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The cardioprotective effects of polyphenols: A focus on classic cardiovascular risk factors

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Abstract

Cardiovascular disease remains the primary cause for death globally. Flavonoids are polyphenolic compoundswith well-known antioxidant properties, found in high concentrations in common dietary sources like fruits, vegetables, legumes. There is growing evidence that flavonoids exhibit cardioprotective properties by influencing classic risk factors for cardiovascular disease: hypertension, diabetes mellitus, dyslipidemia, smoking and stress. Recent data show that flavonoids decrease both systolic and diastolic blood pressure through nitric oxide-dependent mechanisms. Cocoa-derived antioxidants are mostly associated with antihypertensive effects in several trials. Accordingly, rich in flavonoids, other types of food have a beneficial impact on lipid profile, by lowering LDL and increasing HDL levels, accompanied by an ameliorated proinflammatory cytokines' pattern. The propitious influence of flavonoids in several metabolic diseases and particularly in diabetes mellitus, is mediated by their ability of mitigating insulin resistance and increasing insulin sensitivity in peripheral tissues. Tea catechins play a pivotal role in regulating glucose metabolism among other polyphenols too, diminishing diabetic complications such as diabetic neuropathy, nephropathy, retinopathy etc. Interestingly, flavonoid consumption can reduce smoking detrimental effects on the cardiovascular system, by reducing redox state or inflammation. Accordingly, increased flavonoid uptake seems to exert anxiolytic and antidepressant properties, reducing psychological stress. More clinical studies should be conducted to better understand the beneficial impact of flavonoid consumption on cardiovascular health.

Key words: coronary artery disease; flavonoids; hypertension; dyslipidemia; diabetes mellitus; stress; smoking; obesity; atherosclerosis; resveratrol

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1. Introduction

Cardiovascular disease remains the primary cause for death and is strongly associated with complications with increased morbidity. Pharmaceutical treatment is the cornerstone for the primary and secondary prevention of coronary artery, peripheral artery or cerebrovascular disease.[1, 2] Nonetheless, recent data indicate that certain dietary habits may favor patients with increased probability for or suffering from cardiovascular disease. Classic risk factors for cardiovascular disease comprise of hypertension, dyslipidemia, diabetes mellitus, smoking habit, obesity and stress, all with increasing prevalence in countries which have adopted a western type of life.[1, 2]

Polyphenols consist of large multiples of phenol structural units which encompass variety of subgroups; flavonoids, phenolic acids, stilbenes and lignans. Furthermore, polyphenols occur in high concentrations in common dietary sources like fruits, vegetables, legumes e.g. onions, blueberries, grapes, citrus fruits, black and green tea, red wine and cocoa[3] (**Table 1**). Accumulating research data demonstrate that polyphenols exert pleiotropic actions, influencing cardiovascular disease in multiple manners. Moreover, their mechanism of action not only involves scavenging free radicals and other oxidative stress products but additionally includes modulating systemic inflammation and redox state and auspicious regulation of vascular properties.[4] In addition, observations from small interventional studies also suggest that flavonoids, in particular, are implicated in the reduction of atherothrombotic risk affecting several platelet activation pathways e.g. the reduction of platelet aggregation following the administration of purple grape juice[5] or the inhibition ADP-induced platelet activation after various berries consumption[6] and the mitigation of P-selectin expression and thrombin-dependent platelet aggregation succeeding the use of grape seed extract[7].

Among a variety of dietary compounds or substances which likely exert cardioprotective properties, polyphenols have a pivotal and fundamental role in preventing the occurrence of CVD complications, which mainly derives from their anti-inflammatory, antioxidant and antithrombotic capacity. For example, findings from prolonged, prospective cohort studies show that catechins (a flavonoid subgroup), from tea or other sources, not only may prevent ischemic heart disease but they can also reduce the risk for ischemic heart disease death. [8, 9] Resveratrol, is a stilbenoid, found in notable concentrations in red wine, and exerts versatile and pleiotropic effects in numerous aspects of CVD development (**Figure 1**).[10-12]

In this review, we focus on the beneficial impact of various polyphenols intake on the classic risk factors for CAD, with reference to the possible biochemical mechanisms involved in polyphenols' cardioprotective actions.

Abbreviations

AGE, Advanced glycation end-product; AT I: angiotensin I; AUC, area under the curve; BP, blood pressure; CAD, coronary artery disease; COX-2, cyclooxygenase-2; CRP, c-reactive protein; CVD; cardiovascular disease; DM, diabetes mellitus; DOCA-salt, deoxycorticosterone acetate-salt; EDHF, endothelium-derived hyperpolarizing factor; EGCG, epigalloccatechin-3-gallate; eNOS, endothelial nitric oxide synthetase; ET1, endothelin 1; FMD, flow mediated dilatation; GLUT, glucose transporter type; HbA1c, Haemoglobin A1c; HDL, high density lipoproteins; HMG-CoA, hydroxymethylglutaryl-CoA; HUVEC, human umbilical vein endothelial cells; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; LDL, low density lipoproteins, MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; MetS, metabolic syndrome; NF-kB, nuclear factor – kB; NMDA, N-methyl-d-aspartic acid; NO, nitric oxide; PPARγ, peroxisome proliferator-activated receptor γ; PUFA, polyunsaturated fatty acids; RAAS, renin angiotensin aldosterone system; RAGE, advanced glycation end-product receptor; RCT, randomized controlled trial; RNS: reactive nitrogen species; ROS, reactive oxygen species; SGLT, sodium-glucose transport protein; SOD, superoxide dismutase; TNFa, tumor necrosis factor – a; VCAM-1, vascular cell adhesion molecule 1.

2. The impact of polyphenol consumption on classic risk factors for atherosclerosis

2.1 Hypertension

Hypertension is a well-established risk factor for CAD. Recent evidence suggests that blood pressure variability, meaning random fluctuation of BP values, plays a significant role in cardiovascular

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Table 1a. Polyphenols: subgroups and sources [3]

Non-Flavonoids			Flavonoids				
Phenolic acids	Stilbenes	Lignans	Flavonols	Flavan-3-ols	Flavones	Flavonones	Anthocyanidins
Coffee	Grapes	Sesame seed	Onions	Blueberries	Parsley	Oranges	Blueberries
Cinnamon	Red wine	Sunflower seed	Apples	Strawberries	Celery	Grapefruit	Strawberries
Vanilla	Peanuts		Romaine lettuce	Pears	Lettuce	Tomatoes	Cherries
Green Tea	Cocoa		Tomatoes	Black tea	Oranges	Lemons	Cabbage
Salicylic Acid			Almonds	Green tea	Lettuce		Cranberries
			Quinoa	Cocoa			Raspberries

Table 1b. Frequently used polyphenols in diet and occurrence in foods

Non-Flavonoids			Flavonoids			
Chlorogenic Acid	**Resveratrol**	Lignans	Quercetin	Epigallocatechin	Naringenin	Anthocyanins
Arabica Coffee Beans: 5.5-8%	Red Wine: 0.27/0-2.78 mg/150 ml	Sesame seed: 29 mg/100gr	Capers: 234 mg/100 gr	Green Tea: 7380 mg/100 gr	Grapefruit: 1.18mg/100gr	Black Rasberry: 589 mg/100gr
Robusta Cofffe Beans: 7.0-10.0%	White wine: 0.04-0.17 mg/150 ml		Radish: 70 mg/100gr	White Tea: 4245 mg/100 gr	Limes: 3.40mg/100gr	Wild blueberry: 558 mg/100gr
			Onions: 32 mg/100 gr	Black Tea: 3250 mg/100 gr	Oranges: 3.27/100gr	Blackcurrant: 190-270 mg/100gr

prognosis, in certain clinical circumstances.[13] Flavonoids may affect several pathophysiologic pathways involved in the transition from the prehypertension to hypertension stage, including endothelial dysfunction, attenuated NO production and bioavailability, vascular remodeling and increased sympathoadrenal status combined with the stimulation of RAAS axis, according to data from small RCTs.[14-16] Another aspect of BP abnormalities is the appearance of sustained low-grade inflammation and excessive redox state.[17]

Researchers selectively focus on the impact of polyphenols from olive oil (oleuropein and hydroxytyrosol) and red wine (resveratrol and quercetin) on cellular pathways implicated in the inflammatory processes, the most important of which seems to be NF-kB, based on observations from an animal study.[18] Combining data from a translational [19] and an animal study [20], researchers have displayed that the consumption of flavonoids is associated with decreased expression of NF-kB, causing lower levels of pro-inflammatory molecules and ROS, resulting

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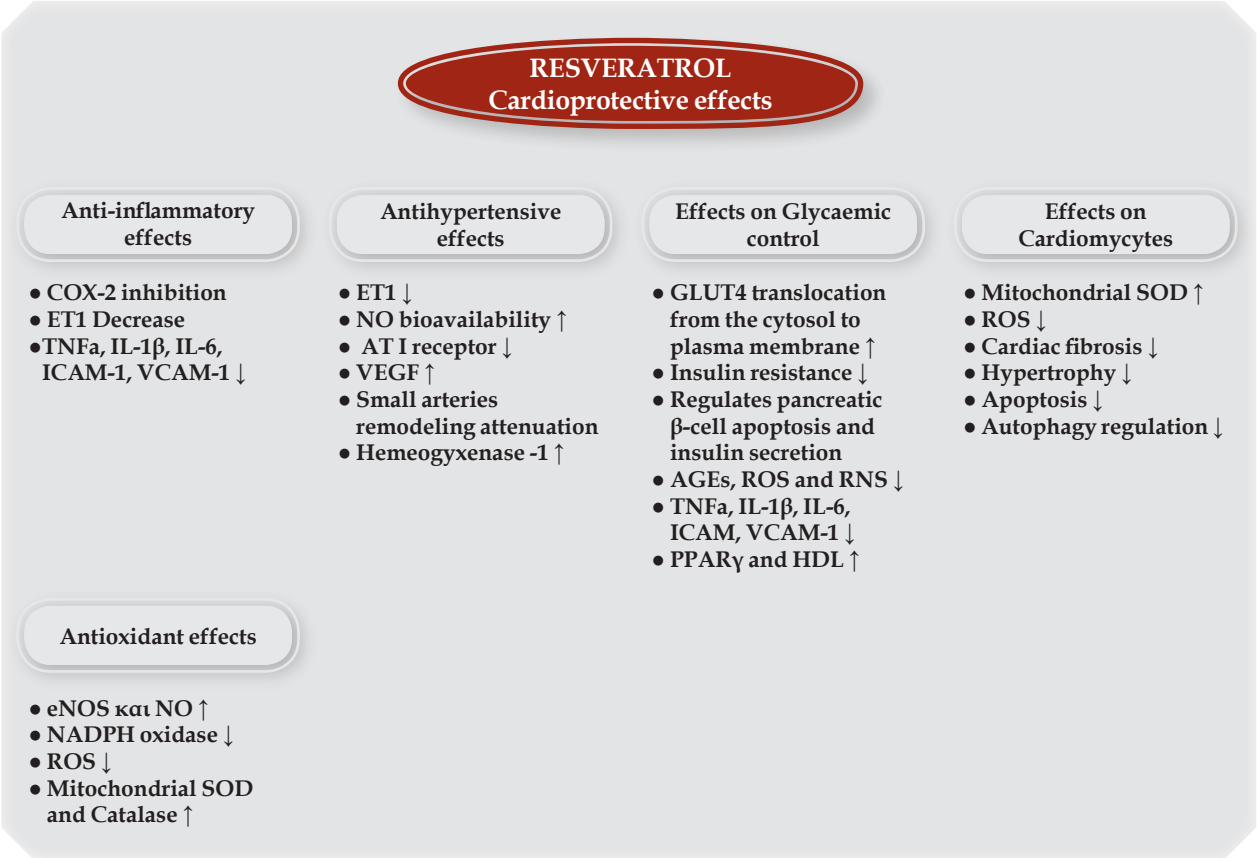

Figure 1. The cardioprotective effects of resveratrol. Resveratrol exerts pleiotropic effects on the cardiovascular system with its antioxidant capacity regulating glycaemic control, vasoconstriction, modulating systemic inflammation and cardiomyocyte microenviroment

in diminished MMP activity and MCP-1 levels,[19, 20] thus suggesting that flavonoids exert favorable anti-inflammatory effects. Added to that, polyphenols' actions are related to the regulation of endothelial-dependent secretion of NO, a potent vasodilatory factor, which plays a key role in vascular health. Moreover, flavonoids may exert their anti-hypertensive capacity by mediating eNOS activity and the activation of other enzymes that mitigate ROS aggravating effects.[21, 22] In addition, data from trial conducted on HUVEC and observations from a rat model, showed that increased polyphenols intake decreases adherence molecules (e.g. ICAM-1, VCAM-1) expression, leading in the attenuation of systemic inflammation.[23, 24] Typical examples are red wine and black tea -derived compounds which induce certain intracellular pathways favoring the phosphorylation of eNOS and NO release in circulation in addition to the secretion of EDHF in some experimental animal models,[25, 26] all playing a crucial role in the balance between vasoconstrictive and vasodilatory agents acting on endothelium.

The above-mentioned data derive mainly from experimental and animal model studies. However, accumulating evidence from human studies indicate that polyphenols and flavonoids could be used in the prevention or even as subsidiary treatment of hypertension. Large observational studies show that the consumption of anthocyanin[27] or cocoa[28] in particular, results in an 8% lower risk for hypertension or a lower prevalence of hypertension, respectively. In addition, the increased consumption of catechin and epicatechin, found in a grape seed extract beverage, for 12 consecutive weeks in patients with prehypertension, resulted in lowering BP values.[29] Similar findings were also observed after the incorporation of red grape

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cell powder (containing catechins, anthocyanins, and resveratrol) in the diet of individuals with prehypertension or mild hypertension, accompanied with favorable effects on FMD, a vascular function index.[30] Noticeably, dark chocolate[31] and olive oil[32] antioxidants seem to modulate NO production, resulting in a BP decrease, suggesting that small amounts of polyphenol-rich foods could be efficient in preventing the occurrence of hypertension.

Several studies have been conducted to investigate the impact of flavonoid-rich products in BP values in individuals with established hypertension. Cocoa, of all products, holds a potent anti-hypertensive capacity, as demonstrated in multiple studies. Moreover, a meta-analysis of 133 trials showed that cocoa, among various substances, could efficiently decrease both systolic and diastolic BP.[33] Similar findings were presented in other, more recent meta-analyses, in which cocoa products were also associated with BP reduction.[34, 35]Albeit flavonoid-containing products are considered to possess anti-hypertensive properties in general, only cocoa and soy protein isolates have been shown to present persistent BP-lowering effects in a series of trials[34, 35] while other products show results in discrepancy; either favorable or negligible effects.[36]

In summary, it appears that the enrichment of diet with polyphenol-rich foods could be of use in the prevention or in the subsidiary, non-pharmaceutical treatment of hypertension, by affecting BP values, endothelial and vascular health.

2.2 Dyslipidemia

It is well-known that lipid metabolism dysregulation and alterations in lipid profile constitute a fundamental aspect in atherosclerosis development. The augmentation of circulating LDL levels is the predominant background regarding the dyslipidemic settings in the pathology of atherosclerosis, accompanied with an escalation of its oxidization in the vascular tunics and concurrently inflammation. HDL holds an anti-inflammatory capacity acting as an oxLDL scavenger and its attenuation comes in second, furtherly enhancing the imbalance between deteriorating and defensive vascular mechanisms[37].

Diet plays a pivotal position in regulating lipid levels. A vast amount of surveys has been held to clarify the protective role of polyphenols in the prevention or treatment of dyslipidemias in atherosclerosis. For instance, flavonoids influence the absorption of lipids in the intestine, by regulating the function of transport proteins[38] and they augment the release of cholesterol in feces, in addition to the decrease of LDL production by liver cells, suggested by the findings in a rat model.[39] Furthermore, flavonoids attenuate LDL levels by decreasing the hepatic secretion of ApoB100,[40] the upregulation of LDL-receptor, the enhancement of the catabolism of fatty acids and the inhibition of foam cells formation through elevated PPAR activation.[41, 42]

In various human studies which enrolled individuals with normocholesterolemia or mild hypercholesterolemia, soybeans (which contain isoflavone and other polyphenols) presented with LDL oxidation inhibitory capacity and LDL-lowering effects.[43, 44] These antioxidant and lipid regulatory properties appear to be dose-dependent in some of the studies.[44] Rich in polyphenols cocoa increases HDL concurrently to attenuated LDL oxidation in patients with CVD risk.[45, 46] In addition, the consumption of 50 gr of dark chocolate per day for 3 weeks by healthy volunteers improved lipid profile, especially in female participants[47] and other studies suggest that cocoa acts beyond decreasing LDL,[48] exerting pleiotropic effects in vascular health.[49] Cranberries exert great anti-inflammatory effects, instantly improving endogenous antioxidant status which reflects in decreased inflammatory indices e.g. CRP. In extent, long-term cranberry juice administration in ovariectomized rats is correlated to LDL decrease along with improved endothelial function.[50] Olive oil consumption also correlates to lower oxLDL levels and the melioration of endothelial function.[32]

A recent meta-analysis including 5 RCTs with a total number of 442 subjects shows that quercetin (found in vegetables like capers, radish or onions) has minor clinical effects in lipids, apart from a significant reduction in triglycerides.[51] On the other hand, resveratrol, which is abundant in red wine, has a

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potent antioxidant and anti-inflammatory properties in animal and human studies, resulting in LDL decrease, lower LDL/HDL ratio,[52] attenuated TNFa and IL-6 levels and a retardation of endothelium degeneration in patients with CAD.[52, 53] Importantly, resveratrol's favorable effects occur through the inhibition of HMG-CoA reductase and increased cholesterol efflux, through bile acid-dependent mechanisms.[54] We should also mention that nuts consumption can improve lipid profile as they contain important amounts of polyphenols (beyond the fact that they are a major source of PUFAs). For example, a 4-week hazelnut consumption benefited the lipid profile of hypercholesterolemic human patients by reducing total cholesterol, LDL and triglycerides and in addition led to elevated HDL levels and improved inflammatory status.[30, 55]

It should be noted that even though several research findings strongly suggest the useful impact of flavonoids in achieving the control of dyslipidemias, we stand far from the determination of the appropriate proportions to maintain a balanced lipid profile. More RCTs are required to investigate the significance of polyphenols in lipid metabolism, especially in hypercholesterolemic patients with CAD or in CVD risk. It should not be neglected that some rich in flavonoid products, e.g. grapefruit may affect the hepatic metabolism of the prescribed pharmaceutical treatment, leading in adverse effects that otherwise could be prevented.[56]

2.3 Diabetes Mellitus and Obesity

Polyphenols and flavonoids consumption potently affects glucose metabolism, in favor of retarding the development of atherosclerosis.[57, 58] The propitious influence of flavonoids in several metabolic diseases is highlighted in recent findings regarding their role in the treatment of non-alcoholic fatty liver disease.[59] In the context of DM, flavonoids are implicated in carbohydrate and lipid metabolism modulation, adipose tissue metabolism, and attenuated oxidative stress and inflammation.[60] Flavonoids are involved in better glucose regulation by two biochemical mechanisms; firstly, by increasing insulin sensitivity and glucose utilization in peripheral tissues and secondly by influencing the activity of transmembrane glucose transporters (e.g. GLUT1, GLUT2, GLUT4, SGLT-1 etc).[57, 61]

Green tea catechins and other polyphenols feature protective characteristics on DM-induced endothelial dysfunction in diabetic mice, while other flavanol compounds promote endothelial repair, as demonstrated in some experimental, animal, diabetic models.[62,63] Interestingly, grape seed-derived procyanidin significantly prevents obesity, while other studies imply its favorable effect on myocardial hypertrophy and remodeling, added on its regulatory effect on lipid and glucose metabolism, in diabetic mice models.[62,64] Fascinatingly, silymarin protectively decreases oxidative stress and cardiomyocyte apoptosis, improves renal, lipid and glucose biomarkers pattern and restores β-pancreatic cells activity followed by a decline in insulin resistance, in rats. [5, 66] In a large observational study with approximately 124,000 participants, the dietary intake of certain flavonoid subclasses was found useful in achieving weight maintenance and prevented obesity.[67] Interestingly, soy isoflavone consumers likely have a better adipose-associated endocrine profile, presenting lower leptin levels, in diabetic women.[68]

A large series of studies have been conducted to investigate the beneficial impact of different flavonoids on diabetic disease and its complications. To begin with, grape seed proanthocyanidins may preserve normal neural tissue morphology and decrease DM-induced oxidative stress in various animal studies.[69, 70] Quercetin also seems to exert a neuroprotective effect in myenteric rat neurons.[71] Fascinatingly, in a double-blind, randomized trial with Type I and II DM patients, Valensi P et al., showed that a 4-week increased intake of quercetin alleviated symptoms of diabetic neuropathy, like numbness, jolting pain and irritation, with contemporaneous improvement of the quality of life.[72] Curcumin antioxidant capacity likely promotes nerve regeneration and functional recovery.[73] Added to that, the administration of icariside may be advantageous in patients reporting diabetic erectile dysfunction, yet another aspect of diabetic

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neuropathy, as demonstrated in a diabetic rat experimental model.[74]

Flavonoids antioxidant and anti-inflammatory capacity suggestively benefits diabetic retinopathy, in resemblance with the abovementioned findings; for example, epicatechin (found in high concentration in cocoa) dose-dependently attenuates AGE accumulation in retinas[75] and green tea EGCG withholds ocular neovascularization and vascular permeability in isolated human retinal tissue cells.[76] Puerarin seems to decrease retinal epithelial cells apoptosis by diminishing localized oxidative stress and leukostasis, in isolated retinal capillary endothelial cells.[77]

Diabetic rats reated with grape seed extracts benefited in terms of better glucose metabolism, insulin resistance and in addition presented with significantly ameliorated renal function indices.[78] In other animal studies, different flavonoids, like chalcone or diosmin, decrease the hyperglycemic-dependent and inflammation-mediated renal injury in terms of AGE levels, hypoalbuminemia and fibrosis, in rats.[79, 80] In summary, a diet enriched with increased flavonoid quantities, has a beneficial impact on diabetic complications yet more randomized, clinical studies should be conducted since the vast majority of research data derives from translational or animal studies.

2.4 Smoking

Smoking causes a variety of detrimental effects on the cardiovascular system, additionally to its association with respiratory and malignant diseases. Smoking ingredients strongly influence the balance between oxidative and anti-oxidant status, favoring pro-inflammatory mechanisms which furtherly augment intra- and intercellular oxidative stress, DNA degeneration etc. which mark the initiation of cardiovascular, respiratory and malignant pathology.[81, 82]

Flavonoid intake seems not only to have positive effects on lung fibroblasts and alveolar cells, reducing emphysematous changes and smoking-induced cytotoxic injury,83 but additionally meliorates vascular properties and improves the proinflammatory and pro-coagulant state. Moreover, novel studies have indicated that everyday dietary intake of concord grape juice, rich in polyphenols, improves aortic stiffness and reduces systemic inflammation and pro-coagulation.[84, 85] Accordingly, a recent meta-analysis indicated that grape polyphenols favorably improve endothelial function, with a more significant impact on smokers. Davinelli S et al., demonstrated that anthocyanidins contributed to the reduction of oxLDL levels in smokers and the other groups of the study.[86] The propitious impact on oxidative stress following flavonoid administration includes reduced proinflammatory cytokines i.e. TNFa, IL-8, attenuated degrading proteases like MMP-9, both in vivo and *in vitro* [87] and reduced redox state in healthy smokers.[88] Noticeably, flavonoid consumption not only affects peripheral vasculature but suggestively exerts cardioprotective and anti-apoptotic capacity in cardiomyocytes, in rats.[89] On top of that, increased intake of flavonols and flavones potentiates a better prognosis and is inversely associated to non-fatal and fatal myocardial infarction.[89] Taken all together, flavonoids antioxidant properties favor the reduction of cellular redox state, while exerting pleiotropic effects to meliorate vascular functionality and improve cardiovascular health.

2.5 Stress

Stress has been introduced as a classic risk factor for coronary heart disease and several emerging findings indicate its fundamental role in cardiovascular disease.[90] Rich in flavonoids, tea and coffee beverages may, shortly after consumption, produce physiological results like heart rate and BP alterations (increase for coffee or decrease for tea), changes in temperature etc., and more importantly, psychological responses like anxiety reduction.[91] These early findings initiated the seeking for deeper investigation and recent evidence indicate that flavonoids exert anxiolytic properties. Furthermore, Vasilopoulou CG et al., demonstrated that mountain tea prevents anxiety-related behaviors and confers mental protection on adult mice.[92] Added to that, apart from its antihypertensive properties, grape seed

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proanthocyanidin[93] and resveratrol[94] had beneficial effects on psychological symptoms and the quality life of menopause women. Interestingly, recent data showed that Icariin has similar beneficial effects on depressive symptoms and the reduction of alcohol drinking in persons with a history of bipolar disorder and alcohol abuse, when compared to naltrexone.[95] Emerging data from animal studies also imply that quercetin, aglycone and polyphenols in rosemary tea[96-98] generate anxiolytic and anti-depressant-like behavior and in some studies even mitigate insomnia as observed in menopausal Japanese females,[96] possibly through the reduction of brain oxidative stress, declined inflammation and neurotransmitters modulation.[96, 98] Resveratrol likely possesses a potent, neuroprotective capacity and quite recent study results indicate that its anti-inflammatory properties modulate neuroinflammation and prevent cellular death, which is reflected in ameliorated anxiety and depression-associated symptoms, in rats.[99, 100] Albeit the abovementioned findings demonstrate a promising, favorable impact of flavonoid intake on behavior, few human studies exist and even fewer have been conducted regarding the influence of flavonoids on psychological aspects in CAD, revealing a knowledge gap needed to be fulfilled in the forthcoming years.

2.6 Bioavailability, source of polyphenols and biologic actions

As we have already discussed the beneficial, cardioprotective role of various polyphenols and flavonoids, a critical issue must be mentioned regarding how the bioavailability of phenolic components affects their biologic actions in the human body. Their absorption and metabolism, thus plasma and presumably active metabolite levels strongly depend on their structural characteristics, molecular size, solubility and the dosage administered.[101]

Polyphenols are mostly too hydrophilic to passively penetrate the gut wall and, except for flavanols, their majority is glycosylated, incommoding absorption and are additionally resistant to acid hydrolysis in the stomach.[102] Moreover, some flavonoids bind to other food like milk proteins or alcohol, raising another obstacle in their efficient absorption,[36] which mainly occurs in the small intestine.[103] Once absorbed, most of the polyphenols undergo conjugation which in several cases has been shown to decrease the antioxidant capacity e.g. of quercetin and other anthocyanins.[104, 105] Affinity for plasma transports, albumin-binding and variances in tissue uptake also influence polyphenol bioavailability and their biologic potency.[106]

These data demonstrate that plasma concentrations may highly vary according to the type of polyphenol or the type of the food source and may not reflect neither the abundancy of particular components in someone's diet or flavonoid concentrations in several food sources.[107, 108] For example, observations from bioavailability studies have shown that relatively low plasma levels of the active metabolites of tea and cocoa polyphenols can be achieved after oral administration.[107, 108]

A plethora of animal and human interventional studies concerns the administration of polyphenols in higher, than in typical food sources, concentrations, raising a reasonable question for the practical use of their research findings in everyday practice (**Table 2 and 3**). It seems that we stand far from determining or predicting achieved plasma levels of polyphenol active metabolites, which is a critical matter since they may possess a critical supplemental role in standard pharmaceutical treatment in near future. More bioavailability studies should be conducted to clarify the desired dosage of flavonoids in diet, in the form of foods, concentrated extracts or enriched and functional foods.

3. Conclusion

Dietary polyphenols act as free radical scavengers and antioxidants, modulating inflammatory processes, reducing thrombotic risk, thus improving vascular and heart function. Flavonoids beneficially influence nearly all known classic risk factors for coronary artery disease, modifying lipid profile, regulating glucose metabolism and exerting antihypertensive properties. Added to that, their pivotal influence in cardiovascular disease progression is also reflected

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in their capacity to ameliorate behavioral symptoms, exerting anxiolytic and antidepressant effects. Nonetheless, poor bioavailability of polyphenols can be a major issue in their clinical use as adjuvant, pharmaceutical treatment. All the above mentioned findings indicate that flavonoids have a direct propitious impact on atherorosclerosis progression. Further research is needed to determine the exact mechanisms connecting polyphenol administration with atherosclerosis regression in cardiovascular disease.

Conflict of Interest

All authors declare no conflict of interest.

Table 2. ***In vitro*** **and animal studies on polyphenol administration and their impact on cardiovascular indices**

Component (frequent in)	Experimental model	Results	Author
Quercetin (capers, red wine)	Cobalt-Chloride induced hypertension in rats	Quercetin administration reversed H_2O_2 and malondialdehyde increase, augmented eNOS activity and NO bioavailability, mitigated NF-kB pathway activation	Ajibade et al. (2017) [18]
	Wistar rats fed with quercetin for 4 weeks	Quercetin regulated lipid metabolism, lowering LDL, by rather increasing cholesterol-to-bile acid conversion than HMG-CoA-dependent pathways	Zhang et al. (2016) [39]
	Olfactory bulbectomy-induced depression in mice, who then were treated with quercetin for 2 weeks	Quercetin prevented depression through NMDA and NO-dependent pathways	Holzmann et al. (2015) [109]
	Rat insulin-secreting beta cells incubated with quercetin	Quercetin increased acute insulin secretion	Kittl et al. (2016) [110]
Curcumin (turmeric, spices)	Streptozocin-induced DMII in rats, fed with curcumin in several dosages for 4 weeks	Curcumin has been shown to enhance neuron axonal regeneration and functional recovery in a dose-dependent manner.	Ma et al. (2016) [73]
	Streptozocin and nicotinamide-induced DMII in rats, receiving curcumin and piperine combination	Curcumin in combination to piperine treatment decreased LDL, glucose and triglycerides elevated levels,	Kaur et al. (2016) [111]
	Rat model presenting with depression and insulin resistance after 12-week exposure to chronic mild stress, receiving curcumin	Curcumin reversed depressive-like behavior, decreased LDL, gluscose, triglycerides, glucagon, leptin, and corticosterone levels, as well as imrpoved insulin sensitivity.	Shen et al. (2017) [112]
Resveratrol (red wine)	HUVEC pre-incubated with polyphenols from red wine (resveratrol) and olive oil	Reduced endothelial cell impaired formation, COX-2 and MMP-9 release, diminished intracellular ROS, reduction of inflammatory angiogenesis	Scoditti et al. (2012) [19]
	DOCA-salt induced hypertension in mice fed with resveratrol	Resveratrol prevented the occurrence of increased BP and aorta vasoconstriction in wild type mice but not in mice lacking AMP-activated protein kinase gene.	Sun et al. (2015) [113]
	Rats with isoproterenol-induced MI, pretreated with resveratrol	Resveratrol pretreatment reduced the increase of cardiac necrosis indices like cardiac troponin, LDL, HDL, triglycerides and inflammatory markers TNF-α, interleukin-6	Abbas et al. (2016) [114]
	Streptozocin-induced DMII rats receiving resveratrol for 40 days	Resveratrol treatment decreased glucose and LDL levels, preventing dyslipidemia and hyperglycemic state.	Chen et al. (2011) [115]

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Table 2. *In vitro* and animal studies on polyphenol administration and their impact on cardiovascular indices

Component (frequent in)	Experimental model	Results	Author
Proanthocyanidins (pome fruits, grapes)	Spontaneously hypertensive rats fed with rich in pro-anthocyanidins-rich extract	Reduction of NADPH and NADPH-induced ROS, attenuated macrophage infiltration in heart and kidney cells, lower inflammatory status	Sato et al. (2011) [116]
	Aortas from spontaneously hypertensive rats fed	Proanthocyanidins confer a vasorelaxant effect on rat hypertensive aortas, with increased NO bioavailability	Kawakami et al. (2011) [117]
	Hepatocytes incubated with naringenin	Decreased apoB100 secretion by hepatocytes	Allister et al. (2005) [40]
	Db/db mice fed with grape seed procyanidin B2 for 10 weeks	Grape seed procyanidin B2 prevented the occurrence of diabetic cardiomyopathy	Luan et al. (2014) [62]
	Streptozocin-induced DMII rats, presenting diabetic peripheral neuropathy, fed with grape seed proanthocyanidins extract for 3 weeks	Grape seed proanthocyanidins extract improved nerve conduction velocity (an index of peripheral neuropathy) and decreased LDL levels	Ding et al. (2014) [69]
	Streptozocin-induced DMII rats, treated with grape seed proanthocyanidins extract for 16 weeks	Grape seed proanthocyanidins extract decreased fasting glucose levels, insulin levels, HbA1 and BP values	Bao et al. (2015) [78]
	Male mice with exposed in cigarette smoke for 3 months, receiving pomegranate juice	Pomegranate juice reduces emphysematous changes and injury secondary to cigarette smoke, decreased inflammatory indices like IL-1β, IL-6, TNF-a	Husari et al. (2016) [83]
Genistein (soy bean)	HUVEC pre-treated with genistein suffered oxLDL-induced injury	Reduced oxLDL-mediated VCAM-1, ICAM-1, MCP-1 expression	Zhang et al. (2013) [23]
Catechins (cocoa, tea)	apoE deficient mice treated with cocoa polyphenols for 16 weeks	Decreased LDL, reduced VCAM-1, ICAM-1, attenuation of atherosclerotic plaque	Natsume et al. (2014) [21]
	Streptozocin-induced diabetes in rats treated with catechin hydrate for 3 weeks	Catechin administration prevented vascular dysfunction and vascular oxidative stress, maintaining eNOS activity and NO production.	Bhardwaj et al. (2014) [63]
	Rats exposed to cigarette smoking for 4 weeks and were administered EGCG	EGCG prevented mitochondrial enzyme-dependent apoptosis and myocardial dysfunction in rats, decreasing caspases activity	Adikesavan et al. (2013) [89]
	Adult mice treated with mountain tea for 6 weeks	Mountain tea flavonoids increased glutathione levels, decreased malondialdehyde and caused anxiolytic-like effects on the subjects	Vasilopoulou et al. (2013) [92]
	Spontaneously hypertensive rats treated with (-)-epicatechin for 2 weeks	(-)-Epicatechin treatment increased eNOS activity, NO levels, prevented the development of hypertension and reduced locomotor hyperactivity.	Kluknavsky et al. (2016) [118]
	Streptozocin-induced diabetes in rats, injected with catechin for 4 weeks	Catechin treatment mitigated the streptozocin-induced increase of LDL, triglycerides, apoB, increasing superoxide dismutase, catalase, HDL and glutathione.	Samarghandian et al. (2017) [119]

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Table 3. Impact of, frequent in diet, polyphenols on classic cardiovascular risk factors

Component	Source of component and Dosage	Participants Characteristics and Duration of the administration	Clinical Significance	Reference
Quercetin	162 mg/day quercetin in onion skin extract powder	70 overweight-to-obese patients with pre-hypertension and stage I hypertension randomized to compound or placebo, for 6 weeks	Decreased systolic BP by -3 -6 mmHg in hypertensive patients	Brüll et al. (2015) [120]
	730 mg/day as a dietary supplement	41 prehypertensive and hypertensive patients, randomized to compound or placebo, for 4 weeks	Decreased systolic and diastolic BP -7 mm Hg and-5 mm Hg, respectively in hypertensive patients	Edwards et al. (2007) [121]
	100 mg/day in onion skin extract	99 male smokers, randomized to compound or placebo for 10 weeks	Decreased systolic and diastolic BP -3.6 and -3.3 mm Hg respectively, increased HDL 7.1 mg/dl, reduced LDL 6.7 mg/dl, improved glucose levels, reduced VCAM-1 and IL-6 levels	Lee et al. (2011) [122]
	150 mg/day as a dietary supplement	99 obese prehypertensive and hypertensive patients, randomized to compound or placebo for 6 weeks	Decreased systolic BP -2.9 mm Hg in the hypertensive group, decreased oxLDL and CRP	Egert et al. (2009) [123]
	>500 mg/day VS <500mg mg/day as a dietary supplement	9 RCTs, 587 patients, randomized to supplement or placebo duration >2 weeks	Dosage >500mg/day reduces systolic BP and diastolic BP -4.45 mm Hg and -2.98 mm Hg respectively, dosage <500 mg Hg had no significant impact	Serban et al. (2016) [124]
	>500 mg/day VS <500mg mg/day as a dietary supplement	5 RCTs, 442 patients, duration >4 weeks	Dosage >500mg/day significantly reduces triglycerides -24,54 mg/dl, without affecting HDL or LDL	Sahebkar A et al. (2017) [51]
	QR 333 cream, topical compound consisting of quercetin, ascorbyl palmitate, Vitamin D3 (uknown concentrations)	34 patients with DM Type I or II, randomly assigned to compound or placebo, application 3 times a day, for 4 weeks	Diabetic neuropathy relief and improvement of quality of life	Valensi et al. (2005) [72]

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Curcumin	150 md/day, a dietary supplement	55 postmenopausal women, investigating the impact of exercise and curcumin administration on hemodynamics	The combination of endurance exercise and curcumin not only reduces brachial systolic BP but also aortic systolic BP	Sugawara et al. (2012) [125]
	630 mg, 3 times a day as curcumin extract	65 patients with MetS, randomly assigned to compound or placebo, for 12 weeks	Increase HDL 2,8 mg/dl, reduced LDL 14,04 mg/dl, reduced triglycerides 65 mg/dl, decreased total cholesterol/HDL ratio	Yang et al. (2014) [126]
	15 mg or 30 mg or 60 mg, 3 times a day of curcumin extracted from tumeric	63 patients with ACS, randomly assigned to the 3 arms compared to placebo, for 8 weeks	LDL trended to decrease in low and medium dosage group	Alwi et al. (2008) [127]
	1000mg/day in C3 complex® formula (Sami Labs Ltd., Bangalore, India) consisting of curcumin and curcuminoids	30 obese patients, randomly assigned to compound or placebo for 30 days	Improvement of anxiety scales but not depression scales	Esmaily et al. (2015) [128]
Resveratrol	250 mg trans-resveratrol/day as a dietary supplement	27 aged men, investigating the impact of exercise and resveratrol administration on cardiovascular health, duration 8 weeks	Resveratrol blunts the beneficial impact of exercise on BP decrease	Gliemann et al. (2013) [129]
	Enriched with 8mg resveratrol red grape extract VS red grape extract alone	35 hypertensive, DMII and stable CAD patients, duration 1 year	Decreased IL-6, CCL3, IL-1β and TNF-α in the arm enriched with resveratrol red grape extract	Tome-Carneiro et al. (2013) [130]
	200mg or 400 mg Red Grape Cell Extract (uknown resveratrol concentration, other polyphenols also present)	50 prehypertensive and mild hypertensive patients, randomly assigned to compound (200 or 400 mg) and placebo, duration 12 weeks	Decreased diastolic BP, decreased lipid peroxidation in 200 mg/day group, improved FMD	Vaisman et al. (2015) [30]
	500mg/day resveratrol as dietary supplement	50 healthy adult smokers, duration 30 days	Decreased CRP, increased Total Antioxidant Status by 74.2 μmol/L, decreased triglycerides by 62,83 mg/dl	Bo et al. (2013) [131]
	250 mg/day resveratrol as dietary supplement	62 DMII patients, randomly assigned to compound or placebo, duration 12 weeks	Decreased HbA1c by 0.34%, decreased systolic BP by -11,88 mm Hg, decreased total cholesterol but not HDL, LDL	Bhatt et al. (2012) [132]
	25mg of resveratrol and 10 mg of equol in 200mg of fermented soy per day	60 menopausal healthy women, randomly assigned to compound or placebo, duration 12 weeks	Increased quality of life, decreased heart discomfort	Davinelli et al. (2017) [94]
	Red wine naturally enriched with resveratrol (unknown concentration)	30 healthy individuals, randomly assigned to compound and McDonalds meal (groups in combination), duration 3 weeks	Decreased oxLDL, decreased inflammation-related genomic pathways in red wine vs McDonald meal and McDonald's plus Red wine vs McdDonald's meal arm	Di Renzo et al. (2015) [133]

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Tea Catechins	1315 mg of catechins (843 mg EGCG) in green tea extract	1075 healthy postmenopausal women, duration 1 year	Decreased LDL cholesterol by -4.1%	Samavat et al. (2016) [134]
	500 mg of green tea extract (245 mg total polyphenols, 75 mg EGCG, 25 mg caffeine) two times per day	24 hypertensive, middle-aged women, being investigated for the impact of green tea extract administration combined with low-intensity resistance exercise on hemodynamic parameters, duration 3 weeks	Consumption of green tea extract improved the response to low-intensity resistance exercise.	Arazi et al. (2014) [135]
	Green tea (4 cups/day) vs Green Tea Extract (2 capsules/day) -same amount of catechins- vs placebo	35 obese patients with MetS, duration 8 weeks	Green tea beverages reduced LDL and LDL/HDL ratio, decreased BMI	Basu et al. (2010) [136]
	Black tea (129 mg catechins) two times per day	19 hypertensive patients, randomly assigned to compound or placebo, duration 8 days	Decreased systolic and diastolic BP (-3.2 mmHg and -2.6 mmHg respectively) and prevented BP increase after a fat load	Grassi et al. (2015) [137]
	Black tea in low dose 110mg or high 220 mg of polyphenols (unknown concentration of catechins)	24 prediabetic patients, randomly assigned to low or high dose or placebo, duration 90 days	Significantly decreased incremental blood glucose AUC after sucrose intake, reduction of waist-hip ratio in females	Butacnum et al. (2017) [138]
	Chamomile tea (unknown concentration of catechins) 3g/150 ml water, 3 times per day	64 DMII patients, randomly assigned to regimen or placebo, duration 8 weeks	Reduced HbA1c by 0.43%, reduced insulin serum levels 5.38 μU/dl, improved insulin resistance, increased total antioxidant capacity	Zemestani et al. (2016) [139]
Cocoa flava-3-ols	Cocoa flavanols rich beverages (900 mg of cocoa flavanols)/day	57 hemodialysis patients, randomly assigned to beverage or placebo, duration 30 days	Improved FMD by 18%, decreased diastolic BP -4 mm Hg, improved hemodialysis-induced vascular dysfunction	Rassaf et al. (2016) [140]
	49 gr of dark chocolate (unknown concentration of flavanols) and reduction of habitual snack consumption	22 hypertensive individuals, duration 8 weeks	No impact on systolic or diastolic BP, reduction of body weight	Koli et al. (2015) [141]
	Cocoa beverage (450 mg flavanols) twice per day	100 healthy individuals, duration 4 weeks	Decreased systolic BP by 4.4 mm Hg, diastolic BP by 3.9 mm Hg, increased HDL by 3.8 mg/dl, reduced LDL by 6.8 mg/dl, improved Framingham Risk Score	Sansone et al. (2015) [49]

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Cocoa flava-3-ols	27 g/day (split dose) flavonoid-enriched chocolate (850 mg flavanols of which 90 mg epicatechin and 100 mg isoflavones)	93 postmenopausal women with DMII, duration 1 year	Improved insulin sensitivity, lower insulin levels, reduced total cholesterol/HDL ratio and LDL levels, diminished 10-year total coronary heart disease risk by 0.1, no impact on glucose or HbA1c levels	Curtis et al. (2012) [142]
	40 g Dark chocolate (>85% cocoa, unknown concentration of flavanols) *vs* milk chocolate (cocoa < 35%, unknown concentration of flavanols) *vs* placebo	20 smokers and 20 healthy patients, duration 14 days	Dark chocolate consumption reduced redox state and platelet reactivity in smokers, milk chocolate had no impact	Carnevale et al. (2012) [143]
	20 gr of dark chocolate beverage either in high dose (500 mg) of polyphenols or low dose (250 mg) of polyphenols or placebo (unknown concentrations of flavanols)	72 middle-aged patients, randomly assigned in the 3 arms of the study, duration 30 days	High dose group experience significantly increased self-rated calmness and contentedness relatively to placebo, no impact on mood	Pase et al. (2013) [144]
Coffee (phenolic acids)	Low (420 mg) or high (780 mg) dosage of chlorogenic acid-enriched coffee and low in diterpenes (0.83 mg/d) and caffeine (193 mg/d) per day	75 healthy adults, duration 8 weeks	Increased total antioxidant capacity, no impact on vascular function or lipid indices	Agudelo-Ochoa et al. (2016) [145]
	Diet supplement containing Chlorogenic acid form decaffeinated Green coffee and Berberine, Tocotrienols	40 overweight patients with hyperlipidemia, duration 8 weeks	Decreased HDL, LDL, triglycerides, fasting insulin, insulin resistance and glucose intolerance.	Cicero et al. (2015) [146]

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Περίληψη

Οι καρδιοπροστατευτικές δράσεις των πολυφαινολών: Εστιάζοντας στους κλασικούς παράγοντες καρδιαγγειακού κινδύνου

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Η καρδιαγγειακή νόσος παραμένει η κύρια αιτία θανάτου παγκοσμίως. Τα φλαβονοειδή είναι πολυφαινολικές ενώσεις με γνωστές αντιοξειδωτικές ιδιότητες, που βρίσκονται σε υψηλές συγκεντρώσεις σε κοινές διαιτητικές πηγές όπως φρούτα, λαχανικά, όσπρια. Υπάρχουν ολοένα και περισσότερες ενδείξεις ότι τα φλαβονοειδή παρουσιάζουν καρδιοπροστατευτικές ιδιότητες επηρεάζοντας τους κλασικούς παράγοντες κινδύνου για καρδιαγγειακές παθήσεις, ήτοι την αρτηριακή υπέρταση, τον σακχαρώδη διαβήτη, τις δυσλιπιδαιμίες, το κάπνισμα και το στρες. Πρόσφατα δεδομένα δείχνουν ότι τα φλαβονοειδή μειώνουν τόσο την συστολική όσο και τη διαστολική αρτηριακή πίεση μέσω μηχανισμών που εξαρτώνται από το μονοξείδιο του αζώτου. Τα αντιοξειδωτικά που προέρχονται από κακάο συνδέονται κυρίως με αντιυπερτασικά αποτελέσματα σε αρκετές δοκιμές. Συνεπώς, πλούσια σε φλαβονοειδή, τρόφιμα έχουν ευεργετική επίδραση στο λιπιδαιμικό προφίλ, μειώνοντας την LDL και αυξάνοντας τα επίπεδα HDL, συνοδευόμενα από ένα βελτιωμένο πρότυπο των προφλεγμονωδών κυτοκινών. Η ευνοϊκή επίδραση των φλαβονοειδών σε αρκετές μεταβολικές ασθένειες και ιδιαίτερα στον σακχαρώδη διαβήτη, μεσολαβείται από την ικανότητά τους να μειώνουν την αντίσταση και να αυξάνουν την ευαισθησία στην ινσουλίνη στους περιφερικούς ιστούς. Οι κατεχίνες του τσαγιού διαδραματίζουν κεντρικό ρόλο στη ρύθμιση του μεταβολισμού της γλυκόζης, μεταξύ των πολυφαινολών, μειώνοντας τις επιπλοκές από τον σακχαρώδη διαβήτη όπως η διαβητική νευροπάθεια, η νεφροπάθεια, η αμφιβληστροειδοπάθεια κλπ. Είναι ενδιαφέρον ότι η κατανάλωση φλαβονοειδών μπορεί να μειώσει τις αρνητικές συνέπειες του καπνίσματος στο καρδιαγγειακό σύστημα, μειώνοντας τα επίπεδα οξειδωτικού στρες ή τη φλεγμονή. Κατά συνέπεια, η αυξημένη πρόσληψη φλαβονοειδών φαίνεται να ασκεί αγχολυτικές και αντικαταθλιπτικές ιδιότητες, μειώνοντας το ψυχολογικό στρες. Περισσότερες κλινικές μελέτες θα πρέπει να διεξαχθούν για την καλύτερη κατανόηση του ευεργετικού αντίκτυπου της κατανάλωσης φλαβονοειδών στην καρδιαγγειακή υγεία.

Λέξεις ευρετηρίου: στεφανιαία νόσος, φλαβονοειδή, αρτηριακή υπέρταση, δυσλιπιδαιμία,σακχαρώδης διαβήτης, στρες, κάπνισμα, παχυσαρκία, αθηροσκλήρωση, ρεσβερατρόλη

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