg/100 mL); oleaginous fruits such as almonds (183 mg/100 g); cereals like wheat germ (344 mg/100 g) and wheat bran (200 mg/100 g); and in addition fruits and vegetables, such as passion fruit (44 mg/100 g), orange (24 mg/100 g), and cauliflower (40 mg/100 g) [51].

Clinical studies consistently indicate that the intake of phytosterols (2 g/day) is associated with a significant reduction (8–10%) in levels of low-density lipoprotein cholesterol (LDL-cholesterol). A typical Western diet contains approximately 300 mg of sterols and 30 mg of plant stanols, while vegetarian diets can achieve a higher content (300–500 mg/day). Phytosterols intake based on regular diets is considered too low to achieve their recommended daily intake -which are able to present therapeutic effects on LDL-cholesterol reduction-, (~2 g/day), and the consumption of foods enriched with phytosterols or, alternatively, the use of supplements of phytosterol are generally required [52].

In the last decades, purified plant sterols or stanols have been added to various food items to obtain functional foods with remarkable hypocholesterolemic activity. A daily intake of plant sterols or stanols of 1.6–2 g/day, incorporated in these foods, is able to reduce cholesterol absorption from the gut by about 30% and plasma LDL-cholesterol levels by 8–10% [53].

Most guidelines and consensus on the treatment of dyslipidemia and/or prevention of CVD recommend the intake of phytosterols in the amount of approximately 2 g/day with the goal of reducing LDL-cholesterol by approximately 10%, in association with lifestyle changes [54].

### 4.4 Hydroxytyrosol

Hydroxytyrosol, 2-(3,4-dihydroxyphenyl)-ethanol (OHTYR), is a phenolic compound present in the fruit and leaf of the olive (*Olea europaea* L.), which belongs to the family Oleaceae, comprising species distributed throughout the temperate

regions of the world, and essentially localized in the Mediterranean basin. Another natural source of OHTYR is red wine [55]. In fact, daily intake of hydroxytyrosol in the Mediterranean area would be 2 mg (considering the maximum 50 mg/day). This amount would be insufficient to reach the recommended amount of 5 mg to develop the benefit of protection of LDL particles from oxidative damage [56].

Numerous human and animal studies have shown that olive polyphenols, particularly hydroxytyrosol, can improve blood cholesterol profiles and reduce the risk of potentially lethal thrombosis [57]. Hydroxytyrosol can be considered antithrombotic, since it significantly reduces platelet aggregation [58].

Various authors support the potential beneficial effects of hydroxytyrosol in atherogenesis through the reduction of LDL oxidation. In addition to hydroxytyrosol, oleuropein has also been shown to effectively inhibit LDL oxidation induced by copper sulfate [59].

#### **4.5 Melatonin**

Melatonin (N-acetyl-5-methoxytryptamine) is a neuroendocrine hormone, which is synthesized primarily by the pineal gland. The synthesis and secretion of melatonin are regulated by light intensity [60]. Melatonin-rich foods include various food components from both animal and plant origins such as chicken, lamb, pork, cow milk, strawberries, tomatoes, olives, grapes, wines, cereals, and cherries. Interestingly, melatonin concentrations are significantly higher in plants than in animals [61].

Importantly, recent research suggests that melatonin plays an important role in various cardiovascular diseases, including myocardial ischemia-reperfusion injury, atherosclerosis, hypertension, heart failure, drug-induced myocardial injury, pulmonary hypertension, vascular diseases, valvular heart diseases, and lipid metabolism.

Early experiments showed that treatment with melatonin can improve dyslipidemia. In patients with nonalcoholic fatty liver disease, treatment with melatonin (2 × 5 mg/day) for 14 months significantly reduced levels of triglycerides and LDL-cholesterol (LDL-C) compared with controls [62].

Yang et al. [63] demonstrated that melatonin reduces flow shear stress-induced bone marrow mesenchymal stem cell injury by acting on melatonin receptors and the adenosine monophosphate-activated protein kinase/acetyl-CoA carboxylase signaling pathway. These findings suggest that targeting melatonin relating signaling in tissue-engineered heart valves may be an effective strategy in treating valvular heart disease.

Melatonin may improve vascular dysfunction by affecting epigenetic regulation. In mice generated with assisted reproductive technologies, treatment with melatonin resulted in decreased arterial hypertension, which was thought to be due to its effects on normalizing nitric oxide levels by preventing impaired methylation of endothelial nitric oxide synthase [64].

Borghi and Cicero [65] confirmed the blood pressure (BP)-lowering effects of melatonin. It was shown that patients treated with melatonin (2–5mg/day for 7–90 days) had a decrease in nocturnal SBP as well as DBP. Additionally, it was demonstrated that the effect of melatonin on decreasing BP was most pronounced from 3:00 am to 8:00 am [66].

Pulmonary hypertension is a disease characterized by elevated pulmonary arterial pressure, which leads to right ventricular hypertrophy and failure. Various authors reported that treatment with melatonin alleviated right ventricular hypertrophy and dysfunction and also reduced interstitial fibrosis and plasma oxidative stress in a rat model of pulmonary hypertension [67].

As an inexpensive and well-tolerated drug, melatonin may be a new therapeutic option for cardiovascular disease [54].

## 5. Conclusions

There is a clear relationship between diet and cardiovascular health. A heart-healthy diet should contain fruits and vegetables, which are rich in fiber and bioactive compounds. Foods rich in omega-3 fatty acids such as nuts or blue fish should not be missing from this diet. There is no scientific evidence relating egg or dairy products consumption with increased cardiovascular risk (CVR). In fact, dairy products protect against CVR. Finally, consumption of processed meats is related to increased CVR, due to its high salt content. In fact, dietary guidelines recommend the reduction consumption of these processed meats.

On the other hand, given that oxidative stress is the basis of CVD, a diet rich in antioxidants may be useful in prevention. Among the antioxidants we must highlight the  $\alpha$ -tocopherols, vitamin C, and the polyphenols present in fruits and vegetables. However, supplementation has not been shown to have preventive effects on CVD.

Both omega-3, polyphenols, and phytosterols have been shown to decrease CVR factors and inflammatory markers in patients with elevated CVR.

Finally, we must highlight the hydroxytyrosol and melatonin, which are involved in the reduction of LDL oxidation and in the improvement of dyslipidemia, respectively.

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## Conflict of interest

The authors declare that they have no conflict of interest.

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