



## Mechanisms of Endothelial Protection by Natural Bioactive Compounds from Fruit and Vegetables

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*Manuscript received on August 2, 2016; accepted for publication on December 5, 2016*

### ABSTRACT

The endothelium is fundamental for the regulation of vascular tone and structure. Under disease conditions, including the presence of cardiovascular disease risk factors, the endothelium loses its protective role and becomes a proatherosclerotic structure. In this article we searched for strategies from PUBMED and Science Direct databases using the following key words: endothelium, natural bioactive compounds, polyphenols and cardiovascular diseases. The search was restricted to english language papers. Studies have identified the contribution of diet to the risk of developing cardiovascular diseases. In this context, high intakes of fruit and vegetables are associated with the decrease of cardiovascular diseases. Thus the most important fruit/vegetables and bioactive compounds to prevent endothelial diseases are berries, apples, virgin olive oil, tomatoes, soybeans, and polyphenols, carotenoids and unsaturated fatty acids, respectively. The bioactive compounds from fruit and vegetables provide endothelial protection through the following mechanisms: improved eNOS/NO bioavailability, attenuates oxidative stress, inhibited NF- $\kappa$ B pathway and decreased cell adhesion molecules expression. In this article natural bioactive compound mechanisms of endothelium protection are thoroughly reviewed.

**Key words:** endothelium, natural bioactive compounds, polyphenols, cardiovascular diseases.

### INTRODUCTION

Heart and blood vessel damage are commonly known as cardiovascular diseases (CVD) (i.e., acute myocardial infarction, cerebrovascular

disease and peripheral arterial thrombosis). CVD are responsible for approximately 30% of deaths worldwide and cause more than 15 million deaths in the world each year (Palomo et al. 2007, Bautista et al. 2006). Among the main risk factors for CVD (RFCVD) are cigarette smoking, elevated blood pressure, elevated serum total cholesterol and diabetes, among others (Icaza et al. 2009, Mujica et al. 2008, Palomo et al. 2006). In addition, these RFCVD contribute to dysregulated endothelium

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\* Contribution to the centenary of the Brazilian Academy of Sciences.

function (Palomo et al. 2003, Cai and Harrison 2000, Versari et al. 2009).

The endothelium is recognized as a crucial homeostatic organ, fundamental for vascular tone and structure regulation. Under disease conditions, including the presence of RFCVD, the endothelium undergoes functional and structural alterations, thus losing its protective role and becoming a proatherosclerotic structure (Versari et al. 2009, Taddei et al. 2003). Alteration in endothelial function precedes the development of morphological atherosclerotic changes and can also contribute to wound development and later clinical complications (Deanfield et al. 2007). Therefore, endothelial dysfunction is a well-established response to RFCVD and precedes the development of CVD (Hadi et al. 2005).

The Framingham Heart Study first identified the contribution of diet and sedentary lifestyles to the risk of cardiovascular disease (O'Donnell and Elosua 2008). Moreover, high intakes of fruit and vegetables were associated with a decrease in RFCVD (Liu et al. 2000). Since natural bioactive compounds from fruit and vegetables present CVD prevention properties, they could be directly associated with endothelial protection (Dauchet et al. 2006). In this context, this article reviews different natural bioactive compound mechanisms of endothelium protection.

## MATERIALS AND METHODS

**SEARCH STRATEGY.** PUBMED and Science Direct databases were researched using the following key words: endothelium, natural bioactive compounds, polyphenols, and cardiovascular diseases.

**INCLUSION CRITERIA.** The inclusion criteria considered the english language and year of paper's publication.

**EXCLUSION CRITERIA.** Only papers with abstract topics on cardiovascular diseases per se,

or in relation with either (1) endothelium or (2) natural bioactive compounds were selected.

## ENDOTHELIAL FUNCTION

The endothelium corresponds to the inner lining of blood vessels, being the largest organ in the human body. Endothelial cells are critical in the regulation, maintenance and control of cardiovascular functions, which occurs through the release of various molecules with antithrombotic activity that can inhibit platelet adhesion, coagulation and regulate the fibrinolytic system (Aird 2007). Moreover, the endothelial cells have several receptors for vasoactive substances (vasodilator and vasoconstrictor). Some mediators of inflammation such as C - reactive protein (CRP), IL-6, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), have been regarded as useful predictive markers of endothelial dysfunction in atherosclerosis, whereas other biomarkers (matrix metalloproteinase-9 and IL-18) have been associated with plaque vulnerability (Casas et al. 2014).

The vascular endothelium is the primary site of dysfunction in many diseases, particularly cardiovascular in patients with RFCVD (Heitzer et al. 2001). Endothelial dysfunction expresses adhesion molecules on cell surfaces and synthesizes plasma proteins such as von Willebrand factor (vWF) that are involved in platelet adhesion during thrombosis and inflammation (Kanaji et al. 2012, Etingin et al. 1993, Palomo et al. 2011).

The endothelial dysfunction allows increased platelet adhesion to endothelial cells, which is the first step in platelet activation. Platelet stimulation causes the affinity of integrin receptors for their ligands to be upregulated and induces platelet degranulation. Secreted products from activated platelets act to recruit further platelets into the growing aggregate, as well as having strong inflammatory effects on the endothelium

(Frenette et al. 1995). Thus, platelet interactions with the endothelium, is the major contributor to pathological thrombus formation (Ruggeri 1997).

#### MEDITERRANEAN DIET

The Mediterranean Diet (MD) is a complete and balanced combination of foods rich in antioxidants, which protect against CVD (Tapsell 2014). Plant-based foods are crucial on the MD, since they are rich in polyphenols (Bonaccio et al. 2012). Fruit and vegetable beverages and purees retain many beneficial components, such as flavonoids, carotenoids, vitamin C and dietary fibers. The PREDIMED (Prevention with MD) study is a randomized clinical trial designed to evaluate the beneficial effects of MD as primary prevention of CVD in high cardiovascular risk elderly patients (Ros et al. 2014). The MD decreases adhesion molecules in T - lymphocytes and monocytes, CRP and IL -6. When including extra virgin olive oil or nuts, MD can double its effect in the prevention of CVD, decreasing typical RFCVD and triggering an intense anti-inflammatory effect, by regulating the reduction of inflammatory markers related to atherosclerosis, such as VCAM-1, ICAM 1, P-selectin Ey, CRP and IL-6 (Domenech et al. 2014, Martinez-Gonzalez et al. 2014b).

#### NATURAL BIOACTIVE COMPOUNDS FROM FRUIT AND VEGETABLES WITH ENDOTHELIAL PROTECTION ACTIVITY

Bioactive compounds in food provide health benefits beyond the nutritional aspects. They are usually found in small amounts in products of vegetable origin and are rich in lipids. The natural antioxidants are generally classified as phenolic compounds such as flavonoids and phenolic acids, vitamins, and volatile compounds found in various fruits, plants, herbs and spices. The active components of antioxidants derived from natural plants are polyphenolic compounds. The most effective

antioxidants are those containing two or more phenolic hydroxyl groups (Ahmad et al. 2013). In figure 1, we show the main mechanisms of endothelial protection by natural bioactive compounds.

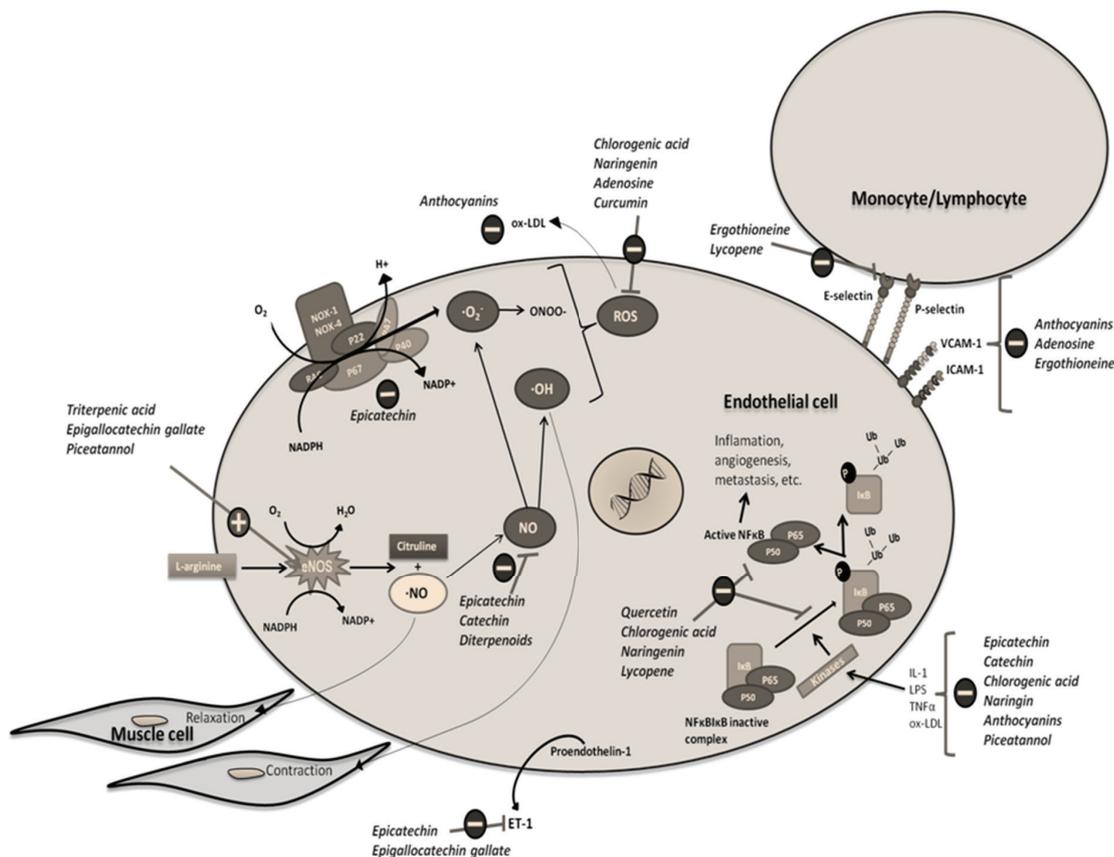
#### POLYPHENOLS

Epidemiological evidence suggests that polyphenols may, in part, explain the cardioprotective properties of fruit. Thus polyphenols have been shown to modulate a variety of targets in the prevention of cardiovascular diseases, which include platelet function, blood pressure, vascular function and blood lipids (Zern and Fernandez 2005, Leifert and Abeywardena 2008).

Pomegranates, red grapes and berries are fruits with relatively high concentrations of flavonols, anthocyanins and procyanidins; therefore they are effective in reducing RFCVD. Fruits rich in flavonols like oranges and grapefruit, have hypocholesterolemic effects (Chong et al. 2010). Furthermore, these compounds have a direct effect on endothelial cells. Polyphenols, grapes and berries can increase endothelial cells; powerful vasoprotectors including NO synthesis factors and endothelium-derived hyperpolarizing factor (Schini-Kerth et al. 2011).

#### *Flavonoids*

Flavonoids are a large family of over 5,000 hydroxylated polyphenolic compounds (Falcone Ferreyra et al. 2012). The dietary flavonoids are one of the main compounds that influence CVD, achieving this function by protecting the bioactivity of NO derived from endothelium. The final effect of flavonoids on NO levels will depend on the structure and concentrations of flavonoids used, in studied cell type, and especially in the presence of inflammatory/oxidative conditions (Duarte et al. 2014). Endothelial function varies widely according to the usual dietary intake and it has been shown that if flavonoids are consumed regularly in the diet by



**Figure 1** - The main mechanisms of endothelial protection by natural bioactive compounds. Anthocyanins, Adenosine and Ergothioneine inhibit adhesion molecules VCAM-1, ICAM-1, E-selectin, P-selectin. Lycopene and Ergothioneine inhibit leukocyte adhesion to endothelium. Epicatechin, Catechin, Chlorogenic acid, Naringin, Anthocyanins and Piceatannol inhibit proinflammatory molecules. Quercetin, Chlorogenic acid, Naringenin and Lycopene inhibit NFκB signaling pathways and preventing inflammation, angiogenesis, metastases, etc. Epicatechin, Catechin and Diterpenoids lower levels of nitric (NO) bioavailability and inhibit rust. Chlorogenic acid, Naringenin, Adenosine and Curcumin decrease reactive oxygen species (ROS). Anthocyanins decreases levels of oxidized LDL (ox-LDL). Epicatechin inhibit NADPH oxidase. Triterpenic acid, Epigallocatechin gallate and Piceatannol activate endothelial nitric oxide synthase (eNOS). Epicatechin and Epigallocatechin gallate reduce endothelin-1 (ET-1).

eating fruit and/or vegetables, endothelial function is significantly enhanced, forming part of a basal endothelial function by its action on the NO (Fisher et al. 2012). Fruit and vegetables that are rich in flavonoids improve vascular health; reduce endothelial dysfunction, inflammation and oxidative stress (Macready et al. 2014).

### Epicatechin

Epicatechin is a polyphenolic flavonoid that has been isolated from a variety of natural sources (Bonilla et al. 1999). Cocoa flavonoids (*Theobroma cacao* L.) reduce blood pressure, improve

endothelial function and increase the capacity of regeneration of the endothelium. Moreover, they also reduce levels of endothelial micro particles improving endothelial integrity (Horn et al. 2014).

Epicatechin is an important bioactive compound of cocoa and improves the endothelial function by stimulating the synthesis of NO (Jimenez et al. 2012), prevents arterial hypertension, proteinuria and endothelial dysfunction. Reduces the ET-1, vascular and systemic oxidative stress and inhibits NADPH oxidase activity (Gomez-Guzman et al. 2012). This compound also reduces synthesis bioavailability of NO and when conjugated with

dextran, epicatechin has the ability to stimulate cellular response, therefore supporting the existence of a possible epicatechin cell membrane receptor by activating the endothelial NO synthase (eNOS) (Moreno-Ulloa et al. 2014). Studies have shown that cocoa improves vasodilation and reduces arterial stiffness in women, and its consumption decreases the endothelial dysfunction in the mesenteric arterioles induced by a high fat diet in mice (Osakabe and Shibata 2012, West et al. 2014, Grassi et al. 2005).

Flavonoids and nitrates from a diet including fruit and vegetables may have a protective cardiovascular effect and cognitive impairment through effects on NO (Bondonno et al. 2014). Reduction on CVD development risk has been associated with the consumption of apples (*Pyrus malus* L.), due to the effect of the main hipocolesterolemic bioactive compounds, which are fiber and polyphenols catechin, epicatechin, procyanidin B1 and  $\beta$ -carotene are the main phytochemicals responsible for the decrease in cholesterol (Serra et al. 2012). The green apple is rich in polyphenols and its epicatechin content increases NO bioavailability (Hollands et al. 2013). Consumption of apples or its bioactive compounds help modulate lipid metabolism and reduce production of proinflammatory molecules (Chai et al. 2012).

### *Catechin*

Catechin is a polyphenolic flavonoid (Nagao et al. 2005). Both pomegranate (*Punica granatum*) juice and peel of are rich in polyphenols (tannins and flavonoids) that have antioxidant, anti-inflammatory and anti-cancer potential (Kelishadi et al. 2011). Pomegranate antioxidant potential comes from a specific type of tannins, the ellagitannins (punicalagin and punicalin). Various kinds of pomegranate flavonoids include anthocyanins, which give color to the fruit juice. Juice and the pomegranate

peel have catechins with high antioxidant activity. Pomegranate flavonoids show antioxidant activity with the indirect inhibition of inflammatory markers, such as TNF- $\alpha$ . Pomegranate juice can reduce macrophage oxidative stress, free radicals, lipid peroxidation, and also prevents cell growth and induces apoptosis. The ellagitannins also inhibit the activation of inflammatory pathways such as MAPK. Furthermore, they could inhibit angiogenesis through down regulation of vascular endothelial growth factor in cancers, thus significantly decreasing levels of reactive oxygen species (ROS). Ellagitannins and ellagic acid are metabolized by the intestinal micro flora to produce urolithins, which have anti-inflammatory properties. Since pomegranate extract is rich in polyphenols (oleanolic, ursolic and gallic acid) it could prevent cardiovascular problems by decreasing low density lipoproteins (LDL), increasing high density lipoproteins (HDL), stability and serum paraoxonase activity 1 and NO production increase (Aviram and Rosenblat 2013, Zarfeshany et al. 2014). Pomegranate juice is rich in bioactive phytochemicals with antioxidant activity and anti-inflammatory and cardioprotective functions (Asgary et al. 2013, Wu et al. 2015).

The pistachio (*Pistacia vera*) contains greater amount of polyphenols in the peel, such as gallic acid, catechin, cyanidin-3-O-galactoside, eriodictiol-7-O-glucoside and epicatechin, which gives it an antioxidant effect (Tomaino et al. 2010). Moreover, it significantly reduces the total peripheral resistance, the increase of cardiac output, and also improves some measures of heart rate variability. It also reduces the systolic blood pressure (BP) during sleep. A moderate-fat diet containing pistachios improves some RFCVD in well-controlled type 2 diabetes adults (Sauder et al. 2014). The pistachio has also shown improved glucose levels in blood, endothelial function, and some indices of inflammation and oxidative state in healthy young men. Moreover, decrease of

glucose, LDL, total cholesterol and triglycerides was significant. It also improved endothelium-dependent vasodilation, decreased serum IL-6, total oxidant state, and lipid hydroperoxide and malondialdehyde, and increased superoxide dismutase (Sari et al. 2010). Thus pistachio and gallic acid as its main constituents decrease inflammatory biomarkers as well as inhibit lipid accumulation (Grace et al. 2015). Gallic acid is well known for its antioxidant and hepatoprotective activity, but its effectiveness is limited due to its rapid metabolism and elimination, so there have been created methods to increase its bioavailability with the formation of phospholipid complexes improving its absorption in rats (Bhattacharyya et al. 2013).

Polyphenols in red wine induce NO synthesis and the endothelium derived hyperpolarization mediated through coronary vasodilation, which includes dependent PI3-kinase / Akt redox-sensitive pathway in the endothelium. The flavonoids act on the endothelium through the bilitranslocase, which is a membrane flavonoids transporter (Zibera et al. 2013). Another study showed that red wine also contains polyphenols such as epicatechin and catechin, showing that the latter appears to be an antiatherogenic compound more effective than epicatechin in hyperhomocysteinemia and should be considered as a new therapeutic approach against induced endothelial dysfunction by this condition (Noll et al. 2013).

#### *Anthocyanidins*

Anthocyanins are members of the flavonoid group of phytochemicals, which is a group predominant in tea, honey, wine, fruit, vegetables, nuts, olive oil, cocoa and cereals. Anthocyanins are water-soluble phytochemicals with a typical red to blue color (Lila 2004, Woodward et al. 2009). Recently, oriental persimmon (*Diospyros kaki* Thunb. Cv. Fuyu) extract has been studied for its antiatherogenic properties (Son et al. 2013). This fruit contains bioactive molecules that can improve endothelial

function through activation of eNOS and reduced secretion of ET-1 (Woodcock et al. 2013). These polyphenols also exhibit an antihypertensive effect of proanthocyanidins due to vascular relaxation via endothelium dependent NO/cGMP pathway, and may be useful in reducing BP (Kawakami et al. 2011).

#### *Epigallocatechin gallate*

Epigallocatechin gallate is the ester of epigallocatechin and gallic acid, and is a type of catechin (Du et al. 2012). Green tea has several functional effects, such as anti-inflammatory and antioxidant activities (Matsumoto et al. 2013). Epigallocatechin-3-gallate (EGCG) is the most abundant polyphenol in green tea and has vasodilatory effect by activating eNOS. EGCG may have beneficial health effects on glucose metabolism and endothelial function through the modulation of the inflammatory response induced by a high fat diet (Kim et al. 2013a). By improving endothelial function, EGCG decreases the progression of atherosclerosis (Minatti et al. 2012). EGCG has therapeutic potential for endotoxin mediated endothelial inflammation (Li et al. 2012). Moreover, EGCG regulates the accumulation of ectopic fat through autophagy flow making it in a potential therapeutic reagent to prevent cardiovascular complications (Kim et al. 2013a). Unfortunately it exhibits low bioavailability due to bad intestinal transport, metabolism and rapid clearance (Peters et al. 2010).

#### *Quercetin*

Quercetin is a polyphenol present in fruit and vegetables that also contributes to cardiovascular health (Arai et al. 2000). It protects against endothelial dysfunction, induced by oxidants, and against atherosclerosis. These effects are associated with increased NO bioavailability and are related with HO-1 blood induction (Shen et al. 2013). Onion (*Allium cepa*) is rich in quercetin. In some *in vitro* studies, quercetin improved endothelial

function associated with atherosclerosis, which is a cause of CVD (Nakayama et al. 2013). Furthermore, it prevents diabetic vascular complications, both in insulin deficiency and resistance through its inhibitory effect on inflammatory pathways especially NF- $\kappa$ B signaling (Mahmoud et al. 2013).

#### *Chlorogenic acid*

Coffee is one of the most widely consumed beverages, both in the United States and worldwide. Three large prospective cohort studies demonstrated that higher consumptions of total coffee, caffeinated coffee, and decaffeinated coffee were associated with lower risk of total mortality (Ding et al. 2015). With respect to the association between coffee consumption and cardiovascular mortality, moderate coffee consumption was inversely significantly associated with CVD, with the lowest CVD risk at 3 to 5 cups/day, and heavy coffee consumption was not associated with elevated CVD risk (Ding et al. 2014, Loomba et al. 2014, Zhang et al. 2009). This is controversial, since other recently published studies show the opposite (Liu et al. 2013, Sugiyama et al. 2010). The heterogeneous findings may be due to differences between case-control and prospective study designs and possibly also to inconsistent control for important confounders such as tobacco smoking. In addition, the numbers of deaths have been small in most studies (Freedman et al. 2012). Therefore, coffee consumption at any dosage appears to be safe and does not represent an increase in mortality risk (Loomba et al. 2014).

The main polyphenol present in coffee is chlorogenic acid (CGA), which has shown to improve endothelial function in mice fed a high-fat diet (Li Kwok Cheong et al. 2014). CGA reduces BP acutely and does not affect endothelial function or NO states (Mubarak et al. 2012). CGA inhibits adhesion of monocytes, production of ROS, translocation of NF $\kappa$ B and expression of adhesion

molecules (Chang et al. 2010). CGA present in coffee is well absorbed and metabolized by humans (Farah et al. 2008).

Polyphenols in lemon grass (*Cymbopogon citratus*) have antioxidant, anti-inflammatory and chemopreventive properties (Rahim et al. 2013). Phytochemically they include tannins, flavonoids, terpenoids and methanol extracts as alkaloids and steroids (Soares et al. 2013). This protects the human umbilical vein endothelial cells (HUVEC) from oxidative damage induced hyperglycemia, hydrogen peroxide and LDL-ox. Its antioxidant properties can prevent endothelial dysfunction associated with oxidative imbalance caused by different oxidative stimuli (Campos et al. 2014). Anti-inflammatory activity is due to its chlorogenic acid content, through proteasome inhibition and consequently NF $\kappa$ B pathway and expression of cytokines in human macrophages (Francisco et al. 2013).

#### *Anthocyanins*

The anthocyanins are the main group of natural water soluble plant pigments (Tanaka et al. 2008). They have beneficial effects in preventing CVD and neurological diseases. They show antihypertensive, endothelium-protective and anti-atherogenic activity, as well as interaction with the estrogen receptor. Different anthocyanin structures not only have an impact on their colors, but also affect their interaction with the different steps of the main pathways related to these diseases. Therefore, different colors can show different molecular mechanisms (de Pascual-Teresa 2014). Moreover, anthocyanins are a group of flavonoids that have anti-inflammatory and antioxidant properties. They showed an increase in HDL cholesterol levels in prehypertensives men without dyslipidemia (Hassellund et al. 2013).

Proanthocyanins are found in grape seeds in abundance. They have antithrombotic properties that are associated with endothelial protection

and inhibition of inflammatory cells adhesion, because it causes a decrease in the expression of P-selectin thus inhibiting leukocytes recruitment and thrombosis (Zhang et al. 2011).

Blueberries (*Vaccinium corymbosum* L.) are a rich source of anthocyanins, which protect cells against oxidative stress, reduce BP and improve endothelial dysfunction induced by high cholesterol diet (Del Bo et al. 2013). Wild blueberries are rich in flavonoids, phenolic acids and anthocyanins, which protect them from oxidation. Cranberries contain polyphenols that improve endothelial function, reduce RFCVD, lipid oxidation, inflammation and dyslipidemia in patients with metabolic syndrome. Moreover, they reduce the levels of total cholesterol and triglycerides; improve endothelium-dependent relaxation in the aorta of ovariectomized rats restoring P-eNOS, changes in regulated levels up to marker of renin-angiotensin system and normalize the expression of NADPH oxidase and oxidative stress (Flammer et al. 2013).

Strawberries (*Fragaria vesca*) have antioxidant activity and reduce RFCVD, such as high BP, hyperglycemia, dyslipidemia and inflammation (Basu et al. 2010). Strawberries contain anthocyanins that improve plasma lipid profile; biomarkers of antioxidant state and modulate platelet function in healthy subjects (Alvarez-Suarez et al. 2014). Furthermore, they trigger antithrombotic effects in mice, inhibit platelet aggregation, reduce the P-selectin expression and decrease sCD40L serum, RANTES and IL-1 $\beta$  (Alarcon et al. 2014). Although strawberry phenolic compounds are known mainly for their anti-inflammatory actions and antioxidant properties, recent studies have shown that their biological activities were also extended to other pathways involved in metabolism and cell survival (Giampieri et al. 2014, Manach et al. 2005).

Nuts are rich in many bioactive compounds, especially anthocyanins that may have beneficial effects on cardiovascular health. Hazelnuts (*Corylus avellana*), for example, contain 6.71 mg of anthocyanins per 100 grams (Kozłowska

and Szostak-Wegierek 2014) and decrease inflammation and endothelial dysfunction markers (Tey et al. 2013). Meanwhile, nuts (*Junglas regia*) have a protective effect on endothelial function and AP (Salas-Salvado et al. 2014). Consuming a diet enriched with hazelnuts significantly improves flow-mediated dilation, levels of total cholesterol, triglycerides, LDL, HDL, reduces LDL-ox, hs-CRP and sVCAM-1. Moreover, they present an antiatherogenic effect by improving endothelial function, prevention of LDL, inflammatory markers and lipid oxidation in addition to lowering lipoproteins (Orem et al. 2013, Tey et al. 2011). Furthermore hazelnut consumption can prevent reduction of HDL (Azadbakht and Rouhani 2013). Hazelnuts can be incorporated into the daily diet, causing no change in a healthy total caloric intake (Orem et al. 2013).

Malvidin is an anthocyanin found in the skin of red grapes that has cardioprotective effects (Quintieri et al. 2013). Malvidin decreases the regulation of NO generation and inhibits the synthesis of TNF, IL-1 and IL-6; making it a powerful anti-inflammatory flavonoid without toxic effect (Huang et al. 2016).

#### *Delphinidin*

Delphinidin is an anthocyanidin, a primary plant pigment, and also an antioxidant (Lamy et al. 2006). Maqui (*Aristotelia chilensis*) is a Chilean species that has health benefits for its high content of anthocyanins (Fredes et al. 2014). It is a good source delphinidins, an anthocyanin that has potent antioxidant activity, as it reduces the oxidative stress (oxLDL) and glucose in blood, increases eNOS expression, decreases the expression of endothelin – 1 vasoconstriction and cell molecules adhesion ICAM 1 and VCAM-1. Furthermore, it decreases platelet activity preventing thrombosis (Watson and Schonlau 2015).

### *Resveratrol*

Resveratrol is a stilbenoid, a type of natural phenol. A high intake of polyphenols, especially of stilbenes and lignans, reduces the risk of overall mortality when compared with individuals with lower intake (Yurdagul et al. 2014). Resveratrol is a stilbene that promotes re-endothelialization after arterial injury and improves wound healing (Yurdagul et al. 2014, Troped et al. 2010). Resveratrol (trans-3,5,4'-trihydroxystilbene) is a phytoalexin found in foods such as grapes, plums, blueberries and peanuts (Atmaca et al. 2014). Its antioxidant efficacy has been demonstrated in traumatic brain injury, methotrexate-induced hepatic toxicity, gentamicin-induced nephrotoxicity, and doxorubicin induced cardiotoxicity (Dalaklioglu et al. 2013, Tunali-Akbay et al. 2010). Resveratrol attenuates endothelial inflammation by inducing autophagy (cellular process that protects cells from stressful conditions), which is mediated through the activation of the signaling cAMP-PRKA-AMPK-SIRT1 pathway (Chen et al. 2013). Resveratrol has low systemic bioavailability, but despite this, their accumulation in the endothelial cells may have a preventive effect of cancer, among others (Walle et al. 2004).

### *Naringenin*

Naringenin is a flavanone compound found in citrus fruit such as oranges (*Citrus sinensis*) and grapes (*Vitis vinifera*). It regulates oxidative stress decreasing levels of ROS and regulates the MAPK / NF -  $\kappa$ B pathway (Xu et al. 2013). It has been found that the main flavonoid in orange juice is hesperidin that decreases diastolic BP when consumed regularly (Morand et al. 2011).

### *Naringin*

Naringin is a flavanone-7-O-glycoside between the flavanone Naringenin and the disaccharide neohesperidose. Grapefruit (*Citrus x paradisi*) has a high

content of antioxidants and anti-inflammatory substances. Naringin, which is responsible for the sour taste of grapefruit, decreases inflammatory cells infiltration, oxidative stress and reduces plasma lipid concentration, and also improves mitochondrial liver function in mice (Alam et al. 2013). A study in diabetics with increased cardiovascular risk found that endothelial function, which is measured as flow mediated dilation, improves significantly and normalizes after a week of grapefruit juice consumption (Buscemi et al. 2012).

### *Piceatannol and scirpusin B*

The piceatannol and scirpusin B are polyphenolic compounds that are present in high quantities in passion fruit (*Passiflora edulis*) seeds. Both compounds have antioxidant activity and vasodilator effect. The latter effect is explained by the increase of NO, which reduces the CVD risk (Sano et al. 2011). There have also been similar studies with passion fruit skin that also showed positive results as a potential source of antioxidant (Wong et al. 2014, Zeraik et al. 2011). Studies show that passion fruit has another bioactive compound named pectin, which significantly reduces neutrophil infiltration and partially decreases TNF- $\alpha$  (Silva et al. 2011, Yapo and Koffi 2006).

### *Tyrosol and hydroxytyrosol*

Tyrosol and hydroxytyrosol are absorbed from moderate and sustained doses of virgin olive oil in humans (Miró-Casas et al. 2003). Consumption of extra virgin olive oil is associated with lower CVD risk and mortality in people with high cardiovascular risk (Guasch-Ferre et al. 2014). Eating a diet rich in polyphenols containing olive oil can decrease the BP and improve endothelial function (Moreno-Luna et al. 2012). The main phenolic in olive oil are tyrosol and hydroxytyrosol, however it also contains flavones apigenin and luteolin (Tagliaferri et al. 2014). Hydroxytyrosol helps to reduce plasma lipid levels and repair oxidative damage associated

with CVD (de la Torre-Robles et al. 2014, Miró-Casas et al. 2001). Moreover, olive oil pomace concentrates triterpene acids, which attenuates the increase in BP, improving dependent endothelium relaxation, increased vascular expression of eNOS, and reduction of TNF alpha and transforming growth beta factor (Valero-Munoz et al. 2014). Its consumption is inversely associated with stroke and coronary heart disease (Martinez-Gonzalez et al. 2014a).

#### CAROTENOIDS

##### *Crocetin*

Crocetin is a natural dicarboxylic acid carotenoid found in the crocus flower (*Crocus sativus*) and fruits of gardenia (*Gardenia jasminoides*). It is used worldwide as an important spice, food coloring and herbal medicine (Higashino et al. 2014). Crocetin effects were studied on induced angiogenesis, vascular endothelial growth factor (VEGF), in *in vitro* tube formation assays and after 14 days of co-culture of HUVEC and fibroblasts. Angiogenesis suppression has been demonstrated that is induced by VEGF through inhibiting migration and expression of p38 - phosphorylated and VE- cadherin protection (Umigai et al. 2012). Antihypertensive and antithrombotic effects of crocetin relate to an increased NO bioavailability, possibly mediated by decreased NO inactivation through ROS (Higashino et al. 2014).

##### *Lycopene*

Lycopene is a carotenoid principally responsible for the characteristic deep-red color of ripe tomato fruits and tomato products (Shi and Le Maguer 2000). Tomato (*Solanum lycopersicum*) is an herbaceous plant that contains several phytochemicals, such as vitamin C, potassium, folate and carotenoids like lycopene, among others. Carotenoids are pigments synthesized during fruit ripening and lycopene in particular is responsible

for the red color of tomatoes (Perveen et al. 2013). Consumption of tomato paste improves endothelial function (Xaplanteris et al. 2012). Lycopene is hypolipidemic and inhibits pro-thrombotic and pro-inflammatory factors (Mordente et al. 2011, Bohn et al. 2013). Consumption of tomato products attenuates postprandial oxidative stress induced by lipemia and associated inflammatory response, demonstrating a protective role of tomato by reducing CVD risk (Burton-Freeman et al. 2012). Tomato oleoresin interferes inflammatory signaling in endothelial cells, imitating the inflammatory processes reduction in the vessel wall and reducing BP. Prevention of adhesion molecules over-expression through inhibition of NF-kB signaling is one of the main mechanisms of carotenoids to reduce leukocyte adhesion to endothelium (Armoza et al. 2013).

#### NUCLEOSIDES

Nucleosides are glycosylamines that can be thought of as nucleotides without a phosphate group. Adenosine is an abundant active ingredient in the extract of black soybean is also associated with antiplatelet activity (Kim et al. 2013b). One study showed that supplemental intake of soy isoflavones for 6 and 12 months had an effect on oxidative stress by decreasing the concentration of malondialdehyde (MDA) (Pusparini et al. 2013). Soy protein reduces lipid and BP, reducing levels of E-selectin and leptin (Rebholz et al. 2013). Fermented soy extracts inhibit ROS production (Lim et al. 2012). Soy isoflavones can be divided into three chemical groups: daidzein, genistein and glycitin, which vary in their bioavailability (Chang and Choue 2013).

#### UNSATURATED FATTY ACIDS

Unsaturated fatty acids have one or more double bonds between carbon atoms. Walnuts improve endothelial function in overweight adults and

visceral adiposity; also they do not increase weight and can prevent CVD (Katz et al. 2012). Studies have shown that consumption of nuts increased the concentration of HDL, and decreased total cholesterol and LDL-C compared with a control diet (Banel and Hu 2009, Cominetti et al. 2012, Ros et al. 2004). Walnuts are a rich source of  $\alpha$ -linoleic acid (ALA) (~ 13% of total lipids) and  $\gamma$ -tocopherol (20 mg/100 g) and contain phytosterols (164 mg/100 g). Walnut oil promotes endothelial function, partly due to ALA and/or increased bioavailability. Decreases the antioxidant potential reduction of iron (FRAP), and whole nuts increase the efflux of cholesterol (Berryman et al. 2013). A study showed that daily consumption of 43 grams of nuts per 8 weeks significantly reduced non-HDL cholesterol and Apo B, decreasing the risk of coronary heart disease (Wu et al. 2014).

#### TERPENOIDS

Curcuminoids and terpenoids are typical bioactive compounds from turmeric (*Curcuma longa* L.) (Lee et al. 2014). Curcumin is recognized for their antioxidant properties, thus it significantly decreases endothelial dysfunction induced by diabetes through lowering superoxide inhibition and PKC inhibition (Rungseesantivanon et al. 2010). Also inhibits LDL-ox from receptor-1 (LOX-1) and suppresses the inflammatory response in HUVEC by antioxidants processes (Lee et al. 2010). Studies suggest that the immunomodulatory effects of curcumin occur because of IL- 1 $\beta$ , IL - 4 and VEGF serum modification (Ganjali et al. 2014, Gao et al. 2004, Varalakshmi et al. 2008). Curcumin has low bioavailability because it is poorly absorbed in the gut and undergoes rapid metabolism in the liver (Tsai et al. 2012).

Sesquiterpenoids and *Siegesbeckia pubescens* diterpenoids isolated inhibit NO production in macrophages. Active terpenoids present in *Siegesbeckia* could be used as anti-inflammatory agents (Wang et al. 2014). The ent-16 $\beta$ ,17-

dihydroxy-kauran-19-oic acid (DDKA) has antiplatelet and antithrombotic activity. Both effects were studied from isolated DDKA *S. pubescens*. DDKA prolonged prothrombin time and partial thromboplastin time in rats after intravenous administration during 5 successive days. DDKA has antiplatelet activity in rats and causes an increase in intraplatelet cAMP levels (Wang et al. 2011).

#### OTHERS

##### *Nitrates*

Nitrate is a polyatomic ion with the molecular formula NO<sub>3</sub>. Presence of nitrates from beet (*Beta vulgaris*) in the diet, reduce BP by sequential reduction of nitrate to nitrite and then to NO in the circulation (Hobbs et al. 2013). Beetroot, which is rich in inorganic nitrates, reduces the deterioration of endothelial function associated with the ingestion of a mixed meal (Joris and Mensink 2013). Moreover, it improves endothelial function, increases nitrite in plasma and improves insulin sensitivity in people with type 2 diabetes (Gilchrist et al. 2013).

Flavonoids and nitrates in the diet can increase the NO through different pathways, which can improve the endothelial function and the BP. Recent studies suggest that the combination of flavonoids and nitrates can enhance NO production in the stomach (Bondonno et al. 2012, Peri et al. 2005). Furthermore, it was shown that diets high in nitrates rich apples flavonoids and spinach (*Spinacia oleracea*) may increase independently NO levels, improve the endothelial function and reduce BP acutely, all of which can benefit cardiovascular health (Bondonno et al. 2012).

##### *Ergothioneine*

Ergothioneine (ET) is a bioactive antioxidant compound present in edible fungi that, although it is not synthesized can be accumulated by humans through diet. ET interrupts proinflammatory induction of adhesion molecules expression

associated with atherogenesis, thus reducing the risk CVD. ET reduces VCAM -1, ICAM-1 and E-selectin (Martin 2010). ET is absorbed by the endothelial cells through type 1 (OCTN-1) organic cation transporter and protects against oxidative stress, therefore reducing the endothelial dysfunction (Li et al. 2014).

### CONCLUSIONS

It was demonstrated in this article that high intakes of fruit and vegetables are associated with a decrease in cardiovascular diseases via endothelial protection. Thus the most important fruit/vegetables and bioactive compounds to prevent endothelial diseases are berries, apples, virgin olive oil, tomatoes, soybeans, and polyphenols, carotenoids and unsaturated fatty acids, respectively. The bioactive compounds from fruit and vegetables provide endothelial protection through the following mechanisms: improved eNOS/NO bioavailability, attenuates oxidative stress, inhibited NF- $\kappa$ B pathway and decreased cell adhesion molecules expression. In table SI (Supplementary Material) we show endothelial cell protection by natural bioactive compounds from fruit and vegetables.

### ACKNOWLEDGMENTS

Eduardo Fuentes thanks Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) N° 11140142. This work was also funded by Interdisciplinary Excellence Research Program on Healthy Aging (PIEI-ES).

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**SUPPLEMENTARY MATERIAL**

**Table SI** - Endothelial cell protection and natural bioactive compounds.