

# THE ROLE OF NUTRACEUTICALS IN THE PREVENTION OF CARDIOVASCULAR DISEASE

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**ABSTRACT:**

Cardiovascular disease (CVD) ranks among the most common health-related and economic issues worldwide. Dietary factors are important contributors to cardiovascular risk, either directly, or through their effects on other cardiovascular risk factors including hypertension, dyslipidemia and diabetes mellitus. Nutraceuticals are natural nutritional compounds, which have been shown to be efficacious in preventative medicine or in the treatment of disease. Several foods and dietary supplements have been shown to protect against the development of cardiovascular disease. The aim of this review is to present an update on the most recent evidence relating to the use of nutraceuticals in the context of the prevention and treatment of cardiovascular disease.

***Key words:*** nutraceuticals, cardiovascular disease, polyphenols.

## **INTRODUCTION**

Cardiovascular disease (CVD) is common, indeed the majority of adults above sixty years of age will experience some manifestation of CVD. Based on data from 2012 and 2013, it has been estimated that CVD is responsible for 17.3 million deaths annually worldwide (1). Morbidity is also high, and in Europe, 200 billion Euros of healthcare expenditure is attributable to CVD (2). Risk factors for CVD can be categorized as modifiable and non-modifiable. Modifiable risk factors include obesity, hypertension, hyperlipidemia, diabetes mellitus, metabolic syndrome and lifestyle risk factors such as unhealthy diet, smoking and physical inactivity. Dietary factors are also important contributors to cardiovascular risk, either directly, or through their effects on other risk factors including hypertension, dyslipidemia and diabetes mellitus. (3). Reduction of risk factors in the population, especially blood pressure reduction and lipid-lowering can have important impacts upon mortality from CVD (4).

Protective effects against CVD have been demonstrated for several foods and dietary supplements (5) thus presenting new possibilities for population-level reduction of CVD risk. Evidence suggests that this approach is very promising. For example, in the PREDIMED observational study, participants in the highest quintile of polyphenol consumption had a relative risk of cardiovascular disease of 54% compared to those in the lowest quintile (6). The aim of this review is to present an update on the most recent evidence relating to the use of nutraceuticals in the context of the prevention and treatment of cardiovascular disease. Unfortunately, few studies have measured the associations between nutraceutical consumptions and 'hard' outcomes such as mortality. Large randomized controlled trials are particularly rare, and thus there is a paucity of evidence in this area. Thus, our discussion will be largely focused on the effects of nutraceuticals on well-characterized risk factors for CVD.

## **NUTRACEUTICALS**

The term 'nutraceuticals' was introduced by Stephen De Felice, founder and chairman of the Foundation for Innovation in Medicine, in 1989. A nutraceutical is defined as a 'food, or parts of a food, that provide medical or health benefits, including the prevention and treatment of disease' (7). The definition encompasses medicinal products made from natural ingredients. Several classes of nutraceuticals have been proposed to have potential benefits in the treatment of CVD and the ones with the strongest evidence are briefly summarized below.

### ***Sterols/stanols***

Plant sterols/stanols are phytosterols, and have been identified in a range of plant products including various fruits and vegetables, cereals, seeds and nuts. Their biological activity results from their molecular structural similarity to cholesterol (8).

### ***Polyphenols***

Polyphenols are phytochemicals with widespread distribution in foods of plant origin. They are found in fruits, vegetables, cereal and legumes. Additionally, they are found in beverages produced from plant products such as tea, coffee, wine and cocoa. Polyphenols are structurally diverse, and over 8000 have been identified. These include flavonoids, phenolic acids, stilbenes and lignans (9). Polyphenols found in grapes and grape derivatives, cocoa and tea are of interest in the prevention of cardiovascular disease. Phenolic compounds are found in grapes and these include anthocyanins, flavanols, flavonols, stilbenes and phenolic acids (10). Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is the most extensively studied grape-derived stilbene contained mainly in grapes. However, resveratrol is common to a variety of species including cranberries, blueberries, peanuts, and Japanese knotweed (11).

Derivatives of cocoa beans (*Theobroma cacao*) are widely consumed in cocoa and chocolate (12). A variety of polyphenols have been identified in cocoa and its derivative. These include catechins, flavonol glycosides, anthocyanins and procyanidins (13). Cocoa-containing foods provide a higher content of flavonoids per serving than other beverages such as red wine and tea (14).

The very widespread and frequent consumption of tea makes investigation of its nutraceutical properties essential. Polyphenols found in tea include catechins, theaflavins, tannins, and flavonoids. The degree of fermentation of tea leaves influences the chemical composition. Green tea, which is minimally fermented, contains more catechins such as epigallocatechin gallate, epicatechin-3-gallate, epigallocatechin and epicatechin (15) whereas the more extensively fermented black tea is rich in flavins and thearubigins (16).

### ***Spirulina***

Spirulina is a blue-green microalga (*Cyanobacterium*). Spirulina is a rich source of protein, vitamins, minerals, carotenoids, and phycocyanins and has a very long history of use as a human foodstuff with no apparent concerns over safety (17,18).

**Table 1** summarizes the methodology and main findings from each study described in the paper.

### **DYSLIPIDEMIA**

Dyslipidemia is an umbrella term for a variety of lipid abnormalities, which increase the risk of cardiovascular disease. Reduction of total cholesterol and low-density lipoprotein-cholesterol (LDL-C) is effective in the primary and secondary prevention of CVD events (19). In particular, low LDL-C levels are associated with lower rates of major coronary events (20). Thus nutraceuticals with the potential to modify the plasma lipid profile have the potential to

reduce the burden of CVD (21). Evidence related to the lipid-modifying effects of nutraceuticals is summarized below.

### *Sterols/stanols*

Consumption of plant sterols/stanols has been shown to be associated with lower circulating concentrations of total cholesterol (TC) in humans (22,23). Their effect is predominantly LDL-C reduction with little or no effect on high-density lipoprotein cholesterol (HDL-C) or triglycerides (24). The mechanism by which sterols/stanols reduce LDL-C is associated with a reduction in the intestinal absorption of cholesterol, the upregulation of hepatic LDL receptors (and consequent increased hepatic cholesterol uptake) and reduced production of endogenous cholesterol (25).

Circulating LDL-C concentrations are inversely correlated with the extent of sterol/stanol consumption. The reduction in plasma LDL-C concentrations associated with sterol/stanol consumption may be as large as 10% (26,27). This could lead to reductions in CVD if the effect is associated with a reduction in cardiovascular events similar to that induced by other drugs with similar lipid-lowering efficacy. As sterols/stanols reduce the intestinal absorption of cholesterol, their effect may be additive to that of statins which act by the reduction of hepatic cholesterol production. Importantly, a meta-analysis of 15 randomized controlled trial would appear to suggest that this is the case. It was found that a combination of statins and stanols/sterols lowered the levels of TC and LDL-C to a greater extent than with statins alone. HDL-C and triglyceride concentrations were not altered by the addition of sterols/stanols to statin therapy (28). Another meta-analysis demonstrated that the lipid-lowering efficacy of plant sterols/stanols was similar when the sterols were consumed as part of the diet and when they administered as a nutraceutical supplement (26), thus allowing for flexibility in the method of drug delivery.

Some evidence exists regarding the effect of sterol consumption on cardiovascular outcomes. Observational data suggest that high intake of plant sterols might be associated with MI prevention in men (29). A recent, large observational study indicated that natural phytosterol intake was associated with TC and LDL-C reduction particularly in men. However, this beneficial effect on lipid profile did not result in a reduction in the risk of CVD (30). One explanation for the LDL-C reduction failing to translate into a reduction in CVD is that sterols/stanols may reduce the absorption of carotenoids and fat-soluble vitamins (31). Such an effect would be expected to be associated with a higher incidence of CVD (32), however further investigations are needed to determine whether this effect occurs in vivo.

### ***Polyphenols***

Several studies have indicated that grape polyphenols may influence plasma lipid concentrations. Consumption of grape juice has been associated with elevated HDL-C (33). A study of the effect of polyphenol-rich grape extract supplement (700 mg) on cardiovascular risk in healthy subjects and found that treatment was associated with a reduction in plasma TC and LDL-C concentrations (34). However, more extensive evidence in the form of a meta-analysis of 9 randomized controlled trials (including 390 participants in total) did not find any effect of grape seed extract on LDL-C (35). While no effect was seen in this combined population, investigations of subpopulations and more sophisticated analysis of lipids has been carried out in other studies. One study found that plasma concentrations of large LDL-C and large LDL particles compared with placebo were decreased in obese subjects supplemented with grape powder for 3 weeks (36). However, the most atherogenic small LDL particles were not affected by treatment (37).

Despite, great enthusiasm with respect to the potential health benefits of resveratrol supplementation, a recent meta-analysis did not demonstrate any effect of this compound on

plasma levels of TC, LDL-C, triglycerides or glucose. A small reduction in HDL-C concentrations was observed (38). Larger, well-designed trials are necessary to confirm these outcomes.

The results of studies investigating the effects of cocoa products on lipid profiles have been summarised in a meta-analysis of six randomized controlled trials (39). The results indicated that short-term cocoa consumption significantly lowered LDL-C by 5.87 mg/dL, marginally lowered TC by 5.82 mg/dL without any evidence of an effect upon HDL-C concentrations. The effects appeared to be dose-dependent and were observed in the subjects with elevated cardiovascular disease risks but not in healthy participants (39). A variety of cocoa derivatives exist and do not all necessarily have similar biological effects. Dark chocolate (which contains cocoa butter and cocoa powder) consumption was compared to white chocolate (which contains cocoa butter but not powder) consumption and no difference between the groups was observed in terms of triglyceride, LDL-C and HDL-C in diabetic patients with hypertension (40). Previous studies have failed to observe benefits of cocoa polyphenols on blood lipids in subjects with hypertension stage 1 (41), overweight (42) and in patients with heart failure (43). A recent meta-analysis of 19 randomized controlled trials of varying designs with a total of 1131 participants indicated that cocoa flavanols were associated with reductions in total triglycerides (-0.10 mmol/L) and increases in HDL-C (0.06 mmol/L) intake (44). Recently published results from the Flaviola Health Study revealed that twice-daily ingestion of 450 mg of cocoa flavanols for 1 month decreased TC by 0.20 mmol/l and LDL-C by 0.17 mmol/l whereas HDL-C increased by 0.10 mmol/l in a low risk, primary prevention population. The authors applied the Framingham Risk Score to their results and concluded that cocoa flavanols predicted a significant lowering of 10-year risk for CVD (45), however only well-designed (preferably randomized) studies can confirm whether this is the case.



Tea polyphenols may also exert lipid-lowering effects. A meta-analysis of 14 randomized controlled trials including 1136 subjects in total found that the administration of green tea beverages or extracts resulted in significant reductions in serum TC and LDL-C concentrations, without altering HDL-C (46). Another meta-analysis of 20 randomized controlled trials appeared to confirm these results (47). In another study, both green and black tea and indicated that both reduced LDL-C whereas green tea also reduced TC (48). Similar properties of black tea were also confirmed by Zhao et al. (49). These observations highlight one of the difficulties of population research into nutraceuticals: Small differences in the preparation of foods, which are not always captured in food-frequency questionnaires, can result in important differences in the composition of the foods and therefore can result in varying biological effects. Black tea consumption was shown to be more effective in lowering LDL-C in subjects with hypercholesterolemia and other markers of elevated cardiovascular risk (49). A recent randomized, placebo-controlled trial demonstrated reduced LDL-C and non-HDL-C after long-term supplementation (12 months) with green tea extract in healthy postmenopausal women (50).

Most studies to date have shown that plasma concentrations of HDL-C in humans are not affected by supplementation with grape products, cocoa and tea polyphenol. The exact mechanisms by green tea exert their LDL-C, lowering effects is not fully understood. Nevertheless, green tea is easily accessible, popular and safe and it may indirectly lead to lower morbidity and mortality rates due to CVD by improving hyperlipidemia outcomes.

Armolipid Plus is a food supplement combining natural ingredients containing red yeast rice, policosanol, berberine, folic acid, astaxanthin and coenzyme Q10. It has been demonstrated that supplementation with this nutraceutical exert reduction of TC (-19.2%), LDL-C (-17.4%) and triglycerides (-16.3%) (51). A very recent meta-analysis of several randomized controlled trials revealed that this nutraceutical is safe, well tolerated and confirmed the beneficial

effects upon lipid profile with reductions in plasma TC of 11-21% and reductions in LDL-C of 15-31% (52).

### *Spirulina*

Spirulina supplementation has been associated with beneficial alterations to blood lipid profiles (53,54). *Spirulina maxima*, given orally (4.5 g/day, for 6 weeks), was associated with significant changes in TC and LDL-C concentrations (55). Furthermore, in a population of individuals with dyslipidemia, consumption of 1 g Spirulina per day for 12 weeks decreased mean levels of triglycerides, LDL-C, and TC without any apparent effect on plasma concentrations of HDL-C (56). A recent meta-analysis of seven randomized controlled trials with Spirulina appeared to confirm these findings (57). Further well-designed trials are required to clarify the mechanism of action of Spirulina supplementation in dyslipidemia and to determine its effects on cardiovascular outcomes.

**Table 1** summarizes the methodology and main findings from each study described in the paper.

## **HYPERTENSION**

Hypertension is an important modifiable risk factor for CVD (58). It has been shown that lowering blood pressure reduces CV risk by 20-25% for myocardial infarction, 35-40% for stroke and about 50% for heart failure (59). The evidence relating to antihypertensive effects of selected nutraceuticals is outlined below.

### *Sterols/stanols*

In contrast to the well-studied effects of sterols and stanols upon lipids, there is a relative paucity of evidence relating to their effects upon blood pressure. Studies have failed to

demonstrate antihypertensive effects of sterols/stanols despite continuing treatment for a year or more (60,61). One recent study, which aimed to analyse the effect of plant stanol esters on arterial stiffness and endothelial function in adults also found no effect on measured blood pressure (62). Although the data are limited there appears to be no antihypertensive effects of these compounds in humans, neither is there any indication of adverse effects on blood pressure.

### *Polyphenols*

It has been suggested that consumption of flavonoid-rich fruits and vegetables may lower blood pressure (63). Studies on the influence of polyphenols on blood pressure are very diverse and have included a great variety of polyphenol-containing foods, including: grapes, berries, cocoa product, tea and other. Some studies have demonstrated a significant beneficial effect of grape-derived polyphenols on blood pressure (64,65). On the other hand, there also numerous studies which did not identify such an association (66,67,68). The conflicting results probably result from the heterogeneity of study design, polyphenol source and population characteristics.

A recently published randomized controlled trial indicated that grape seed extract significantly reduced systolic blood pressure by 5.6% and diastolic blood pressure by 4.7% after 6 weeks of supplementation in subject with mildly elevated blood pressure. Moreover, the blood pressure lowering effects appeared to be dependent on baseline blood pressure, with the greatest reduction observed in subjects with higher baseline blood pressure (69).

The effects of resveratrol on blood pressure have also been studied. A meta-analysis of 6 randomized controlled trials, (247 subjects), appeared to show a dose-response relationship only higher doses ( $\geq 150$  mg day<sup>-1</sup>) of resveratrol significantly reduced systolic blood pressure while there were no significant effects on diastolic blood pressure (70). Another

meta-analysis, which included data from 10 randomized controlled trials indicated that resveratrol supplementation did not affect systolic and diastolic blood pressure (38). Differences in the baseline blood pressure of participants in the study may account for some of these discrepancies.

Cocoa flavanols are the most studied polyphenols in the clinical setting. A meta-analysis of 20 randomized controlled trials involving healthy participants indicated that consumption of polyphenol-rich cocoa products was associated with a reduction in blood pressure (71). A meta-analysis of 42 randomized controlled trials indicated that chocolate or cocoa was associated with reduced diastolic blood pressure and mean arterial pressure (72). Very recent clinical studies also confirm that cocoa flavanols exert a beneficial impact on blood pressure in patients with type 2 diabetes and hypertension (40) and in elderly subjects (73). Moreover, a recent study has demonstrated similar findings after cocoa ingestion in healthy individuals (74). This was associated with a dose-dependent improvement in flow-mediated dilation, decreased endothelin-1 and pulse wave velocity. These findings warrant further investigation into the potential uses for cocoa in the prevention of CVD (74).

Conversely, another study found no evidence of an effect of daily intake of dark chocolate (49 g/day) on blood pressure or arterial stiffness in patients with mild hypertension (75). The Flaviola Health Study found that cocoa flavanol intake (450 mg) for 1 month decreased systolic and diastolic blood pressure by 4.4 mmHg and 3.9 mmHg, pulse wave velocity by 0.4 m/s and led to improved endothelial function in a healthy, primary prevention population, suggesting potential benefits of cocoa in maintain cardiovascular health (45).

Studies on tea polyphenols have also reported blood pressure lowering properties (48,76). A meta-analysis of 10 trials (834 participants) demonstrated that a statistically significant reduction in systolic blood pressure was associated with diastolic blood pressure with black or green tea consumption (77). Furthermore, a recent meta-analysis on the effects of green tea

intake on risk of cardiovascular disease indicated that consumption of green tea is associated with reduced risk of myocardial infarction and stroke (78).

Several clinical studies have demonstrated an antihypertensive effect of pomegranate juice. A recent meta-analysis, which included the results of eight randomized controlled trials investigating the effects of pomegranate juice on blood pressure indicated that consumption of this polyphenol-rich juice significantly reduced both systolic and diastolic blood pressure (79). In addition, lipid-lowering, antioxidant and anti-atherosclerotic actions of pomegranate juice have been reported, making it a very attractive candidate as a nutraceutical with the potential to improve cardiovascular health (80).

The nutraceutical product, Armolipid Plus (containing red yeast rice, policosanol, berberine, folic acid, astaxanthin and coenzyme Q10) was found to be safe, well tolerated and effective in reducing mean 24-h systolic and 24-h pulse pressure in hypertensive and hypercholesterolemic subjects at low cardiovascular risk (51).

### ***Spirulina***

Some studies indicated that *Spirulina maxima* might exert an antihypertensive effect. Oral Spirulina supplementation resulted in systolic and diastolic blood pressure reduction in a small clinical trial (55). Conversely, no effect of Spirulina upon blood pressure was observed after consumption of 1 g Spirulina per day for 12 weeks in a Greek population (56). Administration of 2 g Hawaiian Spirulina for 3 months was associated with improved blood pressure and endothelial function in patients with hypertension. However, evidence relating to cardiovascular outcomes is lacking and further well-designed trials are required to clarify the clinical value of Spirulina supplementation in lowering blood pressure (81).

**Table 1** summarizes the methodology and main findings from each study described in the paper.

## **DIABETES MELLITUS**

Diabetes mellitus is a well-established risk factor for cardiovascular disease. Diabetes mellitus type 2 is associated with high risk for developing cardiovascular complications (82). Moreover, patients with diabetes and hypertension have about twice the risk of cardiovascular events as nondiabetic patients with hypertension (83). It has been estimated that the global prevalence of diabetes mellitus will rise to 552 million by 2030 (84). Observational studies indicated that diet is one of the factors, which might prevent diabetes and its complications (85). The TOSCA observational study demonstrated that a diet characterized by a higher intake of total polyphenols was associated with a better cardiovascular risk factors profile and a lower grade of subclinical inflammation in population with diabetes mellitus type 2 (86).

### ***Polyphenols***

Relatively few studies have evaluated the effects of grape polyphenol on hyperglycemia. Guilford et al. (87) indicated that regular red wine consumption is associated with a 30% risk reduction for type 2 diabetes. Consumption of grape seed polyphenols and red wine grape pomace flour have been associated with significant reductions in blood glucose (88,89). Conversely another study found no effect of grape juice polyphenols in healthy individuals (90).

A randomized controlled trial revealed that supplementation of resveratrol for 3 months significantly improved the mean hemoglobin A1c, in patients with type 2 diabetes mellitus (91). A recent meta-analysis of 11 randomized controlled trials found that resveratrol reduced fasting glucose, insulin, glycated hemoglobin, and insulin resistance in subjects with type 2 diabetes, but not in those without diabetes (92). Conversely, a meta-analysis of 10 randomized controlled trials did not indicate a significant effect of resveratrol supplementation upon glucose level (38). The mechanism of action of resveratrol in the treatment of diabetes

mellitus seems to be multifactorial; resveratrol may have antioxidant properties, increase AMPK activation, and increase internalization of glucose through modulating glucose transporter expression (93,94,95).

Results from studies evaluating influence of cocoa and tea polyphenols on glycemic markers are inconclusive. A meta-analysis of 42 randomized controlled trials indicated that chocolate or cocoa reduced fasting insulin concentrations, insulin after glucose challenge and improved insulin resistance. However, no effect upon fasting glucose or HbA1c was observed (72). Consumption of chocolate high in polyphenols was not associated with differences in fasting insulin in patients with diabetes mellitus type 2 and hypertension (40).

Another study found an independent inverse relationship between daily chocolate intake and concentrations of insulin, homeostatic model assessment of insulin resistance (HOMA-IR) and liver enzymes. Results of that study suggest that chocolate intake result in beneficial changes in liver enzymes and protect against insulin resistance (96). The results of a randomized controlled trial also support a role for cocoa flavanol intake in improving insulin resistance (44). The current data is insufficient to recommend chocolate and cocoa for glycemic control.

A meta-analysis of 17 trials comprising a total of 1133 subjects revealed that green tea consumption was associated with significantly reduced fasting glucose and hemoglobin A1c (97). Furthermore, a meta-analysis of has also indicated changes in fasting glucose but glycated hemoglobin similar as fasting blood insulin and HOMA-IR did not change after green tea catechins administration (98). In a meta-analysis of 10 trials, which evaluated effect of green tea on populations at risk of diabetes mellitus type 2, green tea was not associated with reduced levels of fasting plasma glucose, fasting serum insulin, 2-h plasma glucose in the oral glucose tolerance test, hemoglobin A1c (HbA1c) and HOMA-IR (99).

Recent meta-analysis of 10 trials including 608 subjects which aimed to indicate the effect of green tea in patients with diabetes mellitus type 2 found that tea could alleviate the decrease of fasting blood insulin and reduced waist circumference only when the intervention was extended for longer than 8-weeks. No effects of tea on HOMA-IR, fasting blood glucose, LDL-C, HDL-C, body mass index, systolic blood pressure, diastolic blood pressure, triglycerides and fasting cholesterol were observed (100). These mixed results mean that it is unclear whether green tea has anti-diabetic effects.

Polyphenols might influence glucose homeostasis by several mechanisms, by inhibiting carbohydrate digestion and glucose absorption in the intestine, protecting pancreatic  $\beta$ -cells, reducing glucose release from liver and activating insulin receptors and glucose uptake in insulin-sensitive tissues (101).

### ***Spirulina***

Spirulina might be beneficial in controlling blood glucose level in subject with diabetes mellitus type 2. Supplementation of 2 g/day for 2 months resulted in reduced fasting blood glucose, postprandial blood glucose levels and HbA1c (53). Conversely oral supplementation of Spirulina in a separate trial (4.5 g/day, for 6 weeks) did not result in changes in the markers of glucose metabolism (55). Further trials are required to clarify the clinical value of Spirulina supplementation in treatment of diabetes.

**Table 1** summarizes the methodology and main findings from each study described in the paper.

## **CONCLUSIONS**

Dyslipidemia, hypertension and diabetes are major modifiable risk factors for CVD. Current medical treatments for the management of diabetes and dyslipidemia in some especially high



risk patients are insufficient and current evidence suggests that the application of nutraceuticals may have the potential to increase the effectiveness of therapy (as well as to reduce the residual risk). Many of the nutraceuticals investigated for the prevention and treatment of CVD are well tolerated in patients. However, there is often insufficient data available with respect to long-term safety and effectiveness against clinical outcomes such as myocardial infarction and mortality. Further clinical research should be conducted to identify nutraceuticals with the best clinical and cost-effectiveness in the prevention and treatment of cardiovascular disease (102-105).

**Table 1.** The main findings of the studies on the application of selected nutraceuticals in dyslipidemia and/or diabetes and/or hypertension.

Reference	Study design	Subjects characteristic	Intervention	Results
<b>STEROLS/STANOLS</b>				
(26)	Meta-analysis of 9 RCTs	263 participants	Plant sterols/stanols dose range: 1.0- 3.0 g/day; duration range: 4-6 weeks	LDL-C reduction by 12 mg/dL
(27)	Meta-analysis of 124 RCTs	624 participants	Phytosterols dose range: 0.2 - 9.0 g/d	LDL-C reduction by 6-12% (0.6-3.3 g/d); dose-response relationships
(28)	Meta-analysis of 15 RCTs	500 patients treated with statins	Plant sterols/stanols dose range: 1.8 – 6 g/d; duration range: 4 - 85 weeks	TC and LDL-C reduction by 0.30 mmol/L; no changes in HDL-C and TG
(29)	Nested case-referent study	1005 individuals (219 women, 786 men)	Plant sterols, 128 – 341 g/d	Increasing sterol intake from 150 to 340 mg/d reduces the risk of a first MI by 29% in men
(30)	Observational study	35 597 Dutch men and women	Phytosterols, dose range: 231.3 – 366.0 mg/d; follow-up 12.2 years	TC (-0.06 mmol/l), LDL-C (-0.07 mmol/l) reduction; no effect on CVD risk
(60)	Randomized, double-blind, parallel	282 mildly to moderately hypercholesterolemic subjects	Stanols or sterols, 2 g/day for 1 year	Glucose increased by 1–3%; No effect on BP, CRP
(61)	Case-control study	100 healthy subjects	Plant stanol ester margarine for a period of 2 years or longer	No effect on lipoproteins, BP, FMD and intima-media thickness
(62)	Randomized, controlled, double-blind, parallel trial	92 asymptomatic subjects	Plant stanols, 3.0 g/d for 6 months	TC, LDL-C, non-HDL-C declined by 6.6, 10.2, and 10.6%, reduced arterial stiffness in small arteries; No effect on BP, glucose, TG
<b>GRAPE POLYPHENOLS</b>				
(33)	Single arm intervention	26 healthy meals	Red grape juice 150 ml twice per day for 4 weeks	HDL-C, ApoB increase; Hcy level reduction; no effect on ApoAI level
(34)	Randomized, double-blind, placebo-controlled clinical trial	60 healthy subjects	Grape extract Eminol®, 700 mg/ day for 8 weeks	TC, LDL-C reduction
(35)	Meta-analysis of 9 RCT	390 participants	Grape seed extract dose range:150 – 2000 mg/d; duration range: 2 – 24 weeks	SBP (-1.54 mm Hg), heart rate (-1.42 bpm) reduction; no effect on DBP, lipid levels, CRP

(36)	Randomized, double-blind, placebo-controlled, cross-over	24 obese subjects	Grape powder, 46 g twice per day for 3 weeks	Reduction of large LDL-C and large LDL particles
(64)	Randomized double blind placebo-controlled crossover	24 males with metabolic syndrome	Grape polyphenol powder, 267 mg/day for 30 days	SBP reduction; no change in DPB, HDL-C, fasting plasma glucose
(65)	Randomized double-blinded, placebo controlled, incomplete-crossover	60 males mildly hypertensive	(a) Grape-red wine extract or (b) grape extract, 800 mg/day for 4 weeks	(a)SBP, DBP reduction (a) and (b): no changes in TC, LDL-C, HDL-C, TG and vascular function parameters
(66)	Randomized, double-blind, placebo-controlled, parallel	50 pre- and mild-hypertension subjects	Red grape cell powder, 200 mg or 400 mg for 12 weeks	DBP reduction only in 200 mg group; No effect on SBP, FMD
(67)	Randomized, double-blind, placebo-controlled trial	69 hypertensive individuals	Grape-seed polyphenols 1000 mg/d, vitamin C 500 mg/d	No effect on SBP, DBP and pulse pressure variation
(68)	Controlled intervention	28 healthy young adults	Grape and pomegranate juice, 200 mL/day for 8-week	No effect on lipid profile, inflammation, BP or glycaemia
(69)	Randomized, double-blinded, two-arm, parallel, placebo-controlled trial	36 pre-hypertension subjects	Grape seed; 300 mg/d twice daily for 6weeks	Reduced SBP by 5.6% and DBP by 4.7%; effects were more marked in subjects with higher baseline BP; no effect on fasting plasma lipids, glucose, oxidised LDL, FMD
(89)	Randomized, controlled, prospective, parallel-group trial	38 patients with metabolic syndrome	Red wine grape pomace flour, 20g/day for 16 weeks	Improvement in blood pressure, glycaemia and postprandial insulin
(90)	Randomized, controlled, crossover, intervention trial	24 healthy individuals	Tropical grape juice ( <i>Vitis labrusca L.</i> ), 400 mL for 14 days	Increase in antioxidant biomarkers; No effect on glucose and uric acid level
(91)	Randomized, prospective, open-label, controlled trial	62 patients with T2DM	Resveratrol, 250 mg/d for 3 months	Improvement in HbA1c, SBP, TC, and total protein levels; No changes in body weight, HDL-C, LDL-C
(92)	Meta-analysis of 11 RCTs	388 subjects with and without	Resveratrol, dose range: 10 – 1500 mg/d;	Reduction in fasting glucose, insulin, HbA1c, and insulin resistance in T2DM;

		T2DM	duration range: 2 – 24 weeks	No effect on glycemic measures of nondiabetic participants
(38)	Meta-analysis of 10 RCTs	575 participants	Resveratrol dose range: 8 – 1500 mg/day; duration range: 4 - 26 weeks	Reduction in HDL-C; no effect on TC, LDL-C, TG, glucose, SBP, DBP, CRP
(70)	Meta-analysis of 6 RCTs	247 subjects	Resveratrol, dose range: 16 mg – 1 g/day; duration range: 12 – 48 weeks	At dose $\geq 150$ mg day <sup>-1</sup> SPB reduction no effect on DBP
<b>COCOA POLYPHENOLS</b>				
(39)	Meta-analysis of 8 RCTs	215 participants	Cocoa products dose range: 88 – 963 mg/day; duration range: 2 – 18 weeks	LDL-C and TC reduction by 5.87 mg/dL, changes depend on the dose of cocoa and the healthy status of participants; no effect on HDL-C
(40)	Randomized, placebo-controlled, double-blind study	T2DM patients with hypertension	Dark chocolate, 25 g/day for 8 weeks	Increase in ApoA1; HbA1c, Apo B, SBP, DBP, FBS reduction; No effect on TG, LDL-C, HDL-C, BP, insulin resistance or glycemic control
(41)	Intervention clinical trial	22 subjects with hypertension stage 1	Chocolate 50 g, 70% cocoa/day (2135 mg polyphenols) for 4 weeks	No effect on glucose metabolism, lipid profile, biomarkers of inflammation, adhesion molecules, oxidized LDL, and blood pressure
(42)	Randomized, placebo-controlled, cross-over study	30 overweight adults	Cocoa/chocolate, 37 g/d dark chocolate and a sugar-free cocoa beverage (dose of cocoa = 22 g/d, total flavanols = 814 mg/d) for 4 weeks	Increase in resting BP by 4 mmHg, reduction in arterial stiffness in women; No effect on fasting BP, glucose, blood lipids
(43)	Randomized, double-blind, placebo-controlled trial	22 patients with stable CHF (NYHA $\geq$ II)	Flavanol-rich chocolate 40g/d for 4 weeks	Improvement of endothelial function; No effect on SBP, DBP, HR, glucose, HbA1c, TC, LDL-C, HDL-C, TG
(44)	Meta-analysis of 19 RCTs	1131 participants	Cocoa flavanols, dose: 166 – 2110 mg/d; duration: 2 – 52 weeks	HDL-C increase, TG reduction, improvement in insulin resistance
(45)	Randomized, controlled, double-masked trial	low risk, healthy, middle-aged individuals without history of CVD	Cocoa flavanols, 450 mg twice a day for 4 weeks	Reduction of SBP by 4.4 mmHg, DPB by 3.9 mmHg, PWV by 0.4 m/s, TC by 0.20 mmol/l, LDL-C by 0.17 mmol/l reduction, HDL-C increase by 0.10 mmol/l;
(71)	Meta-analysis of 20 RCTs	856 mainly healthy participants	Flavanol-rich cocoa products, 30 – 1080 mg of flavanols per day, duration range: 2 – 18 weeks	BP reduction by 2-3 mm Hg

(72)	Meta-analysis of 42 RCTs	1297 participants	Chocolate, cocoa, or flavan-3-ols	DBP, mean arterial pressure, fasting insulin and insulin after glucose challenge reduction; improvement in HOMA-IR, FMD
(73)	Randomized, double-blind, controlled, parallel-arm	90 elderly subjects	Cocoa flavanols, 993 mg, 520 mg or 48 mg for 8 weeks	SBP, DBP, glucose, insulin, HOMA-IR, reduction and Increase in HDL-C only among subjects taking 993 mg and 520 mg
(74)	Randomized, double-blind, controlled, cross-over design,	20 healthy individuals	Cocoa flavonoids exert, 10 g cocoa (0, 80, 200, 500 and 800 mg cocoa flavonoids/day) in 5 periods lasting 1 week each	DPB, SBP reduction; FMD improvement, endothelin-1 and PWV reduction by ameliorating blood pressure
(75)	Randomized, controlled, cross-over trial	22 mild hypertension	Dark chocolate, 49 g/day for 8 weeks	No effect on BP and arterial stiffness
(96)	Cross-sectional observation study	1153 individuals	Chocolate	Higher chocolate consumption was associated with lower HOMA-IR, serum insulin levels, $\gamma$ -GT and ALT
<b>GREEN/BLACK TEA POLYPHENOLS</b>				
(46)	Meta-analysis of 14 RCTs	1136 subjects	Green tea beverages or extracts, dose range respectively: 340 – 900 mL, 250 mg – 9 g per day; duration range: 2 - 12 weeks	Reduction of TC by 7.20 mg/dL, LDL-C by 2.19 mg/dL; no effect on HDL-C
(47)	Meta-analysis of 20 RTCs	1415 participants	Green tea catechins dose range: 145 - 3,000 mg/day; duration range: 3 - 24 weeks	TC (-5.46 mg/dL), LDL-C (-5.30 mg/dL) reduction; no effect on HDL-C, TG
(48)	Meta-analysis of 11 RCTs	821 participants	Green and black tea, duration range: 12 - 48 weeks	Green tea: TC (-0.62 mmol/L) , LDL-C (-0.64 mmol/L) , SBP - 3.18 mmHg), DBP (-3.42 mmHg) reduction; Black tea: LDL-C (-0.43 mmol/L), SBP (-1.85 mmHg), DBP (-1.27 mmHg) reduction
(49)	Meta-analysis of 10 RCTs	411 participants	Black tea beverage or extract, duration range: 4 – 24 weeks	LDL-C (-4.64 mg/dL) reduction; black tea more effective in lowering LDL-C in the subject with higher CV risk such as HCh; no effect on TC and HDL-C
(50)	Randomized, double-blind, placebo-controlled, parallel-arm	936 healthy postmenopausal women	Green tea extract, 1315 mg catechins per day, duration: 12 months	TC, LDL-C and non-HDL-C reduction; No effect on HDL-C

	trial			
(76)	Meta-analysis of 13 RCTs	947 participants	Green tea extract or beverages, catechins 100 – 1500 mg, Duration range: 3 – 16 weeks	SBP (-2.08 mm Hg), DBP (-1.71 mm Hg), TC (-0.15 mmol/L), LDL-C (-0.16 mmol/L) reduction
(77)	Meta-analysis of 10 trials	834 participants	Green tea extract or beverages, 250 – 583 mg/day, duration range: 8 – 14 weeks	SBP (MD -2.36mmHg), and DBP (MD -1.77mmHg) reduction
(78)	Meta-analysis of 9 RCTs	259,267 individuals	Green tea beverages, follow-up: 9 week – 13 years	1–3 cups of green tea per day reduced risk of MI and stroke compared to <1 cup/day, ≥4 cups/day reduced risk of MI compared to < 1 cup/day; ≥10 cups/day of green tea lowered LDL compared to the < 3 cups/day group
(97)	Meta-analysis of 17 RCTs	1133 subjects	green tea, catechin content range:208 to 1207 mg/d; duration range: 8 – 24 weeks	Fasting glucose (-0.09 mmol/L) and HbA1c (-0.30%) reduction; no effect on fasting insulin and HOMA-IR
(98)	Meta-analysis of 22 RCTs	1584 subjects	Green tea catechins, dose range: 456 – 1206.9 mg/d; duration range: 3 – 12 weeks	Fasting blood glucose (-1.48 mg/dL) reduction; no changes in FBI, HbA1c or HOMA-IR
(99)	Meta-analysis of 7 RCTs	510 subjects at risk of T2DM	Green tea (900 – 1200 mL) or green tea extract (558 – 1500 mg), duration range: 4 – 24 weeks	No changes in fasting plasma glucose, fasting serum insulin, 2-h plasma glucose in the oral glucose tolerance test, HbA1c and HOMA-IR
(100)	Meta-analysis of 10 trials	608 subjects	Green tea (150 – 1500 mL) or green tea extract, catechins (240 – 750 mg), duration range: 4 – 16 weeks	Alleviate the decrease of fasting blood insulin and reduced waist circumference only in intervention >8-week; no effect on HOMA-IR, fasting blood glucose, LDL-C, HDL-C, BMI, SBP, DBP, TG and fasting cholesterol
<b>ARMOLIPID PLUS</b>				
(51)	Non-randomized, controlled, study	66 patients with HT and HCh with low CV risk	Armolidip Plus, 1 tablet for 6 months	TC (-19.2%), LDL-C (-17.4%), TG (-16.3%), 24-h SBP, DBP reduction; no effect on HDL-C
(52)	Meta-analysis of 13 RCTs	mostly patients with mild to moderate dyslipidemia	Armolidip Plus for 6-48 weeks	TC (11-21%) LDL-C (15-31%) reduction
<b>SPIRULINA</b>				
(53)	Randomized placebo-	25 T2DM subjects	Spirulina, 2 g/day for 2 months	TC, LDL-C reduction, HDL-C increase; fasting blood glucose,

	controlled, parallel-group trial			postprandial blood glucose levels, HbA(1c) reduction; improvement in long-term glucose regulation
(54)	Randomized placebo-controlled, parallel-group trial	37 T2DM subjects	Spirulina, 8 g/day for 12 weeks	TG reduction
(55)	Open-label, non-randomized,	36 healthy subjects	Spirulina maxima, 4.5 g/day for 6 weeks	TC, LDL-C, SBP, DPB reduction; no change in glucose
(56)	Open-label, non-randomized,	52 dyslipidemic subjects	Spirulina, 1 g per day for 12 weeks	TG (16.3%), LDL-C (10.1%), TC (8.9%), non-HDL-C (10.8%), ratio of TC HDL-C 11.5% reduction; no effect on HDL-C, BP
(57)	Meta-analysis of 7 RCTs	522 participants	Spirulina, dose range: 1 – 10 g/day; duration range: 8 - 48 weeks	TC, LDL-C, TG reduction; elevating those of HDL-C (6.06 mg/dL)
(81)	Randomized, double-blind, placebo-controlled trial	40 hypertensive patients with lacking evidence of CVD	Hawaiian Spirulina, 2 g/day for 3 months	Reduction in BMI, weight, SBP and stiffness index

\*Abbreviations: PWV – pulse wave velocity, MI – myocardial infarction, ApoAI – apolipoprotein AI, ApoB – apolipoprotein B, Hcy – homocysteine, FBS – fasting blood sugar, HbA1c – hemoglobin A1c, HOMA-IR – homeostasis model assessment–insulin resistance, CHF – congestive heart failure, HT – hypertension, HCh – hypercholesterolemia, FBG – fasting blood glucose, FBI – fasting blood insulin.

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