Polyphenol protection and treatment of hypertension

Helmut M. Hügel , Neale Jackson , Brian May , Anthony L. Zhang , Charlie C. Xue

PII: S0944-7113(15)00386-4
DOI: 10.1016/j.phymed.2015.12.012
Reference: PHYMED 51945

To appear in: *Phytomedicine*

Received date: 1 September 2015
Revised date: 7 December 2015
Accepted date: 8 December 2015

Please cite this article as: Helmut M. Hügel , Neale Jackson , Brian May , Anthony L. Zhang , Charlie C. Xue , Polyphenol protection and treatment of hypertension, *Phytomedicine* (2016), doi: 10.1016/j.phymed.2015.12.012

Polyphenol protection and treatment of hypertension

Helmut M. Hügel[a,*], Neale Jackson[a], Brian May[b], Anthony L. Zhang[b], Charlie C. Xue[b]

[a]School of Applied Sciences
[b]School of Health Sciences and China-Australia International Research Centre for Chinese Medicine, Health Innovations Research Institute, RMIT University, Melbourne, VIC 3001 Australia

[*]*Corresponding author.*
Associate Professor Helmut M. Hügel, School Applied Sciences, RMIT University, GPO Box 2476 Melbourne, VIC 3001 Australia
Tel.: +61 3 99252626; fax: +61 3 99253747
E-mail address: helmut.hugel@rmit.edu.au

ABSTRACT

Introduction: High blood pressure is the major risk factor for cardiovascular diseases and the rising prevalence of human hypertension precedes the trend towards a global epidemic of unhealthy ageing. A focus on lifestyle and dietary interventions minimizes dependency on pharmacological antihypertensive therapies.
Review: Observational studies indicate that the intake of dietary flavonoids is associated with a decreased risk of cardiovascular disease (CVD). The evidence suggests that the dietary intakes of polyphenol-rich foods, herbs and beverages including flavonols, anthocyanidins, proanthocyanidins, flavones, flavanones, isoflavones and flavan-3-ols, improves vascular health, thereby significantly reducing the risk of hypertension and CVD. Consumption is associated with an improvement in endothelial function via vascular eNOS and Akt activation. Increased NO bioavailability improves vasodilation and blood circulation, effects protein kinases, ion channels and phosphodiesterases, counteracting vascular inflammation and LDL oxidative stress. Importantly, some polyphenols also inhibit the activity of matrix metalloproteinases, inhibit angiotensin converting enzyme activity and thereby improving SBP and DSB. We review the improvement of polyphenol intake on blood pressure and endothelial function for the treatment of hypertension, including not only observational but also RCTs and pre-clinical studies.
Conclusion: The antihypertensive phytotherapy of polyphenol-rich foods for protection and improving endothelial function with vascular relaxation occurs via the NO-cGMP pathway and ACE inhibition. OPCs stimulate endothelium-dependent vasodilation, suppress vasoconstrictor ET-1 synthesis, activate a laminar shear stress response in endothelial cells and also inhibit the activity of metalloproteinases including ACE lowering blood pressure.

Keywords: Flavonoids, Blood pressure, Polyphenols, Herbs, Cardiovascular disease

Abbreviations: CVD, cardiovascular disease; eNOS, endothelial nitric oxide synthase; Akt, protein kinase B; NO, nitric oxide; LDL, low density lipoprotein; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; tp, total population; mm Hg, millimeter mercury; CAD, coronary artery disease; CHD, coronary heart disease; FFAs, free fatty acids; HDL, high density lipoproteins; FMD, flow mediated dilation; ET-1 endothelin-1; OPCs, oligomeric procyanidins; NO-cGMP, nitric oxide-cyclic guanosine monophosphate; RNS, reactive nitrogen species; RAAS, renin-angiotensin - aldosterone system; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers

Table of Contents

1. Introduction

In 2012 and 2013 in the United States, antihypertensives (2013 Trends and Statistics, 2015) were the most dispensed prescriptions (698 million). The number of treated patients (Aitken et al. 2014) (tp in millions) in 2013 across multiple therapies slightly increased: hypertension (45.7), cholesterol (24.4), antidepressants (22.3), anti-ulcerants (15.3), narcotics (14.9), and antidiabetes (14.0). The magnitude of these numbers of patients mirrors the Western lifestyle of consumer diets (Hügel, 2015) stress, and poor work-life balance contributing to the reliance on pharmacological therapies for hypertension, lipid regulators, antidiabetes, antidepressants, and mood regulators to offset unhealthy habits. This dependence is typical of modern global trends.

Cardiovascular disease (CVD) is the most serious public health challenge throughout the world. The World Health Organization (WHO) estimates that the cost of not engaging and investing in CVD prevention and therapy could amount to as much as $47 trillion worldwide in the next 25 years (Ganna, Ingelsson, 2015) and the impact will be more severe in developing countries, as 80% of cardiovascular deaths occur in low and middle income countries. Elevated blood pressure plays a significant role in cardiovascular disease. Preventative strategies and resourceful management of hypertension that can be used by everyone are urgently needed. It is also a heritable trait, experienced by many and is the biggest contributor to the global burden of disease and mortality. This health problem is predicted to increase over the next decade. The rise in demand for preventative strategies and resourceful hypertension

management that are within the reach of everyone are urgently needed. The causes of hypertension are poorly understood, aging is a risk factor as most of the hypertensive population is 60 years or older, and it is a major risk factor of myocardial infarction, heart failure, kidney disease and stroke. Hypertension research suggests multiple links with lifestyle and personal management of hypertension including stopping smoking, having an active lifestyle and managing diabetes, obesity, electrolyte imbalance, stress, and alcohol consumption is highly probable. Lifestyle changes in particular can lower blood pressure and reduce the risk of heart disease. Among the comprehensive lifestyle modifications, dietary adjustment is one of the most effective measures for modulating hypertension (Wengreen et al. 2013). Even a small lowering of blood pressure is considered to have a significant impact on the severity of hypertension and would reduce the risk of heart disease mortality (Prospective Studies Collaboration, 2002). In this review we examine the literature concerning the effectiveness and extent the regular consumption of polyphenol-rich foods, herbs and beverages including flavonols, anthocyanidins, proanthocyanidins, flavones, flavanones, isoflavones and flavanols, as a preventative strategy to improve endothelial function, reduce blood pressure, consequently sustaining cardiovascular health in low-risk subjects and in significantly lowering and managing hypertension, CHD and CVD in medium and high-risk subjects (Scheme 1).

2. Endothelial dysfunction and hypertension

2.1 Flavonoids: composition and mode of action

Polyphenols are plant secondary metabolites that are present in many fruits and vegetables of which flavonoids are the major class of natural products. Flavonoids are polycyclic compounds having a C6ring–C3– C6ring structure substituted with varying numbers of hydroxyl groups, with the major subgroups of dietary value: anthocyanins, isoflavones, flavones, flavonols, flavanones, flavan-3-ols, and the related oligomeric and polymeric proanthocyanidins [also known as condensed tannins] illustrated in Fig. 1 (Crozier, et al. 2006a; Rodriguez‐Mateos, 2014). The oxidative coupling of (-)-epicatechin and/or (+)-catechin occurring between the C-4 of the heterocycle and the C-6 or C-8 positions of the adjacent unit creates type B (or type C) proanthocyanidins that can occur as polymers of up to 50 units in length. Those consisting exclusively of (-)-epicatechin units are called procyanidins (refer to procyanidin C1, Fig. 1). Generally food proanthocyanidins are hetero-oligomers with monomeric units that vary in the number and pattern of hydroxylation. Dark chocolate is a rich source of proanthocyanidins derived from the roasted seeds of cocoa (*Theobroma cacao)* that are also found in red wine and berries. Green tea contains substantial amounts of flavan-3-ols, mainly (−)-epigallocatechin, (+)-gallocatechin, (−)-epicatechin-3-O-gallate and (−)-epigallocatechin-3-O-gallate. However the monomer levels decline during fermentation of the tea leaves so that the major components in black tea are theaflavin-3-O-gallate, theaflavin-3′-O-gallate and theaflavin-3,3′-O-digallate and more substantial quantities of the high molecular weight thearubigins. Black teas contain 5,000 thearubigin components in molecular weights ranging 1 to 2 kdaltons (Balentine et al. 1997; Kuhnert et al. 2010a; Kuhnert et al. 2010b).

Dietary flavonoids exhibit characteristics of both antioxidant and as signaling molecules. The antioxidant activity of flavonoids is attributed to the scavenging of oxygen-derived radicals (Lin et al. 2002; Miyake et al. 2006). By their ability to:

donate hydrogen, metal ion binding, and resonance stabilization of phenoxyl radicals, flavonoids can exhibit antioxidant activity (Rice-Evans, et al. 1996; Bors et al. 2001). Flavonoids function as reducing agents, metal chelators, reactive oxygen species (ROS) scavengers, chain-breaking antioxidants, quenchers of singlet oxygen formation, and protectors of ascorbic acid. As signaling molecules, flavonoids interact with key cellular receptors or proteins (kinases and enzymes) that are involved in signaling cascades to catalyze or regulate signaling or regulatory pathways, resulting in physiological responses or gene expression (Williams et al. 2004).

As well as providing evidence on the efficacy of polyphenols to improve hypertension, several RCTs have attempted to suggest evidence for their mechanisms of action. An increase in serum cGMP in hypercholesterolemic individuals was found after a 12-week supplementation with 320 mg of purified anthocyanins (Zhu, 2011). This was paralleled by increases in flow mediated vasodilation (FMD) ($r = 0.428$, $p < 0.05$). The administration of an intravenous infusion of *L*-N monomethylarginine (*L* -NMMA), a competitive nitric oxide synthase (NOS) inhibitor, to six members, the beneficial effects of the anthocyanins on FMD were abolished, and significant changes in hyperemic blood flow and blood pressure were observed between the anthocyanin and *L*-NMMA/ anthocyanin interventions. This indicates that the mechanism of action of anthocyanins in the vasculature involves the nitric oxide-cGMP signaling pathway. Healthy volunteers, 1, 2, and 6 h post-consumption, showed that blueberry-related increases in FMD correlated with plasma levels of blueberry metabolites and decreases in neutrophil NADPH oxidase activity (Rodriguez-Mateos et al. 2013). The phenolic metabolite structure resembles that of NADPH oxidase inhibitor acetovanillone, prompting the suggestion that in an in vitro model of endothelial cells they act as potent NAPDH oxidase inhibitors (Steffen, et al. 2008). A reduction in NADPH oxidase activity has previously been linked to alterations in nitric oxide levels via inhibition of superoxide production, (Steffen, et al. 2007). The inhibition of NADPH oxidase activity has been attributed the short term improvements in FMD observed after consumption of (−)-epicatechin (Schewe, et al. 2008). These findings suggest that blueberry polyphenol metabolites may mediate improvements in endothelial function by increasing the bioavailability of nitric oxide via their potential to inhibit NAPDH-oxidase. However, further work to substantiate these claims is required.

2.2 Polyphenol protection of endothelium function-smooth muscle cells

Healthy cardiovascular endothelium is better able to cope with to pro-inflammatory stimulants and oxidative insults (Soto-Vaca et al. 2012; Mulvihill, Huff 2010. The maintenance of vascular tone requires vascular endothelial cells to produce NO from L-arginine by the action of nitric oxide synthase or prostacyclin and vasoconstrictors such as endothelin-1. NO is a vasodilator that also suppresses the expression of endothelial adhesion molecules and prevents platelet aggregation (De Caterina et al. 1995). However oxidative and metabolic stress conditions including hyperglycemia, diabetes, hypertension, dyslipidemia, smoking, or oxidized LDLs generate ROS that react with NO forming peroxynitrite RNS. The rapid depletion of NO contributes to endothelial barrier dysfunction, with increased permeability of the endothelial cells. This enables LDLs to accumulate in the arterial intima, the adhesiveness of leukocytes increases, and as leukocytes accumulate in endothelial cells they initiate inflammation (Ross, 1999). Therefore endothelial disorder is characterized by impaired endothelium-dependent vasodilation, reduced NO bioavailability, and a

prothrombic and proinflammatory state of endothelial cells (Perez-Vizcaino, Duarte, 2010). Endothelial dysfunction contributes to hypertension, atherosclerosis, coronary heart disease, hyperglycemia, diabetes, dyslipidemia, and aging. The mechanism by which polyphenolic compounds may improve endothelium functions is under investigation. Some evidence suggests that specific classes of phenolic compounds or their metabolites may prevent endothelial dysfunction by their antioxidant activity in reducing multiple risk factors associated with endothelial malfunctioning including decreasing blood pressure, dyslipidemia, and LDL oxidation. Flavonoids and anthocyanins do not directly induce NO production or increased bioavailability. Instead their redox antioxidative and anti-inflammatory capacities can augment nitric oxide status through distinct pathways, thereby improving endothelial function. For instance flavonoids via NO-cGMP pathway (Follman et al. 2013) can modify protein kinase mediated signal transduction and induce antioxidant and anti-inflammatory gene expression, (Joy et al. 2006; Yang et al. 2010) they can down-regulate inflammatory gene expression and improve blood pressure (Bondonno et al. 2012). Flavonoids are electron rich and function as reducing agents and chelators of metal-catalyzed oxidation of LDL (Huxley, Neil 2003; Aherne, O'Brian 2000). Polyphenols stimulate gut bacterium growth that modulates metabolic syndrome (Roopchand et al. 2015).

3. The Effects of flavonoids on hypertension and CVD

Several systematic reviews (Wang et al. 2014; Hartley et al. 2013) indicate that the dietary intakes of flavonoids, namely flavonols, anthocyanidins, proanthocyanidins, flavones, flavanones, isoflavones and flavan-3-ols shown in Fig. 1 significantly decrease the risk of CVD.

3.1 Berry anthocyanins and flavanols

Hypertension is a major contributor to CVD. Non-pharmacological approaches to lower blood pressure are commonly recommended strategies to reduce the prevalence of hypertension. Emphasis has also been placed on the anti-hypertensive benefits from a diet high in fruit and vegetables that has been investigated in a number of epidemiological studies and randomized controlled clinical trials (Table 1). High anthocyanin intake has been associated with multiple cardiovascular benefits including a reduced risk of myocardial infarction (Cassidy et al. 2013) reduction in oxidative stress Elks et al. 2011) and increases of NO bioavailability (Edirisinghe et al. 2011).

Although there is mounting evidence that supports the beneficial cardiovascular health benefits from berry consumption, more evidence to support the involvement of fruit polyphenols in lowering blood pressure is required. Clinical intervention studies suggest consumption of flavanol-rich cocoa and chocolate may provide protection against and delay the onset of hypertension by improving endothelial function and decreasing BP. However, the serious concern remains that the high calorie content and therefore intake of high sugar/sucrose, cocoa butter fat, particularly in chocolate products, offsets and detracts from its health benefits for therapeutic applications. In the interests of public health, cocoa processing technologies that focus on maximum cocoa extraction and retention, reducing sugar and lipid levels need to be implemented. Then, the real-world practice of utilizing cocoa products to make a

positive contribution for the protective long-term treatment for multiple benefits of healthy aging will be closer to achievement.

3.2 Flavanols: Tea

Green tea derived from the plant Camellia sinensis, is a popular beverage worldwide and the major source of flavonoid intake in the diet. The health-promoting effects of green tea are mainly attributed to catechins such as (-)-epicatechin and (-)-epigallocatechingallate [EGCG] that belong to a family of compounds known as flavanol polyphenols that comprise 30−50% of the solids in green tea and 90% of the total flavonoids (Balentine et al. 1997) (Fig. 1). Green tea extract has been reported to sustain vascular homeostasis and tone by regulation of vasoconstricting substances, including angiotensin II, prostaglandins, endothelin-1 and vasodilating substances, such as prostacyclin and various endothelium-derived hyperpolarizing factors (Bhardwaj, Khanna 2013; Aird 2007; Galley 2004; Schiffrin 2001)
From the meta analysis by Liu and coworkers of twenty-five eligible studies involving 1476 subjects of randomized controlled trials, to determine the changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP), eleven RCTs overlapped with a selected meta analysis of 13 RCTs on green tea by Peng and coworkers (Liu et al. 2014; Peng et al. 2014). Both sets of data shown in Table 2, for drinking green tea showed that the beneficial effects on blood pressure were only evident after consistent consumption for 12 or more weeks and not after consumption of a single cup of tea according to the Grassi outcomes (Grassi et al. 2009). In addition, the dosage of tea polyphenols consumed daily ranged from low (116·1 mg/d) to high (1207 mg/d) in the meta analysis by Liu, there was no dose-dependent data given, so the optimal long-term intake of green tea requires further evaluation.

Another meta-analysis of 18 studies, 13 on black tea and 5 studies on green tea proposed that the daily intake of 1 cup of green tea may correlate with a 10% decrease in the risk of developing coronary artery disease (Wang et al. 2011). Furthermore, an extensive Japanese prospective cohort study including 40,530 persons, 17 of 30 studies indicated statistically significant beneficial effects of green tea intake against cardiovascular disease. The study found that green tea consumption was inversely associated with mortality from all causes, and the inverse association was more pronounced in women (P = 0.03 for interaction with sex). In men, the multivariate HR (95% CI) of mortality from all causes associated with different green tea consumption frequencies were 1.00 for <1 cup (100 ml)/d, 0.93 (0.83–1.05) for 1–2 cups (100–200 ml)/d, 0.95 (0.85–1.06) for 3–4 cups (300–400 ml)/d, and 0.88 (0.79–0.98) for >5 cups (500 ml)/d, respectively (P for trend 0.03). The corresponding figures in women were 1.00, 0.98 (0.84–1.15), 0.82 (0.70–0.95), 0.77 (0.67–0.89) (P for trend, 0.0001). Women who consumed 5 or more cups green tea (500 ml or more)/d had 62% lower risk of death from cerebral infarction compared with women who consumed <1 cup 100 ml/d. It was concluded that the consumption of around 2 cups of green tea intake daily significantly decreased the mortality risk of CVD (Kuriyama et al. 2006)

Black tea polyphenols
The health effect of tea consumption on blood pressure is controversial. Grassi and coworkers reported in 2009 a randomized, double blind, controlled, cross-over design on 19 healthy men, the effects of various black tea doses [0, 100, 200, 400, 800 mg

black tea flavonoids per day] over 5 periods each lasting 7 days on flow mediated dilation, BP and insulin resistance. Remarkably, they reported that black tea consumption dose-dependently from 100 mg ($P < 0.0121$) to 800 mg/day (($P < 0.0001$) improved FMD, SBP, DBP (refer to Tables 1 and 2). Whilst these results require verification on a larger population sample, the bioavailability, metabolism of theaflavins and thearubigens also requires further investigation, these results have enormous human health significance, suggesting that tea drinking provides universal protective cardiovascular benefits for healthy, pre-hypertensive and for hypertensive patients. The same research group also performed a randomized study on hypertensive patients (Grassi et al. 2015). Blood pressure and wave reflection measurements (conducted under fasting and after a fat intake) prior to and 1,2,3,4 h after intake of black tea (129 mg complex flavonoids) scheduled twice daily for 8 days were performed on 19 hypertensive patients. The outcomes shown in Table 2 support the hypothesis that black tea cardiovascular protection is operative under hyperlipidemia induced vascular stress conditions.

The protective effects of black tea against hypertension-related endothelial dysfunction occurs through attenuation of endoplasmic reticulum stress (San Cheang et al. 2015). Tea flavonoids indirectly increase NO production in endothelial cells via the activation of eNOS [Scheme 1] that depends on p38-mitogenactivated protein kinase (p38-MAPK) and ligand-independent activation of estrogen receptor-α, leading to activation of the PI3-K/Akt pathway and eNOS phosphorylation (Anter et al. 2005; Dias, Joshi 2012). Flavonoids also activate specific signaling pathways reducing oxidative stress by increasing the expression of endogenous antioxidant enzymes such as superoxide dismutase, catalase, and peroxidases, responsible for enhancing/protecting the bioavailability of NO for the NO/cGMP signaling pathway to vasorelaxation (Follman et al. 2013). Tea flavonoids have multiple targets (Keske et al. 2015; Agarwal et al. 2010; Legeay et al. 2015). Besides contributing to increasing NO levels in endothelial cells, they combat cardiovascular complications associated with the metabolic diseases characterized by relationships between insulin resistance and endothelial dysfunction including obesity, metabolic syndrome and T2DM.

The overall result of the meta-analyzed clinical data and its subgroup analyses shows that green and black tea consistently have significant protective effects on healthy pre-hypertensive and hypertensive subjects, lowering BP and pulse wave velocity in the short term of one week and also over twelve weeks, mainly by the dual effects whereby the constituent polyphenols/metabolites in tea improve/prolongs NO bioavailability and their antioxidant activity reduces superoxide levels exerting beneficial vascular effects. However the effectiveness of acute versus long-term benefits of tea intake on BP, FMD remains controversial. Very few long-term/chronic studies to date have examined the effects of green or black tea on hypertension and CVD or what the optimal polyphenol dose-response should be in the long term? When do the vascular benefits plateau, how transient are the effects, is it aged-related?

3.3 Flavanols: Cocoa

According to RCT studies, (Mastroiacovo et al. 2015) cocoa flavanol consumption (refer to Table 1) improves verbal fluency function, blood pressure control, and metabolic profile in 90 healthy elderly subjects, reduce the risk of cardiovascular disease and also accounts for other health benefits shown in Fig. 2. Cocoa's high

polyphenol concentration, especially the flavanol monomer/polymer catechin (-)-epicatechin and its metabolite epicatechin-7-O-glucuronide exert favorable effects on endothelium-derived vasodilation via the stimulation of nitric oxide-synthase to elevate levels of NO. Mechanistically, NO stimulates soluble guanylate cyclase [SGC] present in the deeper-layered smooth muscle cells of blood vessels and in platelets. SGC increases the conversion of guanosine triphosphate [GTP] into the messenger substance cyclic guanosine-3', 5'-monophosphate [cGMP], that initiates dilation of blood vessels and improved blood circulation, also effects protein kinases, ion channels and phosphodiesterases (Follman et al. 2013). Cocoa may also have beneficial effects by protecting against oxidative stress alterations, decreased platelet aggregation, decreased lipid oxidation, and improved insulin sensitivity. These effects are associated with a decrease of blood pressure with a positive promotion toward a reduction in cardiovascular events and strokes. Previous meta-analyses have shown that cocoa-rich foods may reduce blood pressure. In a randomized, double-blind, cross-over design with the intake of flavanol-rich cocoa drinks (high-flavanol content = 917 mg, low-flavanol content = 37 mg both made up with 300 ml water, 19% of total flavanols = (-)-epicatechin) by healthy males (25-32 years, BMI 19-23, n = 16) to study the cocoa drinks acute cardiovascular effects and the corresponding causative compounds, only the high flavanol-content drink was associated with acute elevations of circulating NO and the production of a 6% increase in FMD maximum at 2 h post-intake. Multivariate regression analysis confirmed (-)-epicatechin and its 7-O-glucuronide metabolite as predictors of the vascular effects from flavanol-rich cocoa consumption. Furthermore, the intake of pure (-)-epicatechin reproduced these vascular episodes and also the inhibition of endothelial nitric oxide synthase with the NOS inhibitor *L-N*-mono-methylarginine in the subjects and that of isolated aortic rings, eliminated the vascular effects of flavanols. The claims relating the high-flavanol drinks and NO stimulation were corroborated by increased urinary excretion of NO metabolites (nitrite/nitrate excretions). Consequently these results suggest the important need for the preservation and quantification of (-)-epicatechin equivalents in natural and cooked food matrix to improve surrogate markers for CVD and as a vehicle to assess the multiple potential health benefits of flavanol containing herbs and plant foods. Do only high flavanol-rich cocoa drinks produce acute cardiovascular and other benefits? Which natural foods induce the best acute and chronic NO mediated health benefits? (Schroeter et al. 2006; Ferri et al. 2015).

3.4 Proanthocyanins: Pycnogenol

Pycnogenol®, a herbal dietary supplement derived from French maritime pine bark extract, is standardized to contain around 70% oligomeric procyanidins composed of catechin [2,3-*trans-diol*, 4β-8' linked catechins] and epicatechin [2,3-*cis-diol*, 4β-8' linked epicatechins] with varying chain lengths. The microbiota hydrolysed pycnogenol components [catechin and epicatechin] are appreciably bioavailable. Other constituents are polyphenolic monomers, phenolic or cinnamic acids and their glycosides. The effects of pycnogenol on endothelial dysfunction, on 23 patients with coronary artery disease (CAD) completed a randomized, double blind placebo-controlled cross over study (Enseleit et al. 2012). Patients received pycnogenol (200 mg/day) for 8 weeks followed by placebo or vice versa on top of cardiovascular therapy. Herb treatment was associated with an improvement of FMD from 5.3 ± 2.6 to 7.0 ± 3.1 ($P < 0.0001$). This provided evidence that pycnogenol improves

endothelial function in patients with CAD by reducing oxidative stress. The 2012 Cochrane review (Schoones et al. 2012) examined 15 trials with a total of 791 participants utilizing this herbal supplement for the treatment of seven chronic disorders including hypertension (two studies; N = 69). However it was concluded that the limited number of trials, small sample size, and the risk of bias in the included studies, did not allow definitive conclusions to be reached regarding the efficacy or safety of pycnogenol.

A randomized, double blind, placebo controlled cross over study to test the protective effect of oral pycnogenol, administrated for eight weeks to non-smoking, mildly hypertensive patients was performed. Pycnogenol, 200 mg/day, or placebo was provided to eleven patients (4 women, 7 men) with an average age of 50y (mean SD = 50.3 +/- 9.3 years), systolic blood pressure of 140–159 mm Hg, and/or diastolic blood pressure of 90–99 mm Hg were accepted. Pycnogenol treatment decreased systolic blood pressure significantly ($p < 0.05$) to 133 (mean +/- SEM = 132.7 +/- 4.18) as compared to placebo supplementation in the same individuals for 8 weeks. However the data also demonstrated that the pycnogenol supplementation decreases diastolic blood pressure in hypertensive patients with an average diastolic blood pressure of 94 (mean +/- SEM = 93.8 +/- 1.23) the difference did not reach statistical significance to 92 (mean SEM = 92.0 1.7) (Hosseini et al. 2010; Gulati 2015).

The trial treatment of hypertensive 26 patients with early signs of renal function problems, evaluated the effects of pycnogenol 150 mg per day as an adjunct to angiotensin-converting enzyme (ACE)-inhibitor ramipril, 10 mg per day for 6 months. The ramipril/pycnogel combination lowered systolic and diastolic blood pressure more significantly. SBP 188 +/- 16 to 119 +/- 9 mmHg DBP (-36.7%); DBP from 96.3 +/-7 to 83 +/-4 mmHg (-13.8%) more effectively than the administration of only ramipril: SBP 186 +/- 12 to 123 +/- 12 mmHg (-33.8%); DBP from 96.3 +/-8 to 88 +/- 11 mmHg (-8%). Pycnogenol also protected kidney function (Cesarone et al. 2010).

3.5 Proanthocyanins: Chinese hawthorn, *Crataegus pinnatifida*

The antihypertensive activity of Chinese hawthorn (Jurikova et al. 2012; Kocyildiz et al. 2006) (Crataegus pinnatifida Bge.) fruits, leaves, and flowers has been attributed mainly to polyphenols including (-)-epicatechin, proanthocyanidin B_2 dimer, oligomeric proanthocyanidins [procyandinin C1, leaves] and glycosylated derivatives of flavonoids, especially quercetin-3-galactoside [hyperoside, flowers] and apigenin-8-glucoside [vitexin, flowers]. To evaluate brachial artery flow mediated dilation (FMD) that reflects NO release, the response of 21 mildly hypertensive adults to placebo or hawthorn extract (standardized to 50 mg oligomeric procyanidin per 250 mg extract) were studied (Asher et al. 2012). There was no evidence of a dose-response effect of hawthorn extract on FMD ruling out increased NO bioavailability mechanisms. This suggests that its antihypertensive effects may be mediated by other means than by NO release, such as inhibition of the renin-angiotensin pathway, β-blocker, blocking calcium channels or diuretic activity. Previously, hawthorn has been found to have the highest nitrate reductase activity and in combination with beetroot, (rich in natural nitrate) produced a sustained in vitro NO release with a $t_{1/2}$ of approximately 60 minutes with rapid and sustained human plasma NO levels (~1.4 μM) from a single dose in vivo. After a 30-day intake of hawthorn plus supplement, the steady state human plasma nitrite concentrations elevated from 0.10 μM to 0.28 μM that was statistically significantly greater than placebo. Furthermore, mildly hypertensive subjects (SBP 135 - 160 mm Hg, n = 9) experienced a mean 7 mm Hg

systolic and 2.7 mm Hg DBP reduction, although this was not statistically significant (Zand et al. 2011). This suggests that effective in vivo NO augmentation by hawthorn may require nitrate/nitrite supplementation.

3.6 Proanthocyanins: Red wine

Some of the most vasoactive polyphenols in red wine that have been analytically identified (Corder et al. 2006) in plasma are oligomeric proanthocyanidin [4β-8]-linked [B type] straight chain of trimer-, tetramer-, pentamer-gallate [OPCs] structures. Whilst the wine total polyphenols and OPC content was consistent with the suppression of ET-1 production, in practice, the low concentration [5mM] of wine polyphenols is not sufficiently vasoactive. Mechanistic studies (Kaufeld et al. 2013) on a purified hexameric 2,3-*cis*-procyaninidin [4β-8]-linked OPC showed the induction of eNOS and Akt phosphorylation accounted for vascular endothelium dependent relaxation in porcine coronary arteries and the plasma concentration of the vasoconstrictor endothelin-1 decreased by 10%. A double-blind placebo controlled crossover study, demonstrated that intake by 60 mildly hypertensive subjects of polyphenol-rich grape-wine extract containing 800 mg of polyphenols lowered SBP by an average of 3 +/-1.3, DBP by 2+/-0.8 mmHg after four weeks of intervention. As grape juice extract had no effect on BP, this suggests that wine grapes contain more flavanols with oligomeric and polymeric procyanidins, often comprising 25-50% of the total polyphenols (Draijer et al. 2015) that are vasoactive compared to grape juice. Only in the subjects receiving the polyphenol-rich grape-wine extract, were the plasma concentrations of the vasoconstrictor endothelin-1 decreased by 10% (−0.15 pg/ml). Surprisingly in grape-juice intervention, the concentration of endothelin-1 increased by (+0.13 pg/ml). The contrasting effects of the wine and grape juice was attributed to the enhanced absorption/bioavailability of the higher amounts of catechins [monomer and polymer forms] in the grape-wine polyphenols (45.2 mg/g) compared to that in grape-juice polyphenols (0.4 mg/g).

3.7 Flavonoids: Grape juice, Blends

The beneficial effects on endothelial function, lower LDL oxidation and blood pressure (Chou et al. 2001;Vislocky, Fernandez 2010; Stein et al. 1999) derived from dietary grape juice intake has been associated with eNOS activation and increased NO synthesis by the actions of flavanols, Freedman et al. 2001) constituents of concord grape juice (Stalmach et al. 2011) and would be expected to enhance overall vascular function.

A decrease in DBP of 4.4 mmHg and unchanged SBP were observed in 18 hypertensive people after a 28 day RCT involving supplementation (Biesinger et al. 2015) with a polyphenol mix comprised of grape seed extracts [GSE] (330 mg), green tea (100 mg), resveratrol (60 mg) and a combination of billberry, quercetin and ginkgo biloba. However there was no mention of the use of 24 h ambulatory blood pressure, the best technique available for the measurement, monitoring and treatment of hypertension and to diagnose the lack of improvement of SBP. There was no variation observed in ACE levels, but the observed increases of urinary nitrite/nitrate concentrations suggests that the polyphenol metabolites enhanced NO bioavailability. Previously, these individual polyphenols have been evaluated and yielded conflicting results. Studies of 9 RCTs showed GSE (Feringa et al. 2011) only significantly lowered SBP. The meta-analysis of 9 studies showed the intake of grape polyphenols

could significantly increase FMD in healthy subjects, and appeared to be more pronounced in subjects with high cardiovascular risk factors (Li et al. 2011). In contrast, a double blind RCT 8-week intervention study, during which pre- and stage 1 hypertensive subjects consumed either 300 mg/d of GSE (Ras et al. 2013) or a placebo. The SBP was changed by 25·2 (95% CI 27·7, 22·8) mmHg in the GSE group and by 22·2 (95% CI 24·7, 0·2) mmHg in the placebo group. The DBP was changed by 22·5 (95% CI 24·0, 21·0) mmHg in the GSE group and by 21·1 (95% CI 22·5, 0·4) mmHg in the placebo group. Overall SBP modestly decreased by 3 mmHg and DBP by 1.4 mmHg. However in another study (Draijer et al. 2015) confirmed that 24-hour ambulatory BPs were stated to be significantly lower in the grape-wine extract intervention (135.9 ± 1.3 mmHg), compared to placebo (138.9 ± 1.3 mmHg). A 60 mg resveratrol supplementation (Biesinger et al. 2015) is insufficient, as the meta-analysis of 6 studies [247 subjects] indicated that only high-doses of resveratrol consumption (Liu et al. 2015a) (≥ 150 mg/d) significantly reduced SBP of -11.90 mmHg (95% CI: -20.99, -2.81 mmHg, P = 0.01). Similarly, a combination (Thandapilly et al. 2013) of resveratrol ($2.5\,mg\,kg^{-1}$ per day) and hydralazine ($25\,mg\,kg^{-1}$ per day) for 8 weeks was more effective than resveratrol or hydralazine alone in improving overall cardiovascular parameters of hypertensive rats.

3.8 Anthocyanins: Hibiscus *sabdariffa L.*

Hibiscus *sabdariffa Linne* is a traditional Chinese rose tea has been used for treatment of hypertension and is composed of organic acids, polyphenols, anthocyanins, polysaccharides, and volatile constituents. The intake of 3x 240 ml daily servings of hibiscus tea, by 65 pre- mildly hypertensive adults, age 30-70 y, as part of the diet, lowered systolic SBP compared with placebo (-7.2 +/- 11.4 vs. -1.3 +/- 10.0 mm Hg; P = 0.030). DBP was also lower, although this change did not differ from placebo (-3.1 +/- 7.0 vs. -0.5 +/- 7.5 mm Hg; P = 0.160). A greater response/effect to hibiscus treatment (r = -0.421 for SBP change; P = 0.010) was noted for subjects with higher SBP at baseline (Mckay et al. 2010). Furthermore the intake of hibiscus tea may be an effective pattern of dietary change in preventing the progression to moderate or more serious hypertension, potentially reducing the subsequent risk of developing cardiovascular disease. The difference in SBP between the placebo and hibiscus groups was an average decrease of 5.9 mm Hg, similar to the SBP-lowering effect obtained by following the combination dietary approaches to stop hypertension (DASH) diet lasting for 8 weeks. The major H. *sabdariffa* anthocyanins, delphinidin-3-sambubioside and cyanidin-3-sambubioside, (Fig. 3) were not detected in the plasma and urine of participants. Previous bioavailability studies (Williamson, Manach 2005; Manach et al. 2005) indicated that anthocyanins are rapidly absorbed and eliminated and that they are absorbed with poor efficiency of (~0.4%). Now, new data suggest (Czank et al. 2013) anthocyanins such as cyanidin-3-O-glucose have a minimum relative bioavailability of 12.38 ± 1.38% based on the total elimination of the absorbed ^{13}C dose via urine and breath. Therefore anthocyanins are as bioavailable as other flavonoid subclasses, including flavan-3-ols and flavones, which have relative bioavailabilities (Williamson, Manach 2005; Manach et al. 2005) between 2.5% and 18.5%. Recent evidence (Amin et al. 2015) also suggests that anthocyanin metabolites are bioactive at physiologically relevant concentrations and have the potential to modulate cardiovascular disease progression by altering the expression of inflammatory mediators. The cyanidin-3-glucoside metabolites shown in Scheme 2 were found to be bioactive at physiologically relevant concentrations,

possessed anti-inflammatory effects that may contribute to the reduced risk of CVD associated with increased habitual intake of anthocyanins (Cassidy et al. 2013). There was no direct effect of the anthocyanin phenolic metabolite[31] vanillic acid on endothelial protein expression of eNOS or NOX isoforms although HO-1 protein levels were modestly increased, indicating different mechanisms of bioactivity for phenolic derivatives relative to parent anthocyanins. This also suggests a potential indirect activity of anthocyanin metabolites in maintaining vascular homeostasis in vivo (Edwards et al. 2015).

Ferulic acid (FA) has been shown (Alam et al. 2013) to improve both endothelium-dependent relaxation in isolated thoracic aortic rings and antioxidant status by increasing superoxide dismutase and catalase activity in the heart and kidneys isolated from hypertensive rats. FA decreased plasma liver enzyme activities and plasma creatinine concentrations. Thus, FA improved the structure and function of the heart, blood vessels, liver, and kidneys in hypertensive rats (Suzuki et al. 2007). It may therefore be likely that anthocyanins and their metabolites including phenolic acids have hypotensive and protective effects maintaining vascular endothelial function, including their ACE-inhibitory effect (Da-Costa-Rocha et al. 2014) since angiotensin II regulates arterial blood pressure, adhesion molecule expression, cytokines, chemokines, and growth factors within the arterial wall.

3.9 Ferulic acid in chinese herbal decoction Fo Shou San

The extensively used Chinese herbal decoction Fo Shou San (FSS) is used in traditional Chinese medicine (TCM) to treat hypertension (Hou et al. 2004a; Hou et al. 2004b). FSS is composed of Chuanxiong Rhizoma (major constituent *Z*-ligustilide) and Angelicae Sinensis Radix (major component Ferulic acid) with a Z-ligustilide:ferulic acid ratio of 2:3. FSS stimulated the eNOS-derived NO bioavailability via: (i) PKB/Akt signaling pathway; (ii) increased intracellular Ca^{2+}; and (iii) reduced ROS generation and ACE inhibition. This herb has multiple activities against hypertension and cardiovascular disease (Bi et al. 2012).

3.10 Flavones: Luteolin

The flavone luteolin (3′,4′,5,7-tetrahydroxyflavone, Fig. 1) is a constituent of celery, thyme, green peppers, and chamomile tea. In spontaneous hypertensive rats, luteolin can significantly decrease BP and media thickness of aorta in vivo and inhibit angiotensin II- induced proliferation and migration of vascular smooth muscle cells (Lu et al. 2015). The 1:1 combination of luteolin with buddleoside, the major bioactive flavones from TCM chrysanthemum indicum L. reduced SBP by 15.42 mm Hg. A high dose chronic oral administration to spontaneously hypertensive rats of this combination (at 60 mg/kg; p.o. for 30 days) reduced both SBP and DBP by 4.04% and 5.24% compared with those of the vehicle control group, respectively (Lv et al. 2013). This was accompanied by an increased serum NO concentration and the inhibition of the serum levels of angiotensin II, aldosterone and endothelin-1. These results indicate that the combination of luteolin and buddleoside flavonoids may be useful in treating hypertension in humans.

3.11 Flavonols: Quercetin

Cocoa, onions and apples are best food sources of quercetin (3′,4′,3,5,7-pentahydroxyflavonol, Fig. 1) others include citrus fruits, cranberries, red grapes, broccoli, and tea. Epidemiological studies have found an inverse relationship between

dietary quercetin intake and cardiovascular disease (Larson et al. 2010). Research studies found a reduction in BP in hypertensive (>140 SBP and >90 mm Hg DBP) animals and humans supplemented with quercetin (Knekt et al. 2002). The assessment of flavonoid intake of 805 men aged 65-84 years in 1985 by a cross-check dietary history including their follow up for 5 years, in the Zutphen Elderly Study (Hertog et al. 1993) suggested a strong cardio-protective effect of several flavonoids, including quercetin which made up most of the flavonoid intake (16. 3 [10.1] mg daily = 63% of flavonoid intake) with the major sources of flavonoid intake from tea (61%), onions (13%), and apples (10%). Specifically the risk of coronary death was reduced by as much as 68% in men who consumed >29 mg flavonols/day compared to men who consumed <10 mg flavonols/day. During the 5 year study interval 43 men died of coronary heart disease. Quercetin mediates its effects through a variety of mechanisms. Its predominant activity is via inhibition of angiotensin converting enzyme activity, (Shukor et al. 2013) improved endothelial function, direct action on the vascular smooth muscle, and/or modulation in cell signaling and gene expression and its anti-oxidant effect seen as least important. Studies on spontaneously hypertensive rats have shown blood pressure-lowering effects of quercetin (Hackl et al. 2002), ferulic acid (Alam et al. 2013) and tannic acid (Thekkumkara et al. 2012). Quercetin has been reported to be effective against a range of cardiovascular disorders including atherosclerosis, ischemia-reperfusion injury, cardiotoxicity. The in silico analysis of quercetin showed optimum binding affinity with the angiotensin-converting-enzyme having a binding energy of -8.5 kcal/mol as compared to the standard (-7.0 kcal/mol). These results provide supporting evidence that quercetin glycosides could be a potential ligand to treat hypertension, myocardial infarction, and congestive heart failure.(Muhammad, Fatima 2015; Sånchez et al. 2006; Gomaz et al. 2015; Morales-Cano et al. 2014; Barteková et al. 2015; El-Bassossy et al. 2014).

3.12 Flavonones: Hesperidin, G-hesperidin and naringin

The, daily ingestion of the flavonones hesperidin, G-hesperidin and naringin found in citrus fruits and beverages promoted antihypertensive and antithrombotic effects in a stroke-prone spontaneously hypertensive animal model (Ikemura et al. 2012). In a randomized, controlled crossover study involving 24 healthy overweight men, (age 50-65 y) the 4 week consumption of 500 ml orange juice (OJ, 292 mg hesperidin), control drink plus hesperidin (CDH, 2 capsules of pure hesperidin (2 x 146 mg)) or control drink plus placebo (CDP, 2 starch capsules of (2 x 146 mg)), indicated that both orange juice and control drink plus hesperidin intake decreased DBP by 3 to 4 mmHg (CDP-CDH = 3.2 +/-1.5 mmHg; CDP-OJ = 5.5 +/-1.8 mmHg) than after consumption of control drink plus placebo ($P = 0.02$) and both orange juice and herperidin beverage ingestion postprandially increased endothelium-dependent microvascular reactivity compared with control drink plus placebo ($P < 0.05$) when measured at the peak of plasma hesperidin concentration. (Morand et al. 2011). These findings suggest the potential antihypertensive benefits from regular/daily ingestion of a variety of beverages and diets containing citrus flavonones could have significant beneficial effects on hypertension and cardiovascular health.

3.13 Isoflavones: Soy

Soy isoflavones genistein, daidzein, and glycitein activate endothelial nitric oxide synthase, increases the capacity of serum to stimulate prostacyclin release in human endothelial cells (Mann et al. 2007; Garicia-Martinez et al. 2003). Oral supplementation of soy isoflavones to postmenopausal women significantly increased flow-mediated vascular dilation (FMD) of the brachial artery in women with low baseline FMD had no effect in women with high FMD (Cano et al. 2010). Similar improvement in endothelial dysfunction has been observed following oral supplementation of soy isoflavones to patients with ischemic stroke (Chan et al. 2008). The claims that consumption of isoflavone supplements in 2 low-fat test meals in random order 1 week apart, with 80 mg isoflavones (ISO) or without isoflavones (CON) by 22 postmenopausal women acutely increases endothelium-dependent vasodilation in postmenopausal women FMD values (%, mean +/- SD) were: CON, 5.49 +/- 2.32, 4.35 +/- 2.32, 4.40 +/- 2.26; ISO, 5.38 +/- 1.91, 5.08 +/- 1.74, 6.11 +/- 2.60, at baseline, 4 h, and 6 h, respectively ($P < 0.01$) (Hall et al. 2008; Squadrito et al. 2002) have been contradicted by more recent reports. The studies of some 253 women allocated to either one of the three treatment groups, to receive 40 g soy flour (whole soy group), 40 g low-fat milk powder plus 63 mg daidzein (daidzein group) or 40 g low-fat milk powder (active control group) daily, each consumed as a solid beverage powder for 6 months showed that the intake of whole soy and purified daidzein had no significant effect on BP and vascular function among Chinese equol-producing postmenopausal women with prehypertension or untreated hypertension (Liu et al. 2015b). Women with metabolic syndrome on a soy diet showed significant reductions in diastolic BP were found among equol producers. No significant changes were noted in non-equol producers. Similarly, in women without metabolic syndrome, only equol producers had significant reductions in diastolic BP. The effects of isoflavone to restore endothelial function are variable and appear to be correlated to the ability to convert daidzein to equol (Gil-Izquierdo et al., 2012).

In Western countries 25–30% of the adult population produce *S*-(-)equol when soy foods containing isoflavones are consumed. Whereas adults from Japan, Korea or China (Song et al. 2006) or in Western adult vegetarians a 50–60% of equol-producers are found (Setchell, Cole, 2006). The extent to which these metabolic differences are genetic or environmental is not understood. Cardiovascular risk reduction with soy nuts is not uniform and may be greater among producers of equol (Acharjee et al. 2015).

4. Conclusion

This review has shown that flavonoid-rich diets have been associated with an improvement in endothelial function and a decrease in hypertension and CVD. Since flavonoid-rich diets are associated with a lower mortality from cardiovascular disease, the relationship between polyphenol intake and prevention of cardiovascular disease can define nutritional influences on optimal health. This has been linked to improvements in endothelial function and blood pressure. Compared to the flavonoid monomers of catechin and (-)-epicatechin, the oligomeric procyanidins (OPCs) found in herbs, tea, chocolate, cocoa, wine, grapes, vegetables and fruits have by far the most potent effects on endothelial function and have a wider spectrum of anti-hypertensive actions. Oligomeric procyanidins stimulate endothelium-dependent vasodilation, suppress vasoconstrictor ET-1 synthesis, activate a laminar shear stress response in endothelial cells and also inhibit the activity of metalloproteinases

including ACE lowering blood pressure. The bioavailability and colonic metabolism following dietary consumption of products containing oligomeric procyanidins requires more detailed examination to determine the optimal dosage. Considering the aging population and increasing prevalence of hypertension worldwide, increasing the intake of dietary polyphenols may be a relatively cheap tool in the toolbox of cardiovascular specialists.

Authors' contribution

All authors contributed content, ideas and suggestions with HMH collating and writing the manuscript.

Conflict of interest

The authors declare there are no conflicts of interest.

Acknowledgments

The authors at RMIT University are grateful to be members of the Health Innovation Research Institute, enabling their ongoing research collaborations in phytochemical and herbal medicine.

5. References

Acharjee, S.; Zhou, J.R.; Elajami, T.K.; Welty, F. K., 2015. Effect of soy nuts and equol status on blood pressure, lipids and inflammation in postmenopausal women stratified by metabolic syndrome status. Metab. *64*, 236-243.

Agarwal, A.; Prasad, R.; Jain A., 2010. Effect of green tea extract (catechins) in reducing oxidative stress seen in patients of pulmonary tuberculosis on DOTS Cat I regimen. Phytomed. *17*, 23–27.

Aherne, S. A.; O'Brien, N. M., 2000. Mechanism of protection by the flavonoids, quercetin and rutin, against tert-butylhydroperoxide- and menadione-induced DNA single strand breaks in Caco-2 cells. Free Rad. Biol. Med. *29*, 507−514.

Aitken, M., Kleinrock, M., Lyle, J., and Caskey, L., 2014. Medicine use and the shifting cost of healthcare. A Review of the use of medicines in the United States in 2013, IMS Institute for Healthcare Informatics, Danbury, C.T. www.theimsinstitute.org.

Aird, W.C., 2007. Phenotypic heterogeneity of the endothelium: I. Structure, function, and mechanisms. Circ Res. *100*, 158–173.

Alam, M. A., Sernia, C., Brown, L., 2013. Ferulic acid improves cardiovascular and kidney structure and function in hypertensive rats. J. Cardiovasc. Pharmacol. *61*, 240−249.

Amin, H.P., Czank, C., Rahmeem, S., Zhang, Q., Botting, N.P., Cassidy, A., Kay, C.D., 2015. Anthocyanins and their physiologically relevant metabolites alter the expression of IL-6 and VCAM-1 in CD40L and oxidized LDL challenged vascular endothelial cells. Mol. Nutr. Food Res. *59*, 1095–1106.

Anter, E., Chen, K., Shapira, O. M., Karas, R. H., Keaney, J. F., 2005. p38 Mitogen-activated protein kinase activates eNOS in endothelial cells by an estrogen receptor dependent pathway in response to black tea polyphenols. Circ. Res. *96*, 1072−1078.

Asher, G.N., Viera, A.J., Weaver, M.A., Dominik, R., Caughey, M., Hinderliter, A.L., 2012. Effect of hawthorn standardized extract on flow mediated dilation in prehypertensive and mildly hypertensive adults: a randomized, controlled cross-over trial. BMC Compl. Altern. Med. *12*, doi: 10.1186/1472-6882-12-26.

Balentine, D. A., Wiseman, S. A., Bouwens, L. C., 1997. The chemistry of tea flavonoids. Crit. Rev. Food Sci. Nutr. *37*, 693−704.

Bartekovå, M., Simoncikovå, P., Fogarassyovå, M., Ivanovå, M., Okruhlicovå, L., Tribulovå, N., Dovinovå, I., Barancik, M., 2015. Quercetin improves post ischemic recovery of heart function in doxorubicin-treated rats and prevents doxorubicin-induced matrix metalloproteinase-2 activation and apoptosis induction. Int J. Mol. Sci. *16*, 8168-8185.

Basu, A., Du, M., Leyva, M. J., Sanchez, K., Betts, N. M., Wu, M., Aston, C. E., Lyons, T. J., 2010. Blueberries decrease cardiovascular risk factors in obese men and women with metabolic syndrome. J. Nutr. *140*, 1582−1587.

Bhardwaj, P., Khanna, D., 2013. Green tea catechins: defensive role in cardiovascular disorders. Chin. J. Nat. Med. *11*, 345–353.

Bi, C.W., Xu, L., Tian, X.Y., Liu, J., Zheng, K.Y., Lau, C.W., Lau, D.T., Choi, R.C., Dong, T.T., Huang, Y., Tsim, K.W., 2012. Fo Shou San, an ancient Chinese herbal decoction, protects endothelial function through increasing endothelial nitric oxide synthase activity. PLos One, *7*, e51670.

Biesinger, S., Michaels, H. A., Quadros, A.S., Qian, Y., Rabovsky, A.B., Badgerand, R.S., Jalili, T., 2015. A combination of isolated phytochemicals and botanical extracts lowers diastolic blood pressure in a randomized controlled trial of hypertensive subjects. Euro. J. Clin. Nutr. 1-7, Jun 10. doi: 10.1038/ejcn.2015.88. [Epub ahead of print]

Bondonno, C. P., Yang, X., Croft, K. D., Considine, M. J., Ward, N. C., Rich, L., Puddey, I. B., Swinny, E., Mubarak, A., Hodgson, J. M., 2012. Flavonoid-rich apples and nitrate-rich spinach augment nitric oxide status and improve endothelial function in healthy men and women: a randomized controlled trial. Free Rad. Biol. Med. *52*, 95−102.

Bors, W., Michel, C., Stettmaier, K., 2001. Structure-activity relationships governing antioxidant capacities of plant polyphenols. Methods Enzymol. *335*, 166−180.

Cano, A., Garcia-Perez, M.A., Tarin, J. J., 2010. Isoflavones and cardiovascular disease. Maturitas, 67, 219−226.

Cassidy, A., Mukamal, K.J., Liu, L., Franz, M., Eliassen, A.H., Rimm, E.B., 2013. High anthocyanin intake is associated with a reduced risk of myocardial infarction in young and middle-aged women. *Circulation 127*, 188–196.

Cassidy, A., O'Reilly, E. J.; Kay, C., Sampson, L., Franz, M., Forman, J. P., Curhan, G., Rimm, E. B., 2011. Habitual intake of flavonoid subclasses and incident hypertension in adults. Am. J. Clin. Nutr. *93*, 338−347.

Cesarone, M.R., Belcaro, G., Stuard, S., Schönlau, F., Di Renzo, A., Grossi, M.G., Dugall, M., Cornelli, U., Cacchio, M., Gizzi, G., Pellegrini, L., 2010. Kidney Flow and Function in Hypertension:Protective Effects of Pycnogenol in Hypertensive Participants—A Controlled Study. J. Cardiovasc. Pharmacol. Therapeutics, *15*, 41-46.

Chan, Y. H., Lau, K. K., Yiu, K. H., Li, S. W., Chan, H. T., Fong, D. Y., Tam, S., Lau, C. P., Tse, H. F., 2008. Reduction of C-reactive protein with isoflavone supplement reverses endothelial dysfunction in patients with ischaemic stroke. Eur. Heart J. *29*, 2800−2807.

Chou, E. J., Keevil, J. G., Aeschlimann, S., Wiebe, D. A., Folts, J. D., Stein, J. H., 2001. Effect of ingestion of purple grape juice on endothelial function in patients with coronary heart disease. Am. J. Cardiol. *88*, 553−555.

Corder, R., Mullen, W., Khan, N.Q., Marks, S.C., Wood, E.G., Carrier, M.J., Crozier, A., 2006. Red wine procyanidins and vascular health. Nature, *444*, 566.

Crozier, A., Jaganath, I.B., Clifford, M.N. 2006a. Phenols, polyphenols and tannins: an overview. In: Crozier A, Clifford, M.N., Ashihara, H. (eds) Plant secondary metabolites: occurrence, structure and role in the human diet. Blackwell Publishing, Oxford, pp 1–24.

Czank, C., Cassidy, A., Zhang, Q., Morrison, D.J., Preston, T., Kroon, P.A., Nigel, P., Botting, P., Kay, C.D. 2013. Human metabolism and elimination of the anthocyanin, cyanidin-3-glucoside: a ^{13}C-tracer study. Am. J. Clin. Nutr. *97*, 995–1003.

Da-Costa-Rocha, I., Bonnlaender, B., Sievers, H., Pischel, I., Heinrich, M., 2014. Hibiscus sabdariffa L. - a phytochemical and pharmacological review. Food Chem. *165*, 424-443.

De Caterina, R., Libby, P., Peng, H. B., Thannickal, V. J., Rajavashisth, T. B., Gimbrone, M. A., Shin, W. S., Liao, J. K., 1995. Nitric oxide decreases cytokine-induced endothelial activation. Nitric oxide selectively reduces endothelial expression of adhesion molecules and proinflammatory cytokines. J. Clin. Invest. *96*, 60−68.

Dias, P. M., Joshi, M. K., 2012. Endothelial dysfunction as a risk factor for cardiovascular disease; its modulation by phyto-ingredients and implication in better cardiovascular health. Oxid. Antioxid. Med. Sci. *1*, 75−85.

Draijer, R., de Graaf, Y., Slettenaar, M., de Groot, E., Wright, C.I., 2015. Consumption of a polyphenol-rich grape-wine extract lowers ambulatory blood pressure in mildly hypertensive subjects. Nutrients, *7*, 3138-3153.

Edirisinghe, I., Banaszewski, K., Cappozzo, J., McCarthy, D., Burton-Freeman, B. M., 2011. Effect of black currant anthocyanins on the activation of endothelial nitric oxide synthase (eNOS) in vitro in human endothelial cells. J. Agri. Food Chem. *59*, 8616–8624.

Edwards, M., Czank, C., Woodward, G. M., Cassidy, A., Kay, C.D., 2015. Phenolic Metabolites of Anthocyanins Modulate Mechanisms of Endothelial Function. J. Agric. Food Chem. *63*, 2423−2431.

El-Bassossy, H.M., Hassan, N.A., Mahmoud, M.F., Fahmy, A., 2014. Baicalein protects against hypertension associated with diabetes: effect on vascular reactivity and stiffness. Phytomed. *21*, 1742-1745.

Elks, C. M., Reed, S. D., Mariappan, N., Shukitt-Hale, B. Joseph, J.A., Ingram, D.K., Francis, J., 2011. A blueberry-enriched diet attenuates nephropathy in a rat model of hypertension via reduction in oxidative stress. PLoS One *6*, e24028.

Enseleit, F., Sudano, I., Périat, D., Winnik, S., Wolfrum, M., Flamer, A.J., Fröhlich, G.M., Kaiser, P., Hirt, A., Haile, S.R., Krasniqi, N., Matter, C.M., Uhlenhut, K., Högger, P., Neidhart, M., Lüsher, T.F., Rusxhitzka, F., Noll, G., 2012. Effects of Pycnogenol on endothelial function in patients with stable coronary artery disease: a double-blind, randomized, placebo-controlled, cross-over study. Eur. Heart J. *33*, 1589-1597.

Erlund, I., Koli, R., Alfthan, G., Marniemi, J., Puukka, P., Mustonen, P., Mattila, P., Jula, A., 2008. Favorable effects of berry consumption on platelet function, blood pressure, and HDL cholesterol. Am. J. Clin. Nutr. *87*, 323-331.

Feringa, H.H., Laskey, D.A., Dickson, J.E., Coleman, C.I., 2011. The effect of grape seed extract on cardiovascular risk markers: a meta-analysis of randomized controlled trials. J. Am. Diet Assoc. *111*, 1173-1181.

Ferri, C., Desideri, G., Ferri, L., Proietti, I., Di Agostino, S., Martella, L., Mai, F., Di Giosia, P., Grassi, D., 2015. Cocoa, Blood Pressure, and Cardiovascular Health. J Agric. Food Chem. 2015 Jul 13. [Epub ahead of print]

Follman, M., Griebenow, N., Hahn, M.G., Hartung, I., Mais, F.J., Mittendorf, J., Schäfer, M., Schirok, H., Stasch, J.P., Stoll, F., Straub, A., 2013. The Chemistry and Biology of Soluble Guanylate Cyclase Stimulators and Activators. Angew. Chem. Int. Ed. *52*, 9442-9462.

Freedman, J. E., Parker, C., Li, L. Q., Pearlman, J. A., Frei, B., Ivanov, V., Deak, L. R., Iafrati, M. D., Folts, J. D., 2001. Select flavonoids and whole juice from purple grapes inhibit platelet function and enhance nitric oxide release. Circulation, *103*, 2792−2798.

Garcia-Martinez, M. C., Hermenegildo, C., Tarin, J. J., Cano, A., 2003. Phytoestrogens increase the capacity of serum to stimulate prostacyclin release in human endothelial cells. Acta Obstet. Gynecol. Scand. *82*, 705−710.

Galley, H. F., Webster, N. R., 2004. Physiology of the endothelium. Br. J. Anaesth. *93*, 105–113.

Ganna, A., Ingelsson, E., 2015. 5 Year mortality predictors in 498 103 UK Biobank participants: a prospective population-based study. www.thelancet.com Published online June 4, 2015 http://dx.doi.org/10.1016/S0140-6736(15)60175-1

Gil-Izquierdo, A., Penalvo, J.L., Gil, J.I., Medina, S., Horcajada, M.N., Lafay, S., Silderberg, M., Llorach, R., Zafrilla, P., Garcia-Mora, P., Ferreres, F., 2012. Soy isoflavones and cardiovascular disease epidemiological, clinical and -omics perspectives. Curr. Pharm. Biotechnol. *13*, 624-631.

Gomaz, J.G., Quintremil, S., Rodrigo, R., 2015. Cardiovascular Disease: A Target for the Pharmacological Effects of Quercetin. Curr. Top. Med. Chem. *15*, 1735-1742.

Grassi, D., Desideri, G., Necozione, S., Di Giosia, P., Barnabei, R., Allegaert, L., Bernaert, H., Ferri, C., 2015a. Cocoa consumption dose dependently improves flow-mediated dilation and arterial stiffness decreasing blood pressure in healthy individuals. J. Hypertens. *33*, 294−303.

Grassi, D., Draijer, R., Desideri, G., Mulder, T., Ferri, C., 2015b. Black Tea Lowers Blood Pressure and Wave Reflections in Fasted and Postprandial Conditions in Hypertensive Patients: A Randomised Study. Nutrients, 7, 1037-1051.

Grassi, D., Mulder, T.P., Draijer, R., Desideri, G., Molhuizen, H.O., Ferri, C., 2009. Black Tea consumption dose-dependently improves flow-mediated dilation in healthy males. J. Hypertens, *27*, 774-781.

Grassi, D., Lippi, C., Necozione, S., Desideri, G., Ferri, C., 2005a. Short-term administration of dark chocolate is followed by a significant increase in insulin sensitivity and a decrease in blood pressure in healthy persons. Am. J. Clin. Nutr. *81*, 611−614.

Grassi, D.; Necozione, S., Lippi, C., Croce, G., Valeri, L., Pasqualetti, P., Desideri, G., Ferri, C., 2005b. Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. Hypertension, *46*, 398−405.

Gulati, O.P., 2015. Pycnogenol® in Metabolic Syndrome and Related Disorders. Phytother Res. *29*, 949-968.

Hackl, L. P., Cuttle, G., Dovichi, S. S., Lima-Landman, M. T., Nicolau, M., 2002. Inhibition of angiotesin-converting enzyme by quercetin alters the vascular response to brandykinin and angiotensin I. Pharmacol. *65*, 182−186.

Hall, W. L., Formanuik, N. L., Harnpanich, D., Cheung, M., Talbot, D., Chowienczyk, P. J., Sanders, T. A., 2008. A meal enriched with soy isoflavones increases nitric oxide-mediated vasodilation in healthy postmenopausal women. J. Nutr. *138*, 1288−1292.

Hartley, L., Flowers, N., Holmes, J., Clarke, A., Stranges, S., Hooper, L., Rees, K., 2013. Green and black tea for the primary prevention of cardiovascular disease. Cochrane Database Syst. Rev. *6*, CD009934.

Hertog, M.G., Feskens, E.J., Hollman, P.C., Katan, M.B., Kromhout, D., 1993. Dietary antioxidant flavonoids and risk of coronary heart disease: The Zutphen Elderly Study. Lancet, *342*, 1007–1011.

Hou, Y.Z., Zhao, G.R., Yang, J., Yuan, Y.J., Zhu, G.G. 2004a. Hiltunen, R. Protective effect of Ligusticum chuanxiong and Angelica sinensis on endothelial cell damage induced by hydrogen peroxide. Life Sci. *75*, 1775–1786.

Hou, Y.Z., Yang, J., Zhao, G.R., Yuan, Y.J., 2004b. Ferulic acid inhibits vascular smooth muscle cell proliferation induced by angiotensin II. Eur. J. Pharmacol. *499*, 85–90.

Hügel, H.M., 2015. Brain food for AD-free ageing: focus on herbal medicines. Natural compounds as therapeutic agents for amyloidogenic disease. Adv Exp Med Biol. *863*, 95-116.

Huxley, R.R., Neil, H.A., 2003. The relation between dietary flavonol intake and coronary heart disease mortality: a meta-analysis of prospective cohort studies. Eur. J. Clin. Nutr. *57*, 904-908.

Ikemura, M., Sasaki, Y., Giddings, J.C., Yamamoto, J., 2012. Preventive Effects of Hesperidin, Glucosyl Hesperidin and Naringin on Hypertension and Cerebral Thrombosis in Stroke-prone Spontaneously Hypertensive Rats. Phytother. Res. *26*, 1272–1277.

Jennings, A., Welch, A. A., Fairweather-Tait, S. J., Kay, C., Minihane, A. M., Chowienczyk, P., Jiang, B., Cecelja, M., Spector, T., Macgregor, A., Cassidy, A., 2012. Higher anthocyanin intake is associated with lower arterial stiffness and central blood pressure in women. Am. J. Clin. Nutr. *96*, 781–788.

Joy, S., Siow, R. C., Rowlands, D. J., Becker, M., Wyatt, A. W., Aaronson, P. I., Coen, C. W., Kallo, I., Jacob, R., Mann, G. E., 2006. The isoflavone Equol mediates rapid vascular relaxation: Ca^{2+}-independent activation of endothelial nitric-oxide synthase/Hsp90 involving ERK1/ 2 and Akt phosphorylation in human endothelial cells. J. Biol. Chem. *281*, 27335–27345.

Jurikova, T., Sochor, J., Rop, O., Mlcek, J., Balla, S., Szekeres, L., Adam, V., Kizek, R., 2012. Polyphenolic profile and biological activity of Chinese hawthorn (Crataegus pinnatifida BUNGE) fruits. Molecules, *17*, 14490-14509.

Kaufeld, A.M., Pertz, H.H., Kolodziej, H. J., 2013. 2,3-*cis*-Procyanidins Elicit Endothelium-Dependent Relaxation in Porcine Coronary Arteries via Activation of the PI3/Akt Kinase Signaling Pathway. Agric. Food Chem. *61*, 9609−9616.

Keske, M.A., Ng, H.L., Premilovac, D., Rattigan, S., Kim, J.A., Munir, K., Yanh, P., Quon, M.J., 2015. Vascular and metabolic actions of the green tea polyphenol epigallocatechin gallate. Curr . Med. Chem. *22*, 59-69.

Knekt, P., Kumpulainen, J., Jarvinen, R., Rissanen, H., Heliovaara, M., Reunanen, A., Hakulinen, T., Aromaa, A., 2002. Flavonoid intake and risk of chronic diseases. Am. J. Clin. Nutr. *76*, 560–568.

Kocyildiz, Z.C., Birman, H., Olgac, V., Akgün-Dar, K., Melikoglu, G., Mericli, A.H., 2006. Crataegus tanacetifolia leaf extract prevents L-NAME induced hypertension in rats: a morphological study. Phytother Res. *20*, 66-70.

Kuhnert, N., Clifford, M.N., Muller, A., 2010a. Oxidative cascade reactions yielding polyhydroxy-theaflavins and theacitrins in the formation of black tea thearubigins: evdince by tandem LC-MS. Food Funct. *1*, 180–199.

Kuhnert, N., Dryman, J.W., Obuchowicz, J., Clifford, M.N., Witt, M., 2010b. Mass spectrometric characterization of black tea thearubigins leading to an oxidative cascade hypothesis for thearubigin formation. Rapid Commun. Mass Spectrom. *24*, 3387–3404.

Kuriyama, S., Shimazu, T., Ohmori, K., Kikuchi, N., Nakaya, N., Nishino, Y., Tsubono, Y., Tsuji, I., 2006. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA. *296*, 1255–1265.

Larson, A.J., Symons, J.D., Jalili, T., 2012. Therapeutic potential of quercetin to decrease blood pressure: review of efficacy and mechanisms. Adv. Nutr. *3*, 39-46.

Larson, A.J., Symons, J.D., Jalili, T., 2010. Quercetin: A Treatment for Hypertension? — A Review of Efficacy and Mechanisms. Pharmaceut. *3*, 237-250.

Legeay, S., Rodier, M., Fillon, L., Faure, S., Clere, N., 2015. Epigallocatechin Gallate: A Review of Its Beneficial Properties to Prevent Metabolic Syndrome. Nutrients, *7*, 5443-5468.

Li, S.H., Tian, H.B., Zhao, H.J., Chen, L.H., Cui, L.Q., 2013. The acute effects of grape polyphenols supplementation on endothelial function in adults: meta-analyses of controlled trials. PLoS One, *8*, 70:e69818.

Lin, C. M., Chen, C. T., Lee, H. H., Lin, J. K., 2002. Prevention of cellular ROS damage by isovitexin and related flavonoids. Planta Med. *68*, 365−367.

Liu, G., Mi, X.N., Zheng, X.X., Xu, Y.L., Lu, J., Huang, X.H., 2014. Effects of tea intake on blood pressure: a meta-analysis of randomised controlled trials. Brit. J. Nutr. *112*, 1043–1054.

Liu, Y., Ma, W., Zhang, P., He, S., Huang, D., 2015a. Effect of resveratrol on blood pressure: a meta-analysis of randomized controlled trials. Clin. Nutr. *34*, 27-34.

Liu, Z.M., Ho, S.C., Chen, Y.M., Tomlinson, B., Ho, S., To, K., Woo, J., 2015b. Effect of whole soy and purified daidzein on ambulatory blood pressure and endothelial function-a 6-month double-blind, randomized controlled trial among Chinese postmenopausal women with prehypertension. Eur. J. Clin. Nutr. doi: 10.1038/ejcn.2015.24. [Epub ahead of print]

Lv, G.Y., Zhang, Y.P., Gao, J.L., Yu, J.J., Lei, J., Zhang, Z.R., Li, B., Zhan, R.J., Chen, S.H., 2013. Combined antihypertensive effect of luteolin and buddleoside enriched extracts in spontaneously hypertensive rats. J. Ethnopharmacol. *150*, 507-513.

Manach, C., Williamson, G., Morand, C.; Scalbert, A., Rémésy, C., 2005. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am. J. Clin. Nutr. *81*, 230S–242S.

Mann, G. E., Rowlands, D. J., Li, F. Y., De Winter, P., Siow, R. C., 2007. Activation of endothelial nitric oxide synthase by dietary isoflavones: role of NO in Nrf2-mediated antioxidant gene expression. Cardiovasc. Res. 75, 261−274.

Mastroiacovo, D., Kwik-Uribe, C., Grassi, D., Necoxione, S., Raffaele, A., Pistacchio, L., Righetti, R., Bocale, R., Lechiara, M.C.; Marini, C., Ferri, C., Desideri, G., 2015. Cocoa flavanol consumption improves cognitive function, blood pressure control, and metabolic profile in elderly subjects: the Cocoa, Cognition, and Aging (CoCoA) Study-a randomized controlled trial. Am. J. Clin. Nutr. *101*, 538-548.

Mckay, D. L., Chen, C-Y. O., Saltzman, E., Blumberg, J. B. J., 2010. Hibiscus Sabdariffa L. Tea (Tisane) Lowers Blood Pressure in Prehypertensive and Mildly Hypertensive Adults. J. Nutr. *140*, 298–303.

Miyake, Y., Sakurai, C., Usuda, M., Fukumoto, S., Hiramitsu, M., Sakaida, K., Osawa, T., Kondo, K., 2006. Difference in plasma metabolite concentration after ingestion of lemon flavonoids and their aglycones in humans. J. Nutr. Sci. Vitaminol. *52*, 54−60.

Morales-Cano, D., Menendez, C., Moreno, E., Moral-Sanz, J., Barreira, B., Galindo, P., Pandolfi, R., Jimenez, R., Moreno, L., Cogolludo, A., Duarte, J., Perez-Vizcaino, F., 2014. The flavonoid quercetin reverses pulmonary hypertension in rats. PLoS One, *9* e114492.

Morand, C., Dubray, C., Milenkovic, D., Lioger, D., Martin, J.F., Scalbert, A., Mazur, A., 2011. Hesperidin contributes to the vascular protective effects of orange juice: a randomized crossover study in healthy volunteers. Am. J. Clin. Nutri. *93*, 73-80.

Muhammad, S.A., Fatima, N., 2015. In silico analysis and molecular docking studies of potential angiotensin-converting enzyme inhibitor using quercetin glycosides. Pharmacogn Mag. *11*, Suppl 1, S123-126.

Mulvihill, E. E., Huff, M. W., 2010. Antiatherogenic properties of flavonoids: implications for cardiovascular health. Can. J. Cardiol. *26*, (Suppl.A), 17A−21A.

Naruszewicz, M., Laniewska, I., Millo, B., Dluzniewski, M., 2007. Combination therapy of statin with flavonoids rich extract from chokeberry fruits enhanced reduction in cardiovascular risk markers in patients after myocardial infraction (MI). Atherosclerosis, *194*, e179−184.

Peng, X., Zhou, R., Wang, B., Yu, X., Yang, X., Liu, K., Mi, M., 2014. Effect of green tea consumption on blood pressure: A meta-analysis of 13 randomized controlled trials. Sci. Rep. *4*, 6251. doi: 10.1038/srep06251

Perez-Vizcaino, F., Duarte, J., 2010. Flavonols and cardiovascular disease. Mol. Aspects Med. *31*, 478−494.

Ras, R.T., Zock, P.L., Zebregs, Y.E., Johnston, N.R., Webb, D.J., Draijer, R., 2013. Effect of polyphenol-rich grape seed extract on ambulatory blood pressure in subjects with pre- and stage I hypertension. Br. J. Nutri. *110*, 2234-2241.

Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. 2002. Lancet, *360*, 1903–1913.

Rice-Evans, C. A.; Miller, N. J.; Paganga, G., 1996. Structure antioxidant activity relationships of flavonoids and phenolic acids. Free Radical Biol. Med. *20*, 933−956.

Rodriguez-Mateos, A., Rendeiro, C., Bergillos-Meca, T., Tabatabaee, S., George, T., Heiss, C., Spencer, J. P., 2013. Intake and time dependence of blueberry flavonoid-induced improvements in vascular function: a randomized, controlled, double-blind, crossover intervention study with mechanistic insights into biological activity. Am. J. Clin. Nutr. 2013, DOI: 10.3945/ajcn.113.066639.

Rodriguez‐Mateos, A., Vauzour, D., Krueger, C.G., Shanmuganayagam, D., Reed, J., Calani, L., Mena, P., Del Rio, D.; Crozier, A., 2014. Bioavailability, bioactivity and impact on health of dietary flavonoids and related compounds: an update. Arch. Toxicol. *88*, 1803–1853.

Roopchand, D.E., Carmody, R.N., Kuhn, P., Moskal, K., Rojas-Silva, P., Turnbaugh, P.J., Rskin, I., 2015. Dietary Polyphenols Promote Growth of the Gut Bacterium Akkermansia muciniphila and Attenuate High-Fat Diet-Induced Metabolic Syndrome. Diabetes, *64*, 2847-2858.

Ross, R.,1999. Atherosclerosis - an inflammatory disease. N. Engl. J. Med. *340*, 115−126.

San Cheang, W., Yuen Ngai, C., Tam, Y.Y., Yu Tian, X., Tak Wong, W., Zhang, Y., Wai Lau, C., Chen, Z.Y., Bian, Z.X., Huang, Y., Ping Leung, F., 2015. Black tea protects against hypertension-associated endothelial dysfunction through alleviation of endoplasmic reticulum stress. Sci. Rep. *5*, 10340 DOI: 10.1038/srep10340.

Sånchez, M., Galisteo, M., Vera, R., Villar, I.C., Zarzuelo, A., Tamargo, J., Pérez-Vizcaino, F., Duarte, J., 2006. Quercetin downregulates NADPH oxidase, increases eNOS activity and prevents endothelial dysfunction in spontaneously hypertensive rats. J. Hypertens. *24*, 75-84.

Sansone, R., Rodriguez-Mateos, A., Heuel, J., Falk, D., Schuler, D., Wagstaff, R., Kuhnle, G.G.C., Spencer, J.P.E., Schroeter, H., Merx, M.W., Kelm, M., Heiss, C., for the Flaviola Consortium, European Union 7th Framework Program, 2015. Cocoa flavanol intake improves endothelial function and Framingham Risk Score in healthy men and women: a randomised, controlled, double-masked trial: the Flaviola Health Study. British Journal of Nutrition, *114*, 1246–1255.

Schewe, T., Steffen, Y., Sies, H., 2008. How do dietary flavanols improve vascular function? A position paper. Arch. Biochem. Biophys. *476*, 102−106.

Schiffrin, E. L., 2001. A critical review of the role of endothelial factors in the pathogenesis of hypertension. J. Cardiovasc. Pharmacol. *38*, Suppl 2, S3–6.

Schoonees, A.; Vissar, J.; Musekiwa, A.; Volmink, J., 2012. Pycnogenol® (extract of French maritime pine bark) for the treatment of chronic disorders. Cochrane Database Syst Rev. *4*, CD008294. doi: 10.1002/14651858.CD008294.pub4.

Schroeter, H., Heiss, C., Balzer, J., Kleinbongard, P., Keen, C.L., Hollenberg, N.K., Sies, H., Kwik-Uribe, C., Schmitz, H.H., Kelm, M., 2006. (−)-Epicatechin mediates beneficial effects of flavanol-rich cocoa on vascular function in humans. Proc. Natl. Acad. Sci. U.S.A. *103*, 1024–1029.

Setchell, K.D.R., Cole, S.J. 2006. Method of defining equol-producer status and its frequency among vegetarians. J. Nutr. 136, 2188–2193.

Shukor, N. A., Camp, J. V., Gonzales, G.B., Staljanssens, D., Struijs, K., Zotti, M.J., Raes, K., Smagghe, G., 2013. Angiotensin-Converting Enzyme Inhibitory Effects by Plant Phenolic Compounds: A Study of Structure Activity Relationships. J. Agric. Food Chem. 61, 11832-11839.

Song, K.B., Atkinson, C., Frankenfeld, C.L., Jokela, T., Wahala, K., Thomas, W.K., Lampe, J.W., 2006. Prevalence of daidzein-metabolizing phenotypes differs between Caucasian and Korean American women and girls. J. Nutr. *136*, 1347–1351.

Soto-Vaca, A., Gutierrez, A., Losso, J.N., Xu, Z., Finley, J.W., 2012. Evolution of Phenolic Compounds from Color and Flavor Problems to Health Benefits. J. Agric. Food Chem. 60, 6658-6677.

Squadrito, F., Altavilla, D., Morabito, N., Crisafulli, A., D'Anna, R., Corrado, F., Ruggeri, P., Campo, G. M., Calapai, G., Caputi, A. P., Squadrito, G., 2002. The effect of the phytoestrogen genistein on plasma nitric oxide concentrations, endothelin-1 levels and endothelium dependent vasodilation in postmenopausal women. Atherosclerosis, *163*, 339-347.

Stalmach, A., Edwards, C. A., Wightman, J. D., Crozier, A., 2011. Identification of (poly)phenolic compounds in Concord grape juice and their metabolites in human plasma and urine after juice consumption. J. Agric. Food Chem. *59*, 9512-9522.

Steffen, Y., Gruber, C.; Schewe, T., Sies, H., 2008. Mono-Omethylated flavanols and other flavonoids as inhibitors of endothelial NADPH oxidase. Arch. Biochem. Biophys. *469*, 209-219.

Steffen, Y., Schewe, T., Sies, H. 2007. (-)-Epicatechin elevates nitric oxide in endothelial cells via inhibition of NADPH oxidase. Biochem. Biophys. Res. Commun. *359*, 828-33.

Stein, J. H., Keevil, J. G., Wiebe, D. A., Aeschlimann, S., Folts, J. D., 1999. Purple grape juice improves endothelial function and reduces the susceptibility of LDL cholesterol to oxidation in patients with coronary artery disease. Circulation, *100*, 1050−1055.

Su, J., Xu, H.T., Yu, J.J., Gao, J.L., Lei, J., Yin, Q.S., Li, B., Pang, M.X., Su, M.X., Mi, W.J., Chen, S.H., Ly, G.Y., 2015. Luteolin Ameliorates Hypertensive Vascular Remodeling through Inhibiting the Proliferation and Migration of Vascular Smooth Muscle Cells. Evid. Based Complement. Alternat. Med. *2015*, 364876 doi: 10.1155/2015/364876.

Suzuki, A., Yamamoto, M., Jokura, H., Fujii, A., Hase, T., Saito, I., 2007. Ferulic acid restores endothelium-dependent vasodilation in aortas of spontaneously hypertensive rats. Am. J. Hypertens. *20*, 508-513.

Taubert, D., Roesen, R., Lehmann, C., Jung, N., Schömig, E., 2007. Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized

controlled trial. J.A.M.A. 298, 49−60.

Thandapilly, S.J., Louis, X.L., Behbahani, J., Movahed, A., Yu, L., Fandrich, R., Zhang, S., Kardami, E., Anderson, H.D., Netticadan, T., 2013. Reduced hemodynamic load aids low-dose resveratrol in reversing cardiovascular defects in hypertensive rats. Hyperten. Res. *36*, 866-872.

Thekkumkara, T., Gumaste, U., Snyder, R., Karamyan, V., 2012. Tannic acid, an inhibitor for renal angiotensin type 1 receptor and hypertension in spontaneously hypertensive rats. Endocr. Rev. *33*, SAT-248.

Vislocky, L. M., Fernandez, M. L., 2010. Biomedical effects of grape products. Nutr. Rev. *68*, 656−670.

Wang, Z.M., Zhou, B., Wang, Y.S., Gong, Q.Y., Wang, Q.M., Yan, Y.Y., Gao, W., Wang, L.S., 2011. Black and green tea consumption and the risk of coronary artery disease: a meta-analysis. Am. J. Clin. Nutr. *93*, 506-515.

Wang, X., Ouyang, Y.Y., Liu, J., Zhao, G., 2014. Flavonoid intake and risk of CVD: a systematic review and meta-analysis of prospective cohort studies. Br. J. Nutr. *111*, 1-11.

Waterhouse, A. L., 2002. Wine phenolics. Ann. N. Y. Acad. Sci. *957*, 21–36.

Wengreen, H., Munger, R.G., Cutler, A., Quach, A., Bowles, A., Corcoran, C., Tschanz, J.T., Norton, M.C., Welsh-Bohmer, K.A., 2013. Prospective study of Dietary Approaches to Stop Hypertension- and Mediterranean-style dietary patterns and age-related cognitive change: the Cache County Study on Memory, Health and Aging. Am. J. Clin. Nutr. *98*, 1263–1271.

Williams, R. J., Spencer, J. P. E., Rice-Evans, C., 2004. Flavonoids: antioxidants or signaling molecules? Free Radical Biol. Med. *36*, 838−849.

Williamson, G. Manach C., 2005. Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. Am. J. Clin. Nutr. *81*(suppl): 243S-255S.

Yang, D., Liu, J., Tian, C., Zeng, Y., Zheng, Y. H., Fang, Q., Li, H. H., 2010. Epigallocatechin gallate inhibits angiotensin II-induced endothelial barrier dysfunction via inhibition of the p38 MAPK/ HSP27 pathway. Acta. Pharmacol. Sin. *31*, 1401-1406.

Zand, J., Lanza, F., Garg, H.K., Bryan, N.S., 2011. All-natural nitrite and nitrate containing dietary supplement promotes nitric oxide production and reduces triglycerides in humans. Nutr. Res. *31*, 262-269.

Zhu, Y., Xia, M., Yang, Y., Liu, F., Li, Z., Hao, Y., Mi, M., Jin, T., Ling, W., 2011. Purified anthocyanin supplementation improves endothelial function via NO-cGMP activation in hypercholesterolemic individuals. Clin. Chem. 57, 1524-1533.

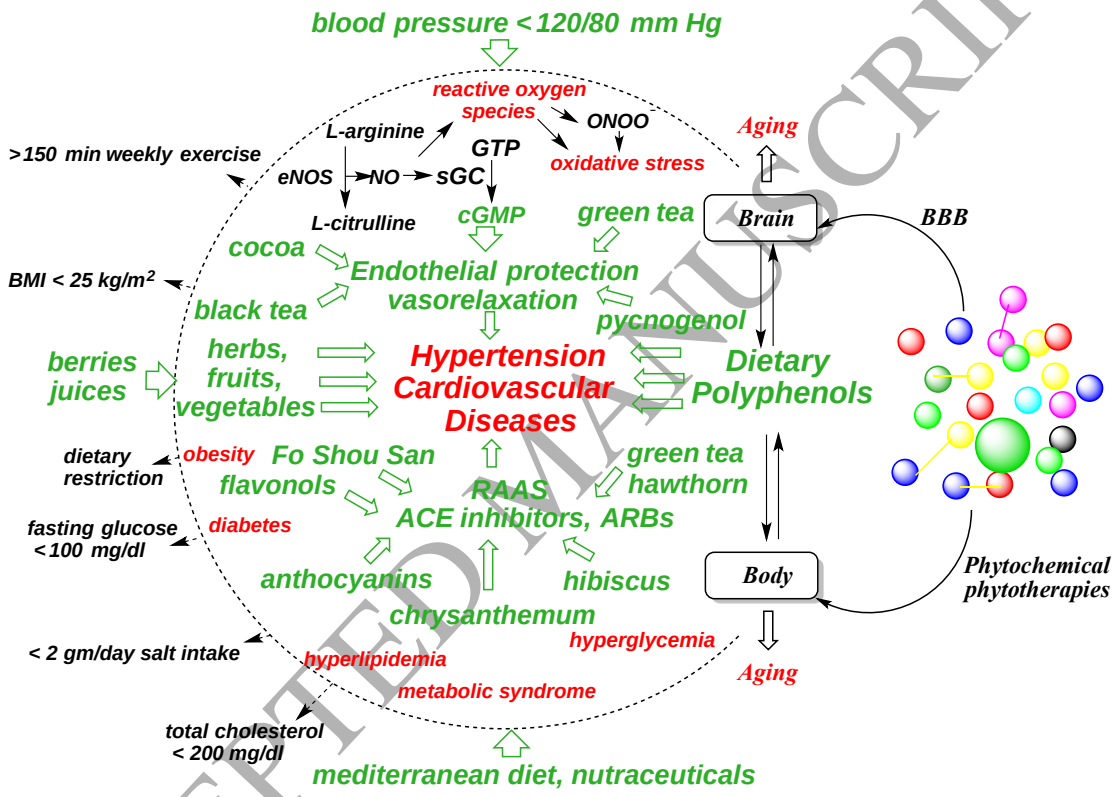
2013 Trends and Statistics for Prescription Medications in the United States: CNS Highest Ranked and Record Number of Prescriptions Dispensed, 2015. A.C.S. Chem.

Neurosci. *6*, 356-357.

Schemes, Figures, Tables

Scheme 1

Antihypertensive Phytotherapy: A snapshot of the risk reduction promoted by various types of dietary polyphenols against hypertension and major health risk factors contributing to CVD. The red colors are health risks and problems to be minimized; peripheral inward green arrows, and black outward arrows represent contributions to wellbeing, dietary metrics for minimizing cardiovascular diseases.



Scheme 2

Anthocyanin metabolites and anti-hypertensive activities

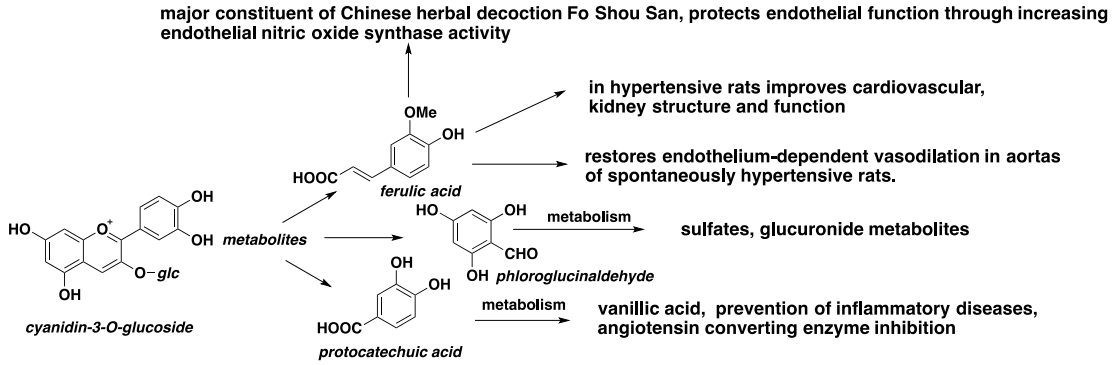


Fig. 1.

Hypertension and cardiovascular disease protective dietary flavonoids

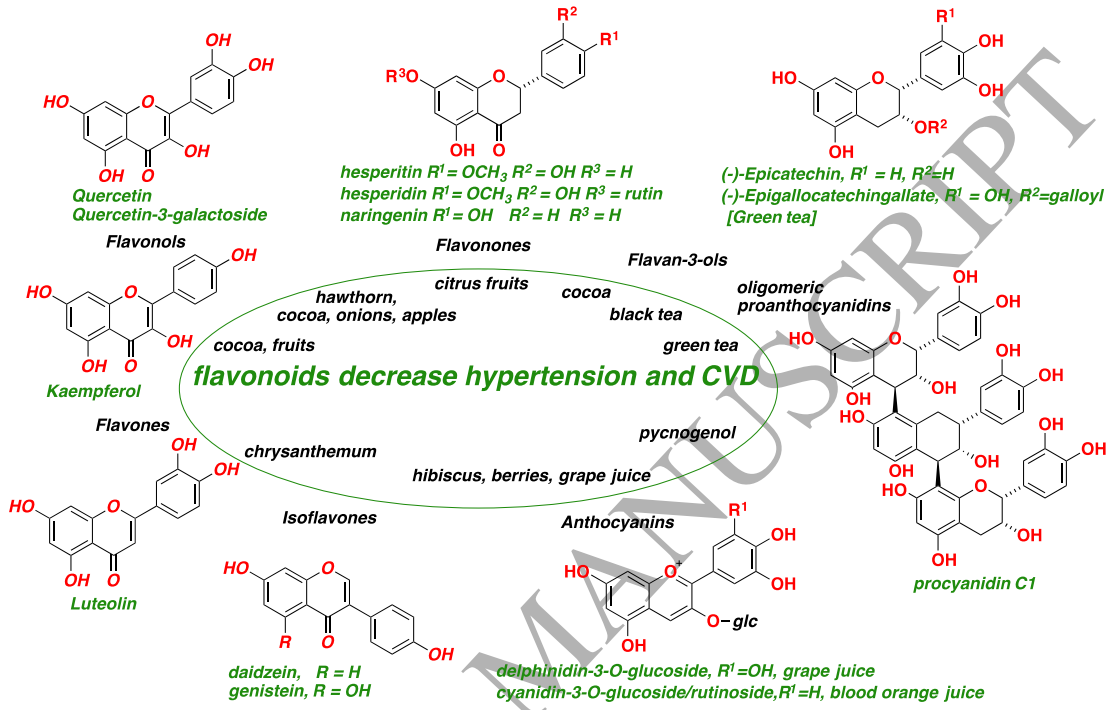


Fig. 2. Snapshot of the diverse health benefits of flavanol polyphenols

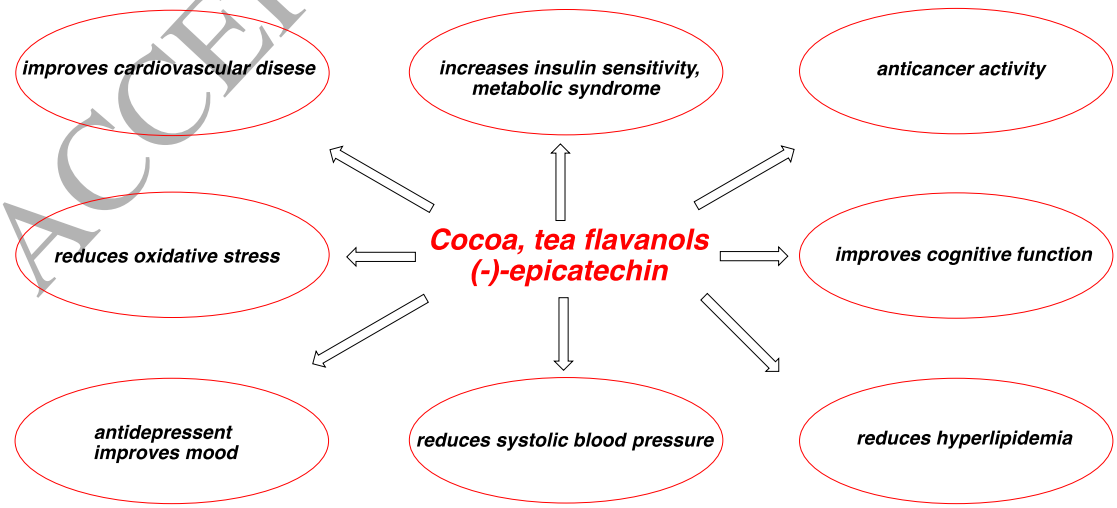
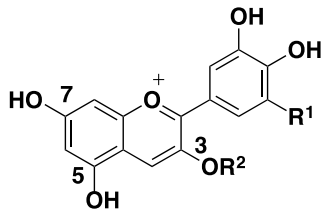


Fig. 3. The major anthocyanin constituents of Hibiscus *sabdariffa L*

Hibiscus sabdariffa anthocyanins



Anthocyanins	R^1	R^2
cyanidin-3-sambubioside	*H*	*sambubioside*
cyanidin-3-glucoside	*H*	*glucose*
delphinidin--3-sambubioside	*OH*	*sambubioside*
delphinidin--3-glucoside	*OH*	*glucose*

sambubiose = β-D-xylosyl-(1-2)-β-D-glucose

Table 1

Intervention studies of polyphenol-flavonoid intake in relation to reduction in blood pressure

Dietary hypertension interventions	Hypertension health
An investigation of around 2000 women aged between 18 and 75 years for 11 years determined an inverse correlation between higher anthocyanin, flavone intake and lower arterial stiffness [pulse wave velocity] and blood pressure measurements (Jennings et al. 2012)	A daily dietary intake of 44 mg of berry [either strawberries, raspberries or blueberries] anthocyanins was associated with a decrease in systolic blood pressure of 3 +/- 1.4 mmHg.
An extensive and large prospective study involving 23,043 men and 87,242 were followed up for 14 years that provided evidence for an inverse association between a higher berry anthocyanin intake in their diets and hypertension. The total flavonoid/subclass intakes were calculated from semi-quantitative food-frequency questionnaires collected every 4 y (Cassidy et al. 2011)	Hypertension was found in 29,018 women and 5629 men. A high dietary anthocyanin intake mainly from strawberries and blueberries was associated with an 8% decreased risk of incident hypertension. The magnitude of the association was greater (12%) in participants <60 years of age (quintile 5 compared with quintile 1, relative risk 0.88; 95% CI 0.84, 0.93; p for trend < 0.001; p for age interaction = 0.02). The intake of catechin and apigenin correlated with a 6% and 5% risk reduction in hypertension
Double blind randomised clinical trials involving 11 women and 33 men myocardial infarction (MI) patients and hypercholesterolemics have shown improvement in hypertension health after berry consumption. Furthermore the serum 8-isoprostans and VLDL levels were lowered by 23% and 29% respectively, indicative of diminished inflammation (Naruszewicz et al. 2007; Zhu et al. 2011)	The MI patients were on statin therapy for at least 6 months [40 mg/day simvastatin], the 6 week dietary supplementation of a commercial chokeberry flavonoind extract composed of 64 mg anthocyanins, 128 mg procyanidins, and 23 mg phenolic acids reduced SBP by a mean average of 11 mmHg and likewise DBP by 7.2 mmHg.
Single-blinded randomised controlled clinical trial involving obese 4 men and 44 females, [BMI: 37.8 +/- 2.3 kg/m^2 mean age 50 y] with metabolic syndrome showed reduced blood pressure after a 56 day supplementation with freeze dried blueberry beverage containing 1624 mg of total polyphenols and 742 mg of anthocyanins (Basu et al. 2010; Erlund et al. 2008)	The blood pressure measurements at week 4 and 8 on the blueberry group resulted in decreases in SBP of 6% and in DBP of 4% that were also accompanied by decreases in plasma oxidized LDL, and serum malondialdehyde and hydroxynonenal concentrations of 28% and 17%, respectively.
A RCT cross over design involving 20 healthy persons were organized to receive 5 doses of cocoa flavonoids with a 10 g daily/weekly intake [0, 80, 200, 500, 800mg] spanning 5 weeks Grassi et al., 2005a;	Cocoa flavonoid intake dose-dependently increased flow-mediated dilation from baseline 6.2% to 7.3, 7.6, 8.1 and 8.2%. Cocoa intake decreased SBP: -4.8 ± 1.03 mmHg, P<0.0001; DBP: -3.03 ± 1.07mmHg, P = 0.0011). Cocoa also dose-dependently decreased endothelin-1 (ET-1), pulse wave velocity.
A randomized, double blind controlled cross over design involving 19 healthy men were organized to consume 5 beverage schedules with a twice daily/weekly intake of black tea [0, 100, 200, 400, 800mg tea flavonoids/day] with each dose regime lasting 1 week (Grassi et al., 2009)	Black tea intake dose-dependently increased flow-mediated dilation from baseline 7.8% to 9.0, 9.1, 9.6 and 10.3%. This beverage intake decreased SBP: -2.6 mmHg, P<0.007; DBP: -2.2 mmHg, P = 0.006) and decreased arterial stiffness.
To investigate the effects of black tea on BP and wave reflections before and after a fat load, a	The fat load increased wave reflection, but was reduced by tea intake. Black tea decreased SBP

randomized double-blind, controlled, cross-over design involving 19 hypertensive patients, who consumed black tea (129 mg flavonoids) or placebo twice a day for eight days (13 day wash-out period) (Grassi et al., 2015)	and DBP (-3.2 mmHg, $p < 0.005$ and -2.6 mmHg, $p < 0.0001$; respectively) whilst also preventing BP increase after a fat load ($p < 0.0001$).
A randomized, controlled, blinded, parallel-group trial including 42 women, 20 men 56 to 73 years, with untreated upper-range prehypertension or stage 1 hypertension was conducted to study the effect of low intake of cocoa per day for an extended period on BP and the underlying BP-lowering mechanisms. Research indicates that cocoa intake is linked to vascular and BP changes. (Taubert et al. 2007)	An 18 week daily supplementation of [6.3g, 30 kcal] of dark chocolate decreased SBP by 2.9 ± 1.6 mmHg and DBP by 1.9 ± 1.0 mmHg. Body weight, plasma levels of lipids, glucose, and 8-isoprostane were unaffected. The prevalence of hypertension was lowered from 86 to 68%. The increase of vasodilative NO, suggests a potential mechanism whereby low amounts of dietary polyphenol supplementation can effectively lower BP.
Clinical studies employing a double-blind, controlled, parallel-arm study to study the dose-cognitive effects of a cocoa beverage on 90 cognitively healthy elderly individuals assigned to consume daily for 8 weeks a beverage of 993 mg [high flavanol (HF)], or 520 mg [intermediate flavanol (IF)], or 48 mg [low flavanol (LF)] cocoa flavanols (CFs). Cognitive capacity was assessed at baseline and after 8 weeks by the Mini-Mental State Examination (MMSE), the Trail Making Test (TMT) A and B, and the Verbal Fluency Test (VFT). (Mastroiacovo et al. 2015)	The changes in MMSE score in response to the 3 different treatments were the same. The data for the IF and HF intake groups showed improvements in verbal fluency test, perhaps by improved insulin sensitivity, blood pressure, lipid peroxidation, suggesting that habitual intake of CFs can support multiple functions of healthy cognitive aging.

Table 2

Effects of duration and consumption of black and green tea on SBP & DBP

Tea, duration intake, health condition	***SBP [mm Hg]***	***DBP [mm Hg]***	***Reference***
Black, 7 days, dose-dependent, healthy subjects	-2.6 ($p < 0.007$)	-2.2 ($p < 0.006$)	(Grassi et al. 2009)
Black, [129 mg flavonoids] 2x/day, 8 days, hypertensive	-3.2 ($p < 0.005$)	-2.6 ($p < 0.0001$)	(Grassi et al. 2015)
Black, > 12 weeks, not dose-dependent, healthy & hypertens.	-1.4 (95% CI - 2·4, - 0·4)	-1.1(95% CI - 1·9, - 0·2)	(Liu et al. 2014)
Green, > 12 weeks, not dose-dependent, healthy & hypertens.	-2.1 (95% CI - 2·9, 1·2)	-1.7(95% CI - 2·9, - 0·5)	(Liu et al. 2014)
Green, > 12 weeks,	-1.98 (95% CI - 2·94, - 1·01 $P < 0.001$)	-1.92 (95% CI – 3.17, 0.68$P < 0.002$)	(Peng et al. 2014)