# 2. Benefits of polyphenol intake on the cardiovascular risk parameters

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**Abstract.** Polyphenols are a large and heterogeneous group of compounds widely distributed in fruits, vegetables, cereals and their products such as coffee or wine. These bioactive compounds can ameliorate our health by improving certain risk factors, especially the cardiovascular ones. Thus, many investigations have focused on the effects of some polyphenols and polyphenol-rich foods on cardiovascular and other chronic diseases.

## Introduction

Cardiovascular diseases (CVD), including coronary heart disease, cerebrovascular disease, rheumatic heart disease and other disorders of the heart and blood vessels, are the leading cause of mortality and disability in developed countries. According to the World Health Organization (WHO), 31% of all deaths in the world are attributed to CVD, and more than 75% occur in low and middle-income countries [1]. Some risk factors for CVD

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are intrinsic and cannot be modified: sex, age, race and genetic predisposition. However, many of them are related to lifestyle and dietary habits and they are also related to each other: stress, obesity, type-2 Diabetes Mellitus (DM) or insulin resistance, dyslipidemia, and hypertension (Fig.1). In addition to these classic risk factors, there are other non-classic factors including homocysteine, fibrinogen, lipoprotein(a), low-density lipoprotein (LDL) particle size and high-sensitivity C-reactive protein (CRP) [1]. Preventive measures such as smoking cessation, following a healthy diet, being physically active, and regular screenings may help to lower cardiovascular risk [2]. In fact, prevention, even more than treatment, is a priority for the public health agencies, which make huge efforts to raise awareness in the population with the aim of reversing this trend [3].

The Mediterranean Diet (MedDiet), as well as other diets rich in fruits and vegetables such as the Dietary Approaches to Stop Hypertension (DASH) dietary pattern, the US Department of Agriculture (USDA) food pattern, or the American Heart Association (AHA) diet, are an effective way to reduce cardiovascular risk factors due to their high content in vitamins, minerals, fiber, and mono and polyunsaturated fatty acids, and other bioactive compounds [4]. The latter, also known as phytochemicals or phytonutrients, have the capacity to alter biochemical reactions and consequently affect human health [5]. Polyphenols are one of these bioactive compounds. They are a large and heterogeneous group of molecules mainly found in fruits, vegetables, cereals and their products. Up to now, hundreds of different polyphenolic structures have been described in many foods and beverages. Polyphenols have received great attention among nutritionists, consumers and researchers since it has been proved that they have beneficial effects on our health. However, due to the great variety of existing structures, different polyphenol subgroups may differ significantly in stability, bioavailability and physiological functions related to human health. Thus, it is difficult to study their health effects, their bioavailability or their mechanisms of action. For this reason, many studies have focused only in one polyphenol group or even in one polyphenol. Globally, polyphenols seems to improve certain CVDs risk factors such as insulin resistance, inflammation biomarkers, or blood pressure (BP), among others [6]. Additionally, polyphenols have been associated to a decreased risk of certain cancers, neurodegenerative diseases, diabetes and osteoporosis [7].

In this chapter, we summarize recent findings about the effects of polyphenol and polyphenol-rich foods intake on cardiovascular risk factors, especially BP and dyslipidemia.
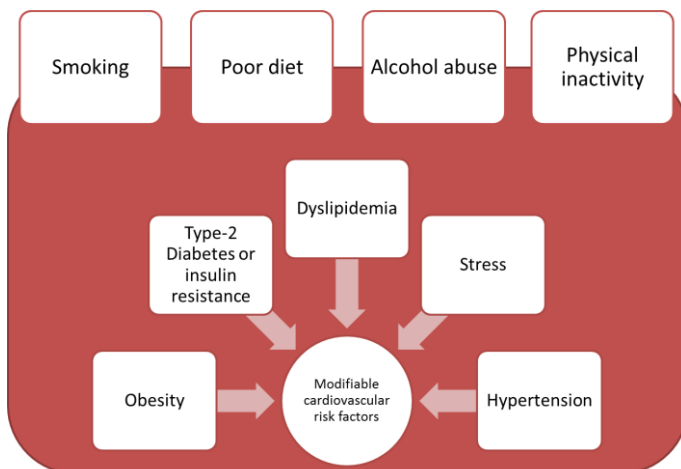
**Figure 1.** Modifiable cardiovascular risk factors.

## 1. Polyphenols: General structure and classification

Polyphenols are one of the most numerous and widely distributed groups of natural products in the plant kingdom. Since polyphenols are secondary metabolites of plants, they are naturally found in fruits, vegetables, cereals and beverages, mainly coffee, tea, wine, fruit juices and beer [8]. This group of compounds constitutes the main source of antioxidants in our diet. Total dietary polyphenol intake is estimated to be around 1 g/day, 10 times higher than that of vitamin C and 100 times higher than intakes of vitamin E and carotenoids [9].

More than 8000 phenolic structures are currently known. The structure of polyphenols consists of at least one aromatic ring carrying one or more hydroxyl moiety. The diversity and wide distribution of polyphenols in plants have led to different classifications, for instance, by their source of origin, biological function, or chemical structure [8]. However, the most common way to categorize them by the chemical structure of the aglycones (according to the number of phenol rings they bear and the structural elements that bind these rings). This broadly accepted classification divides polyphenols into two main groups: flavonoids and nonflavonoids [6].

Flavonoids have a C6-C3-C6 structure, consisting on a skeleton of two benzene rings (A and B) connected by a three-carbon chain forming a closed

pyran ring with the benzene A ring. Flavonoids are divided in subgroups according to the oxidation of the central ring and the type of substituents in the heterocyclic ring. These subgroups are flavones, flavonols, flavan-3-ols (and their polymeric forms, proanthocyanidins), flavanones, anthocyanidins, and isoflavones (Fig. 2).

The nonflavonoid group is classified according to the number of carbons they possess, and include phenolic acids, stilbenes, lignans and other polyphenols that are only found in smaller amounts such as simple phenols, hydrolysable tannins, acetophenones, phenilacetic acids, cinnamic acids or seicoiridoids. Phenolic acids comprise hydroxycinnamic acids, hydroxybenzoic acids, hydroxyphenylacetic acids, and hydroxyphenylpropanoic acids [10].

Besides presenting a huge variety of structures, polyphenols are usually attached to various carbohydrates and organic acids, as well as to other polyphenols. In plants, they are usually glycosylated, mainly with glucose or rhamnose and, less frequently, to galactose, arabinose, xylose, glucuronic acid or other sugars (Fig. 3). The number of glycosyl moieties usually varies from one to three, but can be even higher in some cases [11].
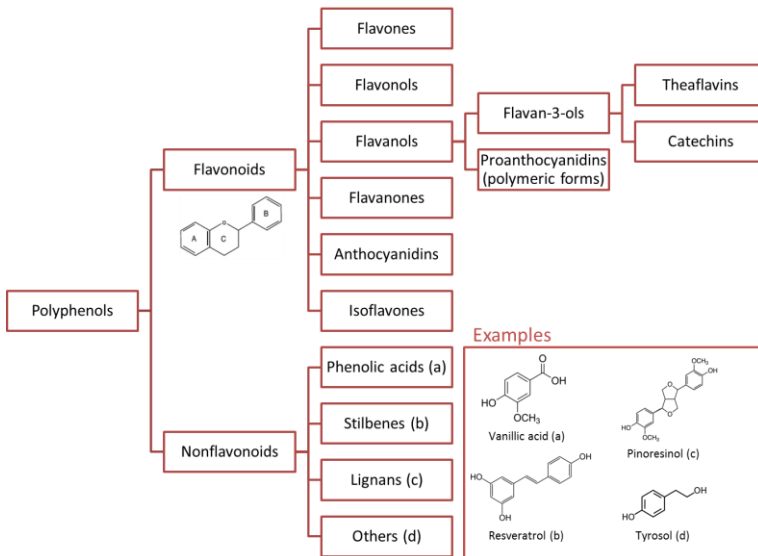


**Figure 2.** Classification of polyphenols.
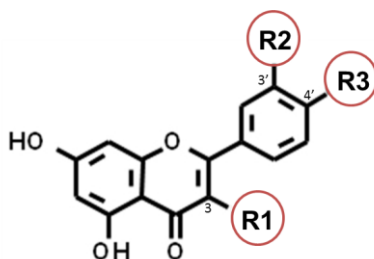
| | R1 | R2 | R3 |
|---|---|---|---|
| Quercetin | OH | OH | OH |
| Quercetin-3-glucuronide | O-glucuronid acid | OH | OH |
| Quercetin-3'-sulfate | OH | OSO₃H | OH |
| Quercetin-3-rutinoside | Rutinoside | OH | OH |
| Quercetin-3-glucoside | Glucose | OH | OH |
| Quercetin-4'-glucoside | OH | OH | Glucose |
| Isorhamnetin | OH | OCH₃ | OH |
| Isorhamnetin-3-glucuronide | O-glucuronid acid | OCH₃ | OH |

**Figure 3.** Example of quercetin metabolites from plants and biological fluids.

## 2. Distribution of polyphenols in food

As stated above, fruits, beverages and vegetables constitute the main sources of polyphenols. Fruits like apples, grapes, and berries contain up to 200–300 mg polyphenols per 100 g fresh weight, whereas a glass of red wine or a cup of tea or coffee contains about 100 mg polyphenols [12]. Herbs and spices often contain very high level of phenolic compounds but their consumption is limited to low amounts, therefore their contribution to total dietary intake is low [13].

Plant polyphenol composition is highly variable. Some of the compounds, such as quercetin, are ubiquitous, whereas others are more specific from particular foods (e.g., epigallocatechin gallate in green tea, isoflavones in legumes, flavanones in citrus fruit, or phloridzin in apples) [14].

Numerous factors affect the polyphenol content of plants. For example, the phenolic content of the skin of a given fruit is higher than that of the pulp since plants synthesize polyphenols as a mechanism of defense against

external agents. For this reason, fruit and vegetables from organic agriculture have also higher content of polyphenols than those from traditional agriculture [15]. Maturity, genetic factors, environment (sun exposure, rainfall), storage or manipulation will also influence the concentration of polyphenols. The degree of ripening has different effects depending on the polyphenol class: in general, phenolic acid concentrations decrease during ripening, whereas anthocyanin concentrations increase. Finally, the cooking method also have great influence: the phenolic concentration of foods decreases while their bioavailability is higher compared to raw foods [16,17].

Flavonols, one of the flavonoid subgroups, are the most abundant polyphenols in food. They are present in onions, spinach, berries, tea, dark chocolate, vegetables, nuts, and in most of the spices. The richest sources of flavanones are citrus fruits like grapefruit, orange, and lemon. Flavones are notably present in celery, red chicory, artichoke, black olives, and citrus fruits, whereas isoflavones are found in soy foods. Anthocyanins are typical of red dark-colored fruits and their products: berries, cherry, black olives, or red wine. Finally, dark chocolate, berries, nuts, tea and red wine are important sources of flavanols and their polymers, procyanidins [13].

Although flavonoids have traditionally been the most broadly studied group, nonflavonoids also contribute significantly to our polyphenol dietary intake. Phenolic acids, including hydroxycinnamic acids and hydroxybenzoic acids, are widely distributed in foods. The latter is present in higher amounts in chestnut, raspberry, pomegranate juice, and blackberry. Hydroxycinnamic acids are mostly found in coffee, artichoke, prune, chicory, blueberry, black olives, plum, and sweet cherry. Stilbenes and lignans are characteristic of red wine and seeds, respectively [13]. The most known and studied stilbene is *trans*-resveratrol, which is reported to have multiple health effects [18–20]. Finally, olive oil contains several simple phenols such as hydroxytyrosol and tyrosol [21].

Analysis of polyphenols in food is a highly complex process that requires multiple factors to be considered: food matrix, interferences, the variable solubility of the compounds, temperature, extraction time, and concentration levels that varies from traces to milligrams. Low temperatures, organic solvents, lyophilization and working under UV-free light conditions are extensively used methods to prevent the oxidation of polyphenolic compounds [22].

When the main objective is a detailed phenolic profile, mass spectrometry coupled to liquid chromatography is the most common

technique for identification and quantification, although in some cases gas chromatography and capillary electrophoresis can also be used. To quantify total polyphenols or those of a given group, spectrophotometric methods are useful and simpler. The Folin-Ciocalteu (F-C) method has been extensively used to determine total polyphenol content, whereas other more specific reactives are used to determine proanthocyanidins, hydrolyzable tannins, anthocyanidins, and flavan-3-ols [10,22].

## 3. Bioavailability and metabolism of polyphenols

Bioavailability is the proportion of the nutrient that is digested, absorbed and metabolized so that is available at the site of action [23]. Therefore, it is important to know, not only how much polyphenols we intake, but in which proportion they are available and reach target tissues.

The chemical structure of polyphenols determines their absorption and the structure of the metabolites circulating in the plasma. Given the huge variety of existing phenolic structures, the biological properties of polyphenols greatly differs from one polyphenol to another. Thus, the most abundant polyphenols in our diet are not necessarily those leading to the highest concentrations of active metabolites in our tissues [24]. Absorption of polyphenols also depends on fat intake, food matrix, dose, intestinal transit, and other factors [23]. Recently, emerging findings suggested that microbiota plays a crucial role in the metabolism of polyphenols and, at the same time, polyphenols contribute to the maintenance of gut health by the modulation of the gut microbial balance enhancing the growth of beneficial bacteria while competitively excluding pathogenic bacteria, exerting prebiotic-like effects. Both the formation of bioactive polyphenol-derived metabolites by the microbiota and the modulation of colonic microbiota by polyphenols contribute to host health benefits [25–28]. For instance, equol, enterolactone and enterodiol are produced by the colonic microflora after consumption of soy (or other isoflavones-rich food) and equol have greater phytoestrogenic properties than those of the original isoflavone [29].

Generally, the metabolism of polyphenols takes place as follows (Fig. 5): after the ingestion, some polyphenols, aglycones and anthocyanins, are directly absorbed in the stomach and small intestine. Esters, glycosides and polymers need to be hydrolyzed by intestinal

enzymes or the colonic microflora. Once absorbed, polyphenols undergo some degree of phase I and II metabolism in the enterocytes as methylation, sulfation and/or glucuronidation depending on the nature of the substrate and the dose. Polyphenol metabolites enter to the bloodstream by the portal vein to the liver, where they may be subjected to more conjugations. Then, metabolites travel through the bloodstream again attached to carriers such as albumin until they are excreted. There are two ways of excretion that depends on the molecular weight. The heavier compounds are usually eliminated as bile components. Back in the intestine (enterohepatic circulation), some of them are deconjugated and regenerated by gut microbial enzymes and are reabsorbed. The unabsorbed ones are eliminated via feces. The lighter polyphenols are excreted through the urine via the kidney [24,28].
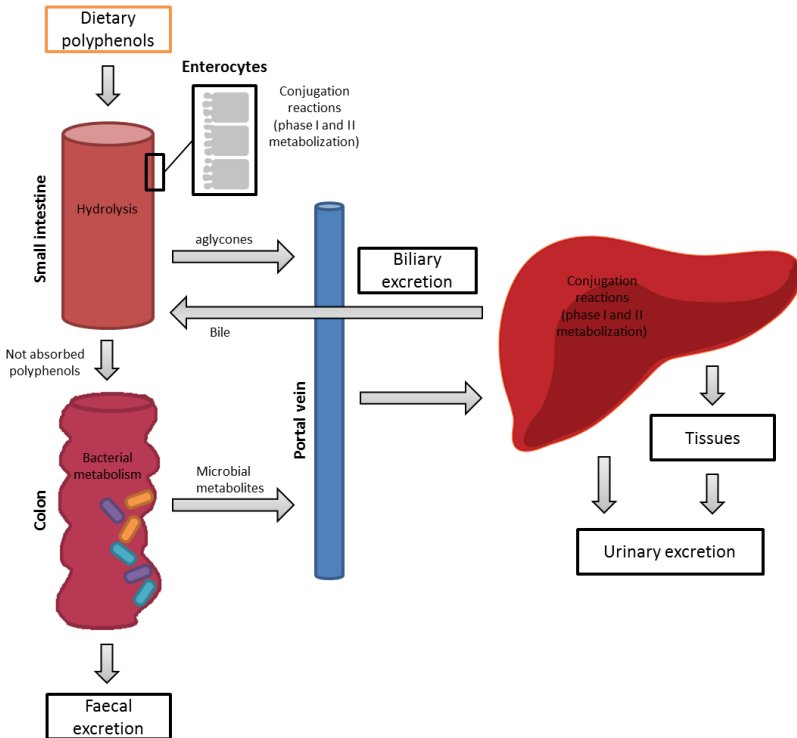


**Figure 4.** Absorption and metabolism of dietary polyphenols in humans.

## 4. Polyphenols and health

Numerous epidemiological and human intervention studies have shown that polyphenol intake may protect against cardiovascular and neurodegenerative diseases, some cancers, insulin resistance, and obesity, among others [6,7,30]. However, most of the evidence on the beneficial effects of dietary polyphenols is derived from in vitro and/or animal studies and using concentrations much higher than those achievable through the diet. Thus, translation of these results to humans needs to be tested. Moreover, the generally used compounds for *in vitro* studies are polyphenol aglycones or their sugar conjugates instead of the physiological metabolites [31].

Normal physiological processes such as respiration and metabolic reactions that take place in our body, as well as other exogenous factors, produce reactive oxygen species (ROS). As defense mechanisms, our body has endogenous antioxidants to eliminate the ROS since these molecules can bind to DNA, lipids and proteins, altering their stability and leading to various diseases, such as diabetes, Alzheimer's, Parkinson's, cancer, CVD related diseases and respiratory diseases. Polyphenols can reduce oxidative stress and delay ageing [32–34].

The effect of polyphenols as chemopreventive agents has been extensively demonstrated in animal models but is still very limited in humans and there is only promising data regarding regular consumption of green tea and its main polyphenol epigallocatechin gallate and oral and prostate cancer development [6]. It has been hypothesized that polyphenols may act by blocking the initial stages of the disease by modulating the expression of cytochrome P-450 enzymes involved in the activation of carcinogens and limiting the formation of initiated cells by stimulating DNA repair. In promotion stages, these compounds slow or stop tumor growth by inhibiting the expression of genes involved in tumor proliferation or inducing apoptosis of malignant cells. In progression stages they can inhibit angiogenesis and limit tumor invasion [7,35,36].

The effect of polyphenols in neurodegenerative diseases has usually been performed in animal models and neuronal cells. Polyphenols like resveratrol, proanthocyanidins, epicatechin, catechin and ferulic acid, as well as polyphenols from different foods have shown to reduce β-amyloid peptides in mice, which are involved in the pathogenesis of Alzheimer's disease [37–39]. Studies carried out in humans showed an improvement of memory in old people with mild cognitive problems. These compounds

interfered in the generation and aggregation of β-amyloid peptides [40]. Flavonoid intake was also associated with better cognitive ability in humans [41]. However, it is unclear whether polyphenols directly interact with neural systems because it is unknown if all polyphenols are able to reach the brain [37]. Nowadays, we only know that some metabolites from gallocatechin gallate epicatechin and anthocyanins are able to cross the blood-brain barrier in animals [42,43].

## 4.1. Cardiovascular effects of phenolic compounds

A large number of epidemiological studies and some human intervention studies have associated the consumption of polyphenols with a decreased risk of CVD. Nowadays, the strongest evidence for the efficacy of polyphenols reducing biomarkers of cardiovascular risk comes from flavan-3-ols-rich foods, especially cocoa and tea [6,44,45]. Other prospective studies associated the intake of anthocyanins and flavanones with a lower risk of CVD and total mortality [46,47].

The protective effect of polyphenols may be explained by the improvements they confer on various risk factors that are much more effective than treating the CVD itself. Indeed, it has been shown that polyphenols improve endothelial function by improving parameters such as LDL cholesterol, platelet aggregation, invasion and proliferation of smooth muscle cells in the arterial wall, nitric oxide (NO) and some markers of inflammation [7,48].

The endothelium is the innermost layer of the blood vessel walls. Endothelial cells, in response to various stimuli, release molecules that are responsible for maintaining normal endothelial function. When the balance is disrupted the homeostatic functions of the endothelium are altered and the process of atherosclerosis, a chronic inflammation of large artery walls, starts. Hypertension, high LDL cholesterol levels or low high-density lipoprotein (HDL) cholesterol levels, diabetes and smoking are risk factors for atherosclerosis [49,50].

Hypertension is a public health issue that affects more than 1 billion people worldwide, causing 7.6 million deaths annually. Hypertension is diagnosed when systolic blood pressure (SBP) is permanently greater than 140 mm Hg and/or diastolic blood pressure (DBP) is greater than 90 mm Hg [51].

Several human intervention studies have related polyphenol-rich foods with a decrease in BP and other related parameters. Results from the most recent studies (from 2010 to 2015) are summarized in Table 1.

**Table 1.** Human intervention studies on polyphenols and blood pressure.

| Type of study | Participants | Age | Administrated substance | Polyphenols [†] | Dose/day | Length of the study | Biomarker | Changes on BP [‡] | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Chronic, controlled, cross-sectional | 35 healthy men | 18-45 | Wine grape or grape seed extract (capsules) | Anthocyanins, phenolic acids | 6 capsules (800 mg) | 14 days | SBP DBP | ↔ ↔ | [52] |
| Crossover, randomized, controlled | 24 healthy and overweight men | 50-65 | Orange juice or hesperidin-enriched drink | Hesperidin | 500 mL (292 mg) | 28 days | DBP | ↓(in both intervention groups) | [53] |
| Crossover, randomized, controlled | 24 men with metabolic syndrome | 30-70 | Grape extract (capsules) | Flavanols, anthocyanins | 46 g/day | 30 days | SBP FMD NO | ↓ ↑ ↔ | [54] |
| Parallel, randomized, controlled | 97 overweight men and women | 19-55 | Algae extract (*Ecklonia cava*) | Fluorotannins | Cans (246 mL and 72 mg extract) | 12 weeks | SBP | ↓ (with the highest dose) | [55] |
| Crossover, randomized, controlled | 10 healthy men | 45-50 | Wine, dealcoholized wine and gin | Flavanols, anthocyanins | 272 mL wine (733-798 mg EAG/day) or 100 mL gin | 20 days | DBP SBP | ↓(with wine) ↓(with both wines) | [56] |
| Crossover, randomized, controlled | 51 healthy men and women | 30-50 | Pomegranate juice | Hydrolizable tannins, anthocyanins | 330 mL/d | 4 weeks | SBP DBP BP | ↓(-3.14 mmHg) ↓(-2.33 mmHg) ↓(-2.60 mmHg) | [57] |
| Crossover, randomized, controlled | 67 men at high cardiovascular risk | 55-75 | Wine, dealcoholized wine and gin | Flavanols, anthocyanins | 272 mL wine (733-798 mg EAG/day) or 100 mL gin | 4 weeks | SBP and DBP Plasma NO | ↓ ↑ (with dealcoholized wine) | [58] |
| Parallel, randomized, controlled | 84 healthy or mild hypertensives men and women | 35-75 | Black tea | Catechins | 3 cups/day (429 mg) | 4 weeks | SBP DBP | ↔ ↔ | [59] |
| Crossover, randomized, controlled | 49 healthy men | 48-68 | Quercetin | Quercetin | Capsules (150 mg/day) | 8 weeks | SBP postprandial | ↓ | [60] |
| Parallel, randomized, controlled. | 70 hypertensives (stage 1 or less) men and women | 35-75 | Grape seed extract | Catechin, proanthocyanidin dimers | Capsules (300 mg/day) | 8 weeks | SBP and DBP | ↓ (not statistically significant) | [61] |
| Pilot study | 6 healthy men and women | 34-68 | Boysenberry juice | Proanthocyanidin dimers, epicatechin | 180 mL/day (351 mg) | 4 weeks | FMD SBP | ↑ ↓ | [62] |
| Crossover, randomized | 18 healthy men and women | - | Green and black coffee | Chlorogenic acid | 40 g (4 cups) | 2 weeks | SBP | ↓ (after green coffee) | [63] |
| Parallel, randomized, controlled | 15 healthy or mild hypertensive men and women | 43.2±12.4 | Japanese plum (*Prunus mume*) | Hydroxycinnamic acid derivatives | Capsules (800 mg/day) | 12 weeks | BP | ↔ | [64] |
| Parallel, randomized, controlled | 56 healthy men and women | 25-65 | Low-calorie cranberry juice | Anthocyanidins, proanthocyanidins | 480 mL/day (173 mg) | 8 weeks | BP | ↓ | [65] |
| Crossover, randomized | 100 healthy men and women | 18-65 | Orange juice (normal or polyphenol-enriched) | Hesperidin | 500 mL/day | 12 weeks | SBP DBP | ↓ (normal) ↓ (normal) | [66] |

SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; AGE: gallic acid equivalents; FMD: flow-mediated dilation.
* Table is organized chronologically.
† Only the top two polyphenols with the highest concentration are listed
‡ ↑increase; ↓ decrease; ↔ no change; unless otherwise stated, % refers to changes from baseline when test substance is given.

A possible mechanism by which polyphenols decrease BP is by enhancing NO production. *In vitro* experiments with isolated arteries showed that polyphenols increased endothelial NO formation and caused NO-mediated endothelium-dependent relaxations [67].

Metabolic syndrome (MS) is a metabolic disorder that consists of a combination of multiple cardiovascular risk factors: obesity, hypertension, dyslipidemia and hyperglycemia. The consumption of polyphenol-rich foods can prevent MS through their protective effect on chronic inflammation linked to obesity, insulin resistance, dyslipidemia, and hypertension [68].

Some *in vitro*, animal and human studies have shown that polyphenols help to control obesity by reducing fat absorption in the intestinal tract, activating thermogenesis and modulating the hormonal response that regulates food intake and satiety [69].

Consumption of cocoa has shown to reduce MS by improving insulin resistance, endothelial function and levels of NO. These effects have been confirmed in multiple literature reviews and meta-analyzes [70]. Similar results were observed with the consumption of green tea [71], olive oil [72] and other polyphenol-rich foods.

Polyphenols could also help to reduce diabetes through different mechanisms. They can inhibit glucose absorption in the small intestine and its reabsorption in the liver, gluconeogenesis, adrenergic stimulation of glucose consumption, or stimulation of insulin release by pancreatic beta cells. For example, polyphenols from cinnamon, resveratrol, isoflavones, and polyphenols from tea, cocoa and grape seeds improve insulin sensitivity, the hormone that regulates plasmatic glucose levels [7,69].

## 5. Polyphenol intake and its effects in the PREDIMED cohort

In the 60s, the Mediterranean diet (MedDiet) was defined for the first time as the dietary pattern followed by Cretan, Greek and Southern Italian citizens. According to Ancel Keys, this diet was low in saturated fat and high in vegetable oils. The MedDiet has deserved much attention in the past decades due to its numerous beneficial effects in our health. The original definition has evolved to a more extensive one. Nowadays, in general terms, we can consider that guidelines to follow a MedDiet include high intakes of vegetables including leafy green vegetables, fruits, cereals, nuts, legumes and extra virgin olive oil, moderate intakes of fish, meat, dairy products and red wine, and low intakes of eggs and sweets [69].

The PREDIMED study (*PREvención con DIeta MEDiterránea*, ISRCTN35739639) was a prospective, randomized, multicentric and controlled trial aimed to assess the health benefits of a traditional Mediterranean diet (MedDiet) in the primary prevention of cardiovascular diseases [70,71]. The study lasted 9 years, from 2004 to 2013, and

included 7447 elderly participants at high cardiovascular risk. Volunteers were recruited through primary health care centers from 8 different Spanish regions and they were randomized to one of the following nutritional intervention groups: Mediterranean diet supplemented with extra virgin olive oil (MedDiet -EVOO), Mediterranean diet supplemented with nuts (MedDiet -nuts), and a control group which followed a low-fat diet according to the recommendations of the American Heart Association (AHA) [72].

After a median of 4.8 years of follow-up, an external scientific committee advised to finish the study due to the marked differences between the MedDiet groups and the control group. Results revealed that both MedDiet groups had 30% less incidence of CVD events than the control group. Specifically, the adjusted hazard ratio (HR) were 0.70 (95% CI 0.54-0.92) and 0.72 (95% CI 0.54-0.96) when comparing the MedDiet -EVOO and the MedDiet -nuts with the control group [73].

Within the PREDIMED, and after only 3 months of intervention, it was demonstrated that improving a diet towards a MedDiet pattern decreased LDL cholesterol, glucose, BP, and biomarkers of inflammation [70,74]. After one year of intervention, results showed that both MedDiet (MedDiet -VOO and MedDiet -nuts), but not the control diet, were able to revert the metabolic syndrome [75,76] and to increase non enzymatic antioxidant capacity of plasma [77], as well as decrease cellular and circulating inflammatory biomarkers related to atherogenesis [78]. Other investigations were aimed to assess the beneficial effects of the MedDiet on obesity [79,80], cognitive impairment [81], hyperuricemia [82], and type-2 diabetes [83]. MedDiet also delayed the progression of internal carotid intima-media thickness and plaque height [84] and reduced oxidative damage to lipids and DNA in individuals with metabolic syndrome [85]. These results provide further evidence to recommend a MedDiet pattern supplemented with nuts and olive oil to decrease CVDs risk factors, especially when these recommendations are addressed to elderly people at high CVDs risk.

Beyond its main objective, the PREDIMED study has been the nest of other numerous sub-studies involving many exposure variables others than MedDiet and CVD-related outcomes. Polyphenols and polyphenol-rich foods have been one of the studied exposure variables. The concentration of total polyphenols in spot urine samples as a biomarker of total polyphenol intake [86] was negatively associated with BP levels and prevalence of hypertension in a cross-sectional sub-study of 589

participants from the PREDIMED trial [87]. This effect was mediated by the increase of nitric oxide (NO) in plasma [88]. Valls-Pedret *et al.* also found that a high consumption of antioxidant-rich foods such as virgin olive oil, coffee, walnuts or wine, and a high intake of polyphenols were associated with better cognitive function [89]. Total polyphenol intake assessed using yearly food frequency questionnaires and the Phenol-explorer database was associated with cardiovascular mortality and events, and all-cause mortality. From them, lignans, flavanols, and hydroxybenzoic acids were associated with decreased CVDs risk [90] while high intakes of stilbenes and lignans showed a reduced risk of overall mortality [91].

Regarding polyphenol-rich foods, moderate red wine consumption was associated with a lower prevalence of the metabolic syndrome and some of its components: increased waist circumference, low HDL-cholesterol, high BP, and high fasting plasma glucose concentrations [92]. Resveratrol in urine, as a biomarker of wine intake, was also inversely associated with cardiovascular risk factors: blood lipid profiles, fasting blood glucose, and heart rate [93]. Finally, consumption of extra virgin olive oil decreased CVD, atrial fibrillation and carotid intima-media thickness [94–96], while consumption of nuts decreased adiposity in the PREDIMED cohort [97].

## 7. Conclusion

Polyphenols are bioactive compounds mainly found in fruits, vegetables, cereals and their products. Several studies have demonstrated that polyphenols and polyphenol-rich foods can improve cardiovascular health through different mechanisms. However, some results are contradictory and more mechanisms still need to be elucidated so future research have to substantiate these findings in order to stablish dietary recommendations or to consider the potential polyphenolic compounds as therapeutic agents.

## Acknowledgements

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