Learning Objectives

- To understand the basis of the physiopathology of the atherosclerotic plaque as a major lesion involved in cardiovascular diseases (CVD);
- To learn about the beneficial effects of omega-3 polyunsaturated fatty acids on cardiovascular function;
- To know the main large-scale clinical studies with omega-3 fatty acids in the prevention of CVD;
- To understand the rationale of plant sterols and stanols in prevention of CVD;
- To know about the effects of polyphenol intake on the CVD risk factors;
- To know the main evidence that links the intake of some foods rich in polyphenols with a decrease in CVD risk, including cocoa/dark chocolate, resveratrol, curcumin and green tea;
- To learn about the effect of lycopene consumption on CVD risk.

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Key Messages

- Cardiovascular disease is the leading cause of death in the world, and can be prevented by addressing behavioural risk factors;
- Several nutrients/foods have been identified that could potentially reduce cardiometabolic disease risk, mainly via modifying lipid profile, or reducing blood pressure or insulin-resistance;
- Omega-3 fatty acids have a positive effect on CVD risk management: a protective effect against cardiovascular risk in healthy adults with overweight, hypertriglyceridaemia, hyperlipidaemia, metabolic syndrome or type 2 diabetes mellitus. The administration of omega-3 PUFAs does not seem to show any benefit for the management of established CVD or associated complications;
- Plant sterols and stanols reduce LDL cholesterol increasing their clearance. Long-term studies focused on the reduction of CVD risk are lacking;
- Higher intake of polyphenols is associated with decrease of CVD risk mediated by their antioxidant properties, but also through the effects on obesity, hyperglycaemia, and modifying endothelial dysfunction;
- High lycopene consumption has been associated with a decreased risk of cardiovascular disease.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in the world (1). An estimated 17.7 million people died from CVD in 2015, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke.

Over three quarters of CVD deaths take place in low- and middle-income countries. Out of the 17 million premature deaths (under the age of 70) due to non-communicable diseases in 2015, 82% were in low- and middle-income countries, and 37% were caused by CVD. Most cardiovascular diseases can be prevented by addressing behavioural risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol, using population-wide strategies.

People with cardiovascular disease or who are at high cardiovascular risk (due to the presence of one or more risk factor such as hypertension, diabetes, hyperlipidaemia or already established disease) need early detection and management using counselling and medical treatment, as appropriate.

For primary prevention in the general population or in persons at risk, several nutrients/foods have been identified that could potentially exert effects that would reduce cardiometabolic disease risk. In this module we review the main nutrients/foods that have been implicated in preventative effects in CVD, mainly through modifying lipid profile or blood pressure (BP).

2. Physiopathology of Cardiovascular Diseases

The major typical feature of CVD is the atherosclerotic plaque. The disease is initiated by the subendothelial retention of lipoproteins (LPs) in focal areas of arteries. Various modifications of the retained LPs trigger a low-grade inflammatory response. This response leads to activation of endothelial and vascular smooth cells, recruitment of monocytes and accumulation of lipid material in the subendothelial space, or intima. The macrophages ingest the retained LPs and become lipid-loaded foam cells. Macrophages also promote
plaque progression by propagating a maladaptive, non-resolving inflammatory response characterized by an imbalance of inflammatory to “pro-resolving” mediators. Atherosclerotic lesions most often undergo a partial resolution process characterized by the formation of an overlying scar. However, over time, certain types of atherosclerotic lesions develop features that can lead to acute thrombotic vascular disease (vulnerable plaques). Matrix metalloproteinases secreted by the inflammatory macrophages can lead to thinning of the fibrous cap and plaque rupture. Environmental factors in these advanced lesions promote macrophage apoptosis yielding debris which can be cleared efficiently by lesional phagocytes. However, in advanced atherosclerosis, this process does not work well, leading to post-apoptotic necrosis. Necrotic cells amplify inflammation and can coalesce into areas (necrotic cores) that promote plaque breakdown and thrombosis (2) Fig. 1.

Another important factor in the initial phase of the process is a dysfunction of the endothelium induced by atherogenic lipoproteins and hypertension. The dysfunctional endothelium loses its capacity to produce nitric oxide (which is a vasodilator and also protects against arterial remodelling and platelet aggregation), but secretes free radicals and inflammatory mediators. The inflammation is involved directly in the thrombus formation at the site of the vascular lesion (3).

3. Nutrients/Foods Involved in the Prevention of CVD

As a dietetic pattern, the Mediterranean diet seems to be the most cost-effective approach to CVD prevention, which will be combined with prevention and cessation of smoking, promotion of physical activity, and control of hypertension, dyslipidaemia, obesity and diabetes. However, it is very difficult to attribute the beneficial effects of the different components of the Mediterranean diet on CVD risk.
A large and growing body of evidence supports the potential protective role of some specific foods and specific nutrients in CVD prevention. Studies focused on foods/nutrients have however tried to identify bioactive components potentially improving CVD risk factors such as LDL-cholesterol, blood pressure or insulin-resistance.

3.1 Omega-3 Polyunsaturated Fatty Acids

The first epidemiological evidence that linked omega-3 PUFAs intake to CVD risk came from the studies in the Inuit population of Greenland. This population, despite following a high fat diet, had a lower prevalence of CVD than seen in other caucasians. The differences were attributed to a high content of eicosapentaenoic acid (EPA) in the diet.

Since this first evidence, multiple randomized controlled trials have assessed the effects of supplementation with EPA plus docosahexaenoic acid (DHA) on the occurrence of CVD. The inclusion of healthy subjects, or patients at high cardiovascular risk, or patients with established CVD for secondary prevention, makes the comparison of these trials difficult.

Furthermore, some studies in secondary prevention were designed to compare omega-3 PUFAs with statins, alone or in combination.

Omega-3 PUFAs have a broad range of beneficial cardiovascular effects including reducing atherogenic dyslipidaemia (reducing triglycerides, very-low-density lipoprotein (VLDL), inflammatory markers, remnant-like lipoparticle cholesterol, oxidized low-density lipoprotein), heart rate, blood pressure, and possibly arhythmia risk (4-7) Importantly, these benefits are observed with omega-3 PUFAs alone or as add-on therapy to statins. The effects of omega-3 PUFAs, as well as statins, are also pleiotropic. EPA has beneficial effects on multiple atherosclerotic processes including endothelial function, oxidative stress, foam cell formation, inflammation/cytokines, plaque formation/progression, platelet aggregation, thrombus formation and plaque rupture (8)(Fig. 2).

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**Fig 2.** Potential beneficial effects of EPA on clinical cardiovascular end-points
Recently, several meta-analyses and systematic reviews of the main RCTs performed with omega-3 PUFAs have been published (9-12). Rangel-Huerta and colleagues have evaluated the scientific evidence provided in the past five years on the effects of the intake of omega-3 PUFAs on CVD risk factors through a systematic review (9). They conclude that supplementation of at least 1 g/day of PUFAs, either through capsules or from marine products, can be demonstrated to have a protective effect against CVD risk in healthy adults with overweight, hypertriglyceridaemia, hyperlipidaemia, metabolic syndrome or type 2 diabetes mellitus. Furthermore, several lines of evidence exist showing that consumption of EPA + DHA reduces systolic blood pressure, and that doses above 2 g/day also might reduce blood pressure in patients with type-2 diabetes mellitus, as well as improving endothelial function and reducing triglyceride levels. Conversely, this systematic review of the RCTs performed in the last 5 years concluded that the use of PUFAs does not show a significant effect in the treatment of CVD. However, the authors recommend further studies including bigger populations.

Watanabe and colleagues have reviewed the studies on omega-3 fatty acids during the last 50 years (10). They conclude that numerous epidemiological/ observational and large-scale randomized studies have investigated the effectiveness of omega-3 fatty acids in the prevention of atherosclerotic diseases, particularly coronary heart disease-related fatal myocardial infarction and sudden cardiac death. However, the effectiveness of omega-3 fatty acids for secondary prevention in patients with multiple cardiovascular disease risk factors is not clear. One of the reasons could be related to the concomitant aggressive drug treatment that could mask an effect of the omega-3 fatty acids. The results of the large-scale clinical studies using omega-3 fatty acids conducted to date are summarized in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>GISSI-P</th>
<th>JELIS</th>
<th>GISSI-HF</th>
<th>ORIGIN</th>
<th>GISSI-R&amp;P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject background</td>
<td>Prior MI (within 3 mo.)</td>
<td>Hypercholesterolemia (&gt; 250 mg/dL) (Primary 80.3%, secondary 19.7%)</td>
<td>CHF</td>
<td>IGT/IFG/DM</td>
<td>Multiple CV risk</td>
</tr>
<tr>
<td>Baseline TG (mg/dL)</td>
<td>162.1</td>
<td>154.2</td>
<td>NA</td>
<td>Omega-3: 142 Control: 140</td>
<td>Omega-3: 150 Control: 150</td>
</tr>
<tr>
<td>Omega-3 preparation</td>
<td>EPA/DHA</td>
<td>EPA</td>
<td>EPA/DHA</td>
<td>EPA/DHA</td>
<td>EPA/DHA</td>
</tr>
<tr>
<td>Dosage (g/day)</td>
<td>1</td>
<td>1.8</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>11,324</td>
<td>18,645</td>
<td>7,046</td>
<td>12,612</td>
<td>12513</td>
</tr>
<tr>
<td>Follow-up (mo.)</td>
<td>42</td>
<td>55.2</td>
<td>47</td>
<td>74.4</td>
<td>60</td>
</tr>
<tr>
<td>CV event reduction</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Statin use (%)</td>
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<td>10</td>
<td>23</td>
<td>54</td>
<td>62</td>
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<tr>
<td>Use of ACE-I/ARB (%)</td>
<td>41</td>
<td>?</td>
<td>94</td>
<td>71</td>
<td>75</td>
</tr>
<tr>
<td>Use of antiplatelets (%)</td>
<td>88</td>
<td>14</td>
<td>87</td>
<td>79</td>
<td>60</td>
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<tr>
<td>Reference number</td>
<td>(7)</td>
<td>(64)</td>
<td>(8)</td>
<td>(66)</td>
<td>(56)</td>
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</tbody>
</table>

mo: months; CV: cardiovascular; MI: myocardial infarction; CHF: chronic heart failure; IGT: impaired glucose tolerance; IFG: impaired fasting glucose; DM: diabetes mellitus; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; NA: not available.
Recently, the American Heart Association reviewed their recommendations with regard to supplementation with omega-3 fatty acids and clinical cardiovascular disease, focusing on the largest RCTs published to date. They conclude (11):

- There are no studies targeted exclusively on primary prevention of coronary heart disease in healthy people.
- There is no benefit from omega-3 supplementation among patients with or at risk of diabetes mellitus to prevent CVD (Treatment not indicated: Class III: No benefit Recommendation).
- There is a lack of consensus on the benefit of omega-3 PUFA supplements among patients at high CVD risk, in part because of differences in the weight given to the results of the JELIS trial. The majority of co-authors concluded that treatment is not indicated (Class II: No Benefit Recommendation); a minority of co-authors concluded that treatment of these patients is reasonable (Class IIb Recommendation).
- Omega-3 PUFA supplementation may reduce coronary heart death among patients with prior coronary heart disease, but the treatment does not reduce the incidence of recurrent non-fatal myocardial infarction (Class IIa Recommendation).
- There is no proven benefit of omega-3 PUFA supplementation to reduce the risk of stroke in patients without previous history of stroke.
- No recommendation for treatment with omega-3 PUFA supplements can be made for the primary prevention of heart failure.
- Treatment with omega-3 PUFAs supplements is reasonable among patients with heart failure with reduced ejection fraction (Class IIa Recommendation).
- No recommendation can be made for primary or secondary prevention of atrial fibrillation.

There are two on-going long-term CV intervention outcome studies, REDUCE-IT (NCT01492361), and STRENGTH (NCT02104817), to investigate the effect of high-dose omega-3 fatty acids on CV risk, which should most probably clarify the potential role of omega-3 fatty acids in reducing CV risk.

### 3.2 Plant Sterols and Stanols

Phytosterols are integral components of plant cell membranes, and are structurally similar to cholesterol. Plant sterols and stanols differ only on their lateral chains and from the presence or not of an unsaturated Δ5 bond. Phytosterols are extracted from vegetable oils such as corn, rapeseed, soybean and olive oil, either in free forms or as fatty acid esters. They are also present in lower concentrations in nuts, seeds, fruits and vegetables. The most abundant plant sterols are sitosterol, campesterol and stigmasterol. Stanols are less abundant in food, and can be produced commercially by hydrogenation of plant sterols. Plant sterols are poorly absorbed from the gastrointestinal tract (0.4-5.0%), and stanols even less (0.02-0.3%). Due to the chemical similarity with cholesterol, plant sterols block cholesterol absorption, increase cholesterol in faeces and increase the synthesis of the hepatic receptors for apolipoprotein B/E, leading to increased clearance of LDL-cholesterol and decreased plasma LDL concentrations (13).

Clinical studies have shown a mean lowering in circulating LDL-cholesterol of 8-15% when plant sterols/stanols are added to the usual diet at a dose of 1.5-3 g/day, in comparison with control groups. No significant differences with regard to efficacy have been found between sterols and stanols.

The effect of plant sterols/stanols on LDL-cholesterol has been explored in a big trial using the Mediterranean diet as the main intervention, which compared three groups of subjects...
with high cardiovascular risk (14). The first group was given Mediterranean diet advice and an additional dose of virgin olive oil. The second group was advised to add nuts to the diet, while the third group followed a low-fat diet. The LDL-cholesterol fell significantly (by 8.3%) in the group on nuts, associated with an increase in the sitosterol/cholesterol ratio, a marker of plant sterol intake. Studies have failed to demonstrate other surrogate markers of cardiovascular risk, like intima-media thickness, endothelium dependent vasodilation or plasma markers of endothelial dysfunction and inflammation. The effect of phytosterols/ stanols on oxidized LDL is still controversial. In general, most of the studies that support the beneficial effect of plant sterols/stanols are of short-term design, and we have very few long-term data. For this reason, although their efficacy in lowering LDL cholesterol is not in doubt, their effect on cardiovascular risk remains unknown.

3.3 Polyphenols

Polyphenols are one of the largest groups of phytochemicals, and more than 8,000 different molecules are known. Chemically characterized as compounds with phenolic structural features, the group is highly diverse and contains several subgroups including flavonoids, phenolic acids, lignans, stilbens, and more. Polyphenols are common constituents in the diet, and are present in most foods and beverages of plant origin (eg coffee, tea, wine). The consumption of a diet rich in plant foods, fruits and vegetables is associated with a lower risk of CVD, and this relationship can be ascribed, at least in part, to their polyphenol content. The “French paradox”, that describes a relatively low incidence of CVD in France despite a relatively high dietary intake of saturated fat, can potentially be attributable to the consumption of red wine, very rich in polyphenols.

Quantification of polyphenols in the food can be performed by high-performance liquid chromatography, but it is difficult to calculate the total amount of polyphenols because of the limited range of standard molecules. The decreased CVD risk associated with a higher intake of polyphenols is mediated by their antioxidant properties, but also through their effects on obesity, hyperglycaemia, and modification of endothelial dysfunction (15).

Polyphenols and phenolic acids are related with the decrease in LDL oxidation shown after the intake of red wine (16), although resveratrol also could be a contributor. Several polyphenols have been shown in vivo to modulate physiological and molecular pathways that are involved in obesity and diabetes. The intake of 3-4 cups of coffee per day is associated with an approximate 25% lower risk of developing type 2 diabetes compared with consuming none or <2 cups, and this effect is independent of caffeine intake (17). Among Japanese adults, consumption of >6 cups/day of green tea is associated with a reduction of risk of diabetes by 33% (18). Some studies have demonstrated that tea catechins can influence the intestinal absorption of dietary fat, and lower levels of triglycerides (TG) are reported in people with higher intake of green tea. However, postprandial elevation of TG levels may be more closely related to CVD risk than fasting TG. In this way, red wine polyphenols and oolong tea (China dark-coloured tea) polyphenols can attenuate the postprandial plasma lipid response, probably through suppression of pancreatic lipase activity.

Polyphenols can also affect HDL-Cholesterol function and structure. Extra-virgin oil consumption increases the polyphenol content of HDL particles, which prevents lipid peroxidation and promotes the anti-atherogenic effects of HDL. In addition to the
antioxidant properties of coffee, an increase of expression of some ATP-binding cassette transporters can enhance the HDL-mediated cholesterol efflux.

3.3.1 Cocoa / Dark Chocolate

Cocoa is a rich source of dietary polyphenols, specially catechins, anthocyanins and proanthocyanidins. In vitro as well as cell culture data indicate that cocoa polyphenols may exhibit antioxidant, anti-inflammatory and anti-atherogenic activity, switching on some important signalling pathways such as toll-like receptor 4/nuclear factor κB/signal transducer and activator of transcription. In particular, cocoa polyphenols induce release of nitric oxide through activation of endothelial NO synthase which, in turn, accounts for vasodilation and cardioprotective effects. Consumption of cocoa or dark chocolate has been associated with best flow-mediated dilatation (as a measure of endothelial dysfunction), and the effect seems to be mediated through the epicatechin content. Flavonoids, especially flavanols, are also mediators in the improvement of endothelial dysfunction in healthy and hypertensive subjects through the increase of nitric oxide bioavailability (19).

A recent meta-analysis of 20 double-blind, placebo controlled RCTs involving 856 healthy participants demonstrates a small but statistically significant blood pressure (BP) reducing effect of flavanol-rich cocoa compared with controls in short-term trials (2-18 weeks) (20). Subgroup meta-analysis of trials using a flavanol-free control group revealed a significant blood pressure reducing effect of cocoa, whereas analysis of trials using a low-flavanol control product did not. Other subgroup meta-analysis showed significant BP-reducing effects only for the hypertensive or prehypertensive subgroups of patients, while BP was not significantly reduced in the normotensive group (21). The mechanisms that explain the reduction in BP can be attributed to the NO increase, although in vitro, flavanols and flavonol are able to inhibit angiotensin-converting enzyme activity. Long-term trials are needed to determine whether or not BP is reduced on a chronic basis by daily ingestion of cocoa, to assess whether cocoa has an effect on CV events, and to judge potential adverse effects associated with chronic ingestion of cocoa products.

Some studies have demonstrated platelet inhibitory effects from cocoa in healthy individuals, and in heart transplant patients who had consumed cocoa or dark chocolate (22). Taking into account that platelet activation greatly contributes to the inflammation and thrombosis in the progression of CVD, their inhibition by a polyphenol-rich diet, even including consumption of cocoa and dark chocolate, could be of clinical relevance.

With regard to the effects of cocoa on serum lipid profile, some studies have demonstrated that consumption of cocoa and high-polyphenol chocolate leads to an increase in HDL while lowering LDL cholesterol levels. Inhibition of LDL oxidation is another effect of both cocoa and dark chocolate consumption. In healthy human volunteers, cocoa consumption led to decrease of F-2 isoprostane and thiobarbituric acid reactive substances, markers of LDL oxidation and lipid peroxidation, respectively. A meta-analysis of studies confirmed the ability of cocoa to reduce LDL cholesterol and total cholesterol in subjects with high cardiovascular risk (23). Other studies failed to demonstrate significant differences in serum lipids between consumers of high and low-flavanoid chocolate or cocoa beverages. Many polyphenols, including catechin and epicatechin, have been found to alter glucose metabolism in animal and in vitro studies (inhibition of intestinal alpha-glucosidase activity in rats, increasing insulin secretion and insulin sensitivity). Insulin sensitivity improved significantly in overweight and obese adults consuming high-flavanol cocoa for 12 weeks.
in comparison with low-flavonol cocoa, but these effects have not been demonstrated after 2 weeks of daily dark chocolate (24). In diabetic patients on medical treatment, the consumption of flavonol-rich cocoa three times daily for 30 days increased flow-mediated dilatation by 30%. Although more human studies are lacking, a number of animal studies support a biologic plausibility for an insulin-sensitizing effect of cocoa. Finally, as a secondary prevention, chocolate consumption was associated with a significantly reduced cardiac mortality in patients surviving a first acute myocardial infarction in the Stockholm heart epidemiology programme (25), comprising more than 1100 non-diabetic patients.

3.3.2 Resveratrol

Resveratrol is a polyphenolic compound present in several plants. The major dietary sources of resveratrol include grapes, wine, apples, peanuts and soy, although in very different concentrations. It exerts multiple biological activities, including anti-inflammatory, antiproliferative and antioxidant effects. Experimental and preclinical studies have attributed several health-promoting effects to this compound, including cardioprotective effects (26). Resveratrol may account in part for the so-called French paradox involving moderate drinking of red wine in the lower incidence of mortality from coronary heart disease in France, despite high levels of dietary fat and cigarette smoking. There are a number of reports describing the beneficial effects of resveratrol on improvement of heart dysfunction, heart failure, BP and myocardial hypertrophy based in its antioxidant, antihypertensive and coronary vasodilating activity. At the molecular level, some of these effects are mediated through activation of SIRT1 (Sirtuin 1), 5′ adenosine monophosphate-activated protein kinase, and endogenous antioxidant enzymes. The therapeutic effects of resveratrol in animal models could be attributable to the capacity of resveratrol to protect against drug-induced glutathione depletion and superoxide dismutase activity. In in vitro studies, resveratrol prevents collagen expression in cardiac fibroblasts and protects against drug-induced cardiotoxicity. In humans, a recent meta-analysis of RCTs including 247 subjects showed that high levels of resveratrol consumption significantly decreased the systolic but not the diastolic blood pressure (27). In overweight or slightly obese patients (BMI 28.3 ± 3.2 kg/m²), the intake of 150 mg of trans-resveratrol, the active isomer of resveratrol, for 4 weeks does not change plasma biomarkers of endothelial function or inflammation (E-selectin, ICAM-1, VCAM-1, TNF-α) either in the fasting state or in the postprandial phase (28). Designing human studies with resveratrol is difficult because we do not yet know the correct therapeutic dose, and because it has low bioavailability after oral intake, making it impossible to reach high doses by consuming conventional food products alone.

3.3.3 Curcumin

Curcumin or diferuloylmethane, is a well-known dietary polyphenol found in turmeric (Curcuma longa, of the ginger family). Curcumin has proven anti-inflammatory and bactericidal effects without drug-associated toxicity. Curcumin exerts protective effects on a variety of diseases, including cardiac diseases (29). Curcumin alleviates drug-induced ischaemic myocardial injury by increasing the levels of SOD, catalase and glutathione, as well as suppressing the production of TBARS and the
leakage of LDH. Curcumin ameliorates myocardial ischaemia/reperfusion injury by enhancing anti-oxidative activity and suppressing apoptosis upregulating the anti-apoptotic protein Bcl-2 and downregulating the pro-apoptotic protein caspase-3. In addition, curcumin alleviates myocardial ischaemia/reperfusion injury by attenuating inflammation (inhibits upregulation of IL-1, IL-6, IL-8, TNF-α, and attenuates the release of the cytoplasmic NF-κB). Administration of curcumin one week before myocardial ischaemia/reperfusion, selectively inhibits toll-like receptor 2, reduces infarct size, alleviates ischaemic injury, and improves cardiac contractility in rats fed with curcumin 300 mg/kg/day.

In animal models of diabetic cardiomyopathy, curcumin or curcumin analogues can reverse the increased levels of eNOS and iNOS, alleviating the oxidative damage of DNA and proteins in the diabetic rat myocardium. Also, curcumin analogues can reduce the glucose overexpression of TNF-α and IL-6 which is correlated with improved diabetic myocardial injury.

Similarly, curcumin lowers the levels of proinflammatory cytokines and chemotactic factors secreted by monocytes cultured in high glucose concentrations and in the diabetic rat myocardium.

Few studies have been conducted in patients with cardiac diseases. In a placebo-controlled study involving patients undergoing coronary artery bypass grafting, the study group (curcumin 4 g/day) showed a lower incidence of in-hospital myocardial infarction and improved physical status. The levels of CRP, MDA and pro-β-type natriuretic peptide levels were also lower in the curcumin group. In a group of postmenopausal women allocated to exercise, curcumin or control, those women on curcumin treatment for 8 weeks exhibited increased flow-mediated dilatation and decreased BP, the same effect observed in the exercise group. Patients with metabolic syndrome on curcumin treatment (1 g/day) present a reduced LDL-cholesterol, total cholesterol, triglycerides and lp(a) levels, as well as elevated HDL-cholesterol concentrations. Finally, in a RCT including 240 diabetic patients, curcumin intervention significantly increased the levels of serum adiponectin and decreased pulse wave velocity (both associated with reduced insulin-resistance, triglycerides, uric acid, visceral fat and total body fat).

Caution must be observed, given the potential pro-oxidant and pro-apoptotic effects of some curcuminoids at high doses.

### 3.3.4 Green Tea

Green tea has been consumed for centuries in Japan, China and Morocco. More recently, the consumption of tea has been extended to western countries. Leaves of green tea are non-fermented, in comparison with black tea, and this results in less oxidative changes in green tea.

Epidemiological and observational studies in humans suggest that regular consumption of green tea may be associated with a lower cardiovascular risk.

Phenolic compounds form 26% of the dry extracts of green tea; the most important are flavonoids, especially catechins. Recent studies have revealed that green tea has positive biological activities against chronic diseases such as cancer, metabolic syndrome, type 2 diabetes mellitus, cardiovascular and neurodegenerative diseases, among others. These protective properties are related to the potent antioxidant and anti-inflammatory activities of xanthic bases (caffeine and theophylline), essential oils, minerals, and mostly, catechines and other phenolic compounds (30).
According to some human intervention studies, a moderate consumption of green tea (1-6 cups per day) increases the total antioxidant capacity of the plasma. The consumption of green tea has been associated with protection against stroke, hypertension and atherosclerosis, due to its antithrombotic and anti-inflammatory effects. Green tea consumption decreases blood levels of total cholesterol through decreases in intestinal absorption, and LDL-cholesterol and LDL oxidation. Furthermore, green tea consumption increases HDL cholesterol.

Gallic acid, present in tea leaves, can interact with the function of P-selectin, an adhesion molecule involved in atherothrombosis which mediates the interaction between leucocyte and endothelium and platelets.

Oral intake of green tea extracts with high catechin content increases the resistance of plasma LDL cholesterol to oxidation. In animal studies, the administration of catechin concentrates equivalent to 8-10 cups of green tea can decrease blood pressure, inhibiting the action of angiotensin converting enzyme. Several observational studies conclude that regular ingestion of green tea for one year can reduce the risk of hypertension.

With regard to the effect on glycaemic control, the consumption of a green tea extract 20 minutes before an oral dose of glucose significantly reduced the blood glucose levels, due to the inhibition of the activity of α-amylase and α-glycosidase by catechins (31). The effects of green tea supplementation on risk of type 2 diabetes have been controversial because of the variable forms of administration, concentration of bioactive compounds, and the presence or the absence of caffeine. The effect of green tea on body composition, mainly total and abdominal adipose tissue, is also controversial and seems to be ethnicity-dependent, with more positive results in Asian people.

The anti-inflammatory effects of green tea are primarily based on the suppression of the inflammatory route mediated by nuclear factor-kappa β. Obese and hypertensive subjects supplemented with 379 g of green tea extracts for 3 months presented a significant reduction in the levels of TNF-α and C-reactive protein.

3.4 Lycopene

Lycopene is a carotenoid without provitamin-A activity, that is naturally present and is the pigment responsible for the distinctive red colour of tomatoes, watermelon and other fruits. Their ripening, and cooking and processing can modify lycopene content and bioavailability. Among the natural carotenoids, it is the most potent antioxidant and free radical quencher. High lycopene consumption has been associated with a decreased risk of cardiovascular disease, including atherosclerosis, myocardial infarction and stroke (32). Several studies have reported that serum lycopene levels are inversely related to intimal wall thickness or lesions in the carotid artery and aorta, suggesting that lycopene may protect against atherosclerosis. Lycopene protects LDL from oxidation in vitro, and some dietary studies have shown that lycopene-containing foods increase resistance of LDL to oxidation in vivo. In addition to its antioxidant properties, lycopene has been proposed to reduce cholesterol levels by the suppression of cholesterol synthesis, increase in LDL degradation, and inhibition of the hydroxyl-methyl-glutaryl-coenzyme A-reductase enzyme.

A meta-analysis of intervention trials suggests that lycopene is effective in reducing total cholesterol and LDL cholesterol if taken in dosages higher than 25 mg daily (reduction of mean LDL cholesterol of -10.35 ± 5.64 mg/dl, approximately 10% in patients with slightly elevated LDL cholesterol, similar to the effect of low doses of statins). The hypolipidaemic effect is dose-dependent, and is lower with lower doses of lycopene. The absorption of lycopene is influenced by several factors, including the processing of tomato products and
the presence of dietary fat. Heating and homogenization enhance the release of lycopene, and dietary fat enhances lycopene absorption via stimulation of bile production. Lycopene also has a significant effect in lowering blood pressure, particularly in hypertensive subjects (4 trials). Blood pressure properties of lycopene have been attributed to the stimulation of nitric oxide production in the endothelium. Other mechanisms that can explain the protective effects in atherosclerosis prevention are: through inhibition of LDL oxidation, inhibition of foam cell formation, inhibition of the pro-inflammatory cascade generated by the macrophages, and inhibition of smooth muscle cell proliferation (Fig. 3) (33).

![Fig 3. Possible mechanisms by which lycopene (LYC) may prevent atherosclerotic process](image)

4. Summary

Cardiovascular disease (CVD) is the leading cause of death in the world. Most cardiovascular diseases can be prevented by addressing behavioural risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol, using population-wide strategies. For primary prevention in general populations or in persons at risk, several nutrients / foods have been identified that could potentially reduce cardiometabolic disease risk.

A large and growing body of evidence supports the potential protective roles of some specific foods and specific nutrients in CVD prevention. The studies focused on foods/nutrients have tried to identify bioactive components potentially improving CVD risk factors such as LDL-cholesterol, blood pressure or insulin-resistance. Plant sterols/stanols, polyphenols and lycopene have well-founded evidence in the literature as nutrients with potential to reduce CVD risk.
5. References

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