



Natural Products to Promote Vascular Health

Valérie Schini-Kerth, Ibrahima Diouf, Hira Muzammel, Amissi Said, Cyril Auger

► To cite this version:

Valérie Schini-Kerth, Ibrahima Diouf, Hira Muzammel, Amissi Said, Cyril Auger. Natural Products to Promote Vascular Health. Natural Products as Sources of Novel Drugs, Springer Berlin Heidelberg, 2024, Handbook of Experimental Pharmacology, 978-3-031-80293-5. <10.1007/164_2024_721>. <hal-04766164>

HAL Id: hal-04766164

<https://hal.science/hal-04766164v1>

Submitted on 5 Nov 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Natural Products to Promote Vascular Health

Valérie B. Schini-Kerth ^{1*}, Ibrahima Diouf ¹, Hira Muzammel ¹, Amissi Said ¹, Cyril Auger ²

*¹ University of Strasbourg, UR 3074, Médecine Cardiovasculaire Translationnelle,
Strasbourg, France.*

*² INSERM UMR 1260, Regenerative Nanomedicine, University of Strasbourg, Strasbourg,
France.*

* Name and complete address of corresponding author

Pr Valérie B. Schini-Kerth

UR 3074, Médecine Cardiovasculaire Translationnelle

Université de Strasbourg, CRBS

1 rue Eugène Boeckel

67000 Strasbourg, France

Phone : +33 3 68 85 41 27

Email: valerie.schini-kerth@unistra.fr

Abstract:

Maintaining a good vascular health is a major component in healthy ageing as it reduces the risk of cardiovascular diseases. Endothelial dysfunction, in particular, is a key mechanism in the development of major cardiovascular diseases including hypertension, atherosclerosis and diabetes. Recently, endothelial senescence has emerged as a pivotal early event in the age-related endothelial dysfunction. Endothelial function is characterized by an imbalance between the endothelial formation of vasoprotective mechanisms, including the formation of nitric oxide (NO) and endothelium-dependent hyperpolarization, and an increased level of oxidative stress involving several pro-oxidant enzymes such as NADPH oxidase and, often also, the appearance of cyclooxygenase-derived vasoconstrictors. Pre-clinical studies have indicated that natural products, in particular polyphenol-rich foods, can trigger activating pathways in endothelial cells promoting an increased formation of NO and endothelium-dependent hyperpolarization. In addition, some can even exert beneficial effects on the endothelial senescence. Moreover, some of these products have been associated with the prevention and/or the improvement of an established endothelial dysfunction in several experimental models of cardiovascular diseases and in Humans with cardiovascular diseases. Therefore, intake of certain natural products, such as dietary and plant-derived polyphenol-rich products, appears to be an attractive approach for a healthy vascular system in ageing.

Keywords: Endothelium, cardiovascular diseases, dietary polyphenols, natural products

1. Introduction

According to the World Health Organization, cardiovascular diseases (CVDs) remain the first cause of death worldwide, both in developed and developing countries, accounting for about 18 million deaths per year and 32% of death worldwide ¹. In addition, CVDs are a major cause of morbidity and are estimated to cost per year €210 billion to the European economies and \$407.3 billion to the US economy ^{2,3}.

Aging is a major independent risk factor for cardiovascular diseases as CVDs incidence increases exponentially with increasing age ⁴. This is due to the fact that aging leads to deterioration of cardiac and vascular structure and function ⁵. In particular, aging is associated with the development of an endothelial dysfunction, which in turn promote the development of CVDs ^{6,7}.

Recently, the American Heart Association indicated that amongst the major risk factors for CVDs, unhealthy diet is the major contributor to CVD in US, with less than 1% of the population meeting the ideal criteria for Healthy Diet score ⁸. In 2017, a study indicated that cardiometabolic deaths in the US were related to several diet-related factors including low intake of omega-3 rich products (nuts, seeds and seafoods), as well as low intake of fruits and vegetables ⁹.

Thus, this review will discuss in a non-exhaustive manner the studies indicating that dietary and plant-derived polyphenol-rich products have the ability to induce the endothelial function and/or to improve the endothelial dysfunction *in vitro* and *ex vivo*. In addition, experimental and clinical studies evaluating the beneficial effects of natural products on the endothelial function *in vivo* will also be discussed.

2. Physiological role of the endothelium

The endothelium is a cellular monolayer at the luminal surface of all blood vessels that exert a key role in the maintenance of vascular homeostasis due, at least in part, to the formation and release of potent vasoactive factors ^{10,11} (Figure 1). In physiological situation, the endothelium induces vasorelaxation of blood vessels mainly through the formation of nitric oxide (NO), prostacyclin (PGI₂) and endothelium-derived hyperpolarization (EDH). Endothelial cells also exert the control of vascular homeostasis through endothelium-dependent vasoconstrictive responses involving mostly endothelin-1 (ET-1), angiotensin II (Ang II), reactive oxygen species (ROS), thromboxane A₂ (TXA₂) and vasoactive prostanoids termed ECDF (endothelium-derived contracting factors) ¹¹. The most potent vasoprotective factor in the body is NO generated by endothelial NO synthase (eNOS) from L-arginine. It is due to its ability to regulate a great variety of responses contributing to vascular homeostasis and prevention of cardiovascular diseases such as arterial wall remodeling and atherosclerosis ^{12,13}. Indeed, NO can prevent the adherence of monocytes to the endothelial surface, inhibit the expression of adhesion molecules, inhibit platelet adhesion and aggregation, prevent vascular smooth muscle cells migration and proliferation, and limit the expression of extracellular matrix molecules ¹⁴.

In addition to NO, EDH and PGI₂ also contributes to the maintenance of vascular homeostasis. Whereas having a small contribution in large conductance arteries, EDH allows the transmission of hyperpolarization from the endothelium to the underlying smooth muscle, thus inhibiting the vascular tones in resistance arteries such as coronary microcirculation and arterioles. The mechanisms underlying the EDH responses are complex and can involve different molecules such as arachidonic acid metabolites, H₂O₂, CO, H₂S or peptides, all leading to opening of small and intermediate conductance Ca²⁺-activated K⁺ channels on endothelial cells ¹⁵. Finally, the endothelial formation and releases of arachidonic acid-derived

prostacyclin PGI₂ have a role in the vascular homeostasis by regulating the vascular tone, but also by acting synergically with NO to inhibit platelets activation ¹¹.

In Humans, the endothelial function can be evaluated by flow-mediated vasodilation (FMD), which has been recognized as a prognostic marker of future cardiovascular events in patients ¹⁶.

3. Age-related endothelial dysfunction/ endothelial senescence

Ageing is a physiological process affecting every system within the body, including the vascular system. The vascular ageing is a complex process involving multiple mechanisms and leading to specific features such as arterial wall remodeling, increased arterial stiffness and pulse wave velocity, increased blood pressure and age-related endothelial dysfunction. In humans, the endothelium-dependent vasodilation induced by acetylcholine infusion decrease with increasing age, whereas the endothelium-independent vasodilatation induced by sodium nitroprusside is not affected by ageing ¹⁷. Aging is the key risk factor for cardiovascular disease with endothelial dysfunction a prime indicator. The age-related endothelial dysfunction is characterized by a loss of balance with reduced formation of beneficial vasoprotective factors (NO and EDH) and increased formation of factors favoring the development of cardiovascular diseases ¹¹. Similarly, an endothelial dysfunction is observed in major cardiovascular diseases such as atherosclerosis, hypertension, diabetes and obesity, and is often associated with an increased level of oxidative stress in the arterial wall ¹⁸⁻²⁴.

Ageing and age-related endothelial dysfunction also been associated with an increase in endothelial senescence, especially at arterial site at risk such as curvatures and bifurcation with turbulent blood flow and low shear stress. Indeed, senescent endothelial cells are found at site of atherosclerotic plaques in human coronary arteries ²⁵. Cellular senescence is defined by a permanent state of cell cycle arrest, and is associated with morphological changes such

as enlarged and flattened cell bodies, associated with increased adhesive phenotypes and a specific senescent-associated secretory phenotype (SASP). The SASP released from vascular cells includes pro-inflammatory mediators such as IL-1, IL-6, IL-8, TNF- α , chemokines such as MCP-1, growth factors such as EGF, VEGF and IGFBP, matrix metalloproteinases as well as reactive oxygen species (ROS) ^{26,27}. In addition to modify the micro-environment of the senescent cell, SASP also act as a paracrine factor for the propagation of senescence to neighboring cells ²⁶⁻²⁸.

The accumulation of senescent cells in organs is associated with the development of age-related diseases ²⁹. Cellular senescence was first described by Hayflick in cell culture, where cell cultures submitted to continuous division and replication ended with a loss of proliferation capacity associated with phenotypic modifications ³⁰. This “replicative senescence” was later associated with the shortening of telomeres during DNA replication (for review, see³¹. In addition, senescence could also be induced by various cellular events and stressors independently of replication, leading to “premature senescence” ³². While different types of endothelial cells could be similarly induced in premature senescence, they can show different responses to senolytic drugs due to different molecular modifications ³³.

Oxidative stress plays a central role in the induction of endothelial senescence. Urea induces senescence in endothelial progenitor cells through oxidative stress ³⁴. Replicative senescence in endothelial cells is associated with decreased eNOS expression and NO formation through an overexpression of NADPH oxidase and COX2, leading to an increased oxidative stress and reduced NO bioavailability ³⁵. Similarly, we shown that premature senescence of coronary endothelial cells induced by two feedforward loops centered on increased oxidative stress, the first involving the local angiotensin system and the second involving the sodium-glucose co-transporter (SGLTs) ³⁶⁻³⁹. Senescent endothelial cells are also more susceptible to infectious agents such as SARS-CoV-2, and thus to subsequent

endothelial dysfunction ⁴⁰. Conversely, plasma of COVID-19 patients has been shown to induce senescence in cultured endothelial cells ⁴¹.

Interestingly, removal of senescent cells by genetic or pharmacological approaches have been associated with extended lifespan in mice, and with improvements in age-related diseases including cardiovascular outcomes such as atherosclerosis (for review, see ⁴²).

Thus, targeting the endothelial dysfunction and underlying premature senescence seems to be a promising approach for healthy ageing.

4. Protective effects of natural products on the endothelial function

a. Dietary phenols: structures and bioavailability

In 2017, a study indicated that some cardiometabolic deaths were related to low intake of fruits and vegetables ⁹. Similarly, in China, a 4-years follow-up study including more than a half-million people from 10 localities have shown that daily fresh fruit consumption was associated with reduced blood pressure, with a risk reduction for cardiovascular death of 37%, and with a risk reduction for major coronary events or ischemic strokes of 30% ⁴³.

The beneficial effects of diet rich in fruits and vegetables have been attributed, at least in part, to their high content in micronutrients such as phenolic compounds. These phenolic compounds are secondary metabolites of plants that can be found in various form throughout the plant kingdom, and can accumulate at high concentration in plants ⁴⁴. These phytochemicals represent the main non-energetic component in plant-based food ⁴⁵. Several thousand of different phenolic structures have been identified in plants, including edible parts, and new structures are regularly identified. The general structure of phenolic compounds is characterized by at least a simple phenol ring bearing at least one hydroxyl group, but can include much larger and complex molecules⁴⁴. In addition, some phenolic compounds have the ability to form polymers, and/or can also be conjugated to other molecules such as acids or sugars, thus further complexifying the number of possible molecules. Thus, phenolic compounds, also sometime named polyphenols, are classified according to the arrangement of the carbon atoms and their substituents in several classes including phenolic acids, hydroxycinnamic acids, coumarins, stilbenes and flavonoids ⁴⁶. They are traditionally classified into two groups: flavonoids and non-flavonoids.

Flavonoids are composed of a 15-carbon skeleton (C6-C3-C6) with two aromatic rings linked by a 3-carbon bridge forming an oxygenated heterocycle. They are subdivided into several

subclasses, mainly flavan-3-ols, anthocyanins, flavonols, flavanones, flavones and isoflavones. Flavan-3-ols, also known as catechins and condensed tannins, are characterized by the presence of a saturated carbon in position C3 and are structurally complex. They also bear two chiral centers (C2 and C3), leading to 4 isomers for the simple monomers. However, only two of them are widespread in dietary plants, namely (+)-catechin and (-)-epicatechin ⁴⁴. The monomers of catechin and epicatechin can be hydroxylated into gallocatechins and/or esterified with gallic acid to form structure such as epigallocatechin-gallate. In addition, the monomeric structures can be assembled into larger structures such as oligomeric and polymeric proanthocyanins, also known as condensed tannins. Moreover, in tea processing, the fermentation of green tea leaves (*Camellia sinensis*) into black tea will produce dimer-like structures named theaflavins and thearubigins ⁴⁷. Flavan-3-ols are abundant in tea, wine and grapes, cocoa and chocolates, beer and cider.

Anthocyanidins are characterized by the fact that they are cationic structures, thus leading to pigments responsible for the pink/red to purple/blue colors of fruits, vegetables and flowers ⁴⁶. In plants they are always found conjugated to sugars and named anthocyanins, and they can be further conjugated to hydroxycinnamic acid and/or organic acids.

Flavonols, including quercetin and kaempferol, are widespread throughout the plant kingdom with the exception of fungi and algae. They are generally found conjugated to sugars with a large number of possible combination due to the available positions and type of glycosides (more than 200 described conjugates for kaempferol)⁴⁷.

Flavanones are found as O-glycosides mainly in citrus fruits along with polymethoxylated flavones.

Flavones occur predominantly in some herbs such as parsley or celery, whereas isoflavones are found in vegetables such as soybean and soy-derived products including soy milk, miso and tofu ⁴⁸.

The dietary intake of phenolic compounds is still difficult to assess due to the highly variable content in phenolic compounds of food items, the lack of systematic standardized dosage and the variability of dietary pattern. The median energy-adjusted dietary intake of polyphenols was estimated to be 884.1, 214.5 and 204 mg/day/1000 kcal, respectively in the US, China and Brazil ⁴⁹⁻⁵¹. In Europe, the European Prospective Investigation into Cancer and Nutrition (EPIC) study reported a median intake of 1177 and 1192 mg/d, for men and women, respectively, with large disparities between the 10 countries, with Greece having the lowest median intake (744 and 584 mg/d, respectively for men and women) and Aarhus in Denmark the highest (1786 and 584 mg/d, respectively for men and women) ⁵². The main sources of phenolic compounds were coffee, fruits, tea and wine ⁵².

Another aspect of the difficulty to study phenolic compounds *in vivo* is their complex bioavailability. Indeed, they are absorbed to various extent in the digestive tracts as intact molecules or after deconjugation ⁴⁷. Contrary to some plant-derived micronutrients that are readily absorbed, such as minerals and vitamins, phenolic compounds are handled by the human body as xenobiotics. Thus, absorbed compounds are submitted to phase II metabolism where they are methylated, sulphated and/or glucuronidated ⁴⁷. The only compounds that seem to escape this metabolism are (epi)gallocatechin-3-O-gallate, and to some extent (epi)catechin-3-O-gallate ⁵³⁻⁵⁵. Moreover, unabsorbed compounds reaching the colon are submitted to degradation by the microflora, leading to the production of phenolic acids and ring fission products that in turn can be absorbed and metabolised ⁴⁷.

In addition, accumulation of polyphenols has been observed in specific cells and thus, the circulating concentration may not reflect the actual concentration in target tissues ⁵⁶⁻⁵⁹.

b. Effects of dietary phenols using *in vitro* and *ex vivo* models

During the last decades, the potential health benefit of dietary phenolic on the cardiovascular system has been reported in various studies. These data indicated that the effect is, at least in part, due to their effects on the vasculature and, especially, on the endothelium ^{60–63}.

First indication of a direct effect of polyphenol-rich product on the endothelium was reported for wine and grape-derived extract. Indeed, these extracts were able to induce pronounced relaxations of pre-contracted arterial rings with an intact endothelium, whereas only small relaxations are observed in those without endothelium ⁶⁴. In a subsequent study, the same group reported similar endothelium-dependent relaxations in response to extract derived from various dietary sources, including vegetables, fruits, teas, herbs and spices ⁶⁵. As the relaxations were markedly blunted in presence of pharmacological inhibitors of NO pathway, the authors suggested the involvement of an extract-induced eNOS-derived formation and release of NO. However, the fact that the relaxation induced by grape-derived polyphenols in porcine coronary artery rings is only partially inhibited by an inhibitor of eNOS implies that other pathways could contribute to the vasorelaxant effect of polyphenols. Indeed, a further inhibition is obtained by the addition of inhibitors of the EDH pathway, indicating that EDH contributes also to the vasorelaxant effect of grape-derived phenolic compounds ^{66,67}. In addition, phenols extracted from extra virgin olive oil are able to induce vasodilation in rat 3rd order mesenteric artery through a direct effect on smooth muscle cells mediated by the activation of large conductance calcium-activated potassium channels (BK_{Ca}) ⁶⁸.

Further investigations demonstrated that the endothelium-dependent relaxation induced by phenolic extracts due to an intracellular pro-oxidant responses in endothelial cells in a physiological status, whereas phenolic compounds are still generally described as antioxidants ^{66,67,69–71}.

Interestingly, compared to physiological stimulators, such as bradykinin, that induce only short-lasting (within minutes) endothelial formation of NO, polyphenols are able to induce a

relatively sustained eNOS activation persisting for several hours, resulting in a long-lasting formation of NO, which seems optimal for a sustained vascular protection ⁷². Indeed, the vasorelaxation induced by grape-derived phenolic compounds were significantly reduced in presence of membrane-permeant analogues of superoxide dismutase (SOD) and catalase, while non-permeant anti-oxidants such as native SOD and catalase were without effect ^{66,71}. In addition, these grape-derived phenolic compounds increased the intracellular formation of ROS in cultured coronary artery endothelial cells in a time- and concentration-dependent manner, and also in healthy coronary arteries they induce formation of ROS in the endothelium but not in the underlying vascular smooth muscle ^{67,70}.

The increase in ROS formation induced by phenolic compounds in turn activate a redox-sensitive pathway involving a Src-mediated phosphatidylinositol-3-kinase (PI-3-kinase)-dependent phosphorylation of Akt, which, in turn, induces the activation of eNOS by phosphorylation of the activator site Ser1177 to increase the formation of NO in endothelial cells ^{66,69,71,73–75}. In addition to this redox-sensitive Src/PI-3-kinase pathway, studies have reported that the NO formation could be induce by certain phenolic compounds through other pathway such as estrogen receptor activation ^{76–78}, AMPK ^{79,80} or transient calcium signaling ⁸¹.

While some polyphenol-rich products such as grape-derived products are able to induce the endothelial function, some other show lower potency. Indeed, the comparison of several commercially available fruit juices has indicated that the vasorelaxant activity is dependent on their concentration of polyphenols ^{82,83}. Moreover, the vasorelaxing activity is dependent not only on the quantity but also on the quality of the polyphenolic content, as juices from cranberry, aronia, blackcurrant and blueberry induced potent relaxations, whereas polyphenol-rich juices from elderberry and blackberry induced only small effects ⁸⁴.

In addition to their effect on the endothelial function, phenolic compound can also exert beneficial effects through other cellular pathways. Indeed, hydroxytyrosol, a phenolic compound from olive oil, have been reported to reduce inflammation levels in LPS-induced human vascular endothelial cells (HUVECS) as well as reduced cholesterol accumulation and endothelial adhesion in human THP-1 monocytes ⁸⁵. Similarly, an anthocyanin-rich extract from red Chinese cabbage suppressed monocyte adhesion to TNF α -stimulated HUVECS through reduction of NF- κ B-mediated expression of endothelial adhesion factors ⁸⁶. Moreover, low dose (10 μ M) of chlorogenic acid prevented the glucose induced downregulation of Nrf2 in human endothelial cells, and the associated upregulation of NADP oxidase, resulting in lower oxidative stress and improved NO bioavailability ⁸⁷. As endothelial senescence has to be an early event in the induction of cardiovascular diseases, phenolic compounds able to act on the endothelial senescence are of interest. Amongst senolytic drugs, quercetin have been shown to kill senescent endothelial cells *in vitro* ⁸⁸. While showing only a weak senolytic effect, curcumin attenuated premature senescence induced by H₂O₂ in endothelial cells via the activation of the Sirt1/eNOS pathway ^{89,90}. Similarly, resveratrol prevented endothelial senescence induced by high glucose via the AMPK/Sirt1 and the p300/p53/p21 signaling pathways ⁹¹. Moreover, resveratrol can reduce senescence in primary human endothelial progenitor cells associated with increased expression of PPAR γ , hTRET and HO-1 ⁹². Pterostilbene, another stilbenoid related to resveratrol, can also prevent endothelial senescence induced either by angiotensin II or H₂O₂ via Sirt1 activation ⁹³.

c. Beneficial cardiovascular effects of dietary phenols reported in experimental *in vivo* models

Whereas cellular models and *ex vivo* studies are helpful for deciphering the molecular and cellular mechanism underlying the vasoprotective effect of phenolic compounds, they lack the interplays between physiological systems and pathological processes involved in the multifactorial development of cardiovascular diseases. Thus, experimental animal models are required to take into account the integrated responses involving the vascular tissues, the neurovascular axis, the hormonal system, the immunity and the interaction of the vascular tissues with blood flow and blood cells. Moreover, when studying the effect of dietary compounds, the *in vivo* models will help to take into account the bioavailability of natural products following oral absorption and their metabolism. As phenolic compounds are often metabolized by the tissues and/or catabolized by the microbiota, the net biological effect can be due not to the initial compounds, but to secondary circulating metabolites or catabolites. Moreover, recent studies suggest that the beneficial effects of phenolic compounds can be due to some extent to their effect on the microbiota by acting as prebiotics ⁹⁴.

However, a major point to be kept in mind when using experimental models is to take into account the fact that, while being mammals, most of the widely used animals have differences with humans. First of all, their body size and composition are different from human, and it should be accounted for when extrapolating the dose of phenolic compound by using metabolic conversion factors ⁹⁵.

Hypertension is a major risk factor for cardiovascular diseases that is characterized in several experimental models by an endothelial dysfunction associated with vascular oxidative stress ⁹⁶. Numerous studies have reported the effects of phenolic-rich dietary products or of extract derived from such products. Several studies reported that red wines, or wine extracts, reduced systolic blood pressure in the spontaneously hypertensive rat model and improves endothelium-dependent relaxation in arteries ^{97–100}. Similar beneficial effect of red wines and

extracts on blood pressure and endothelial function were also reported in other models of hypertension such as DOCA-salt rats, L-NAME rats and angiotensin II-infused rats ^{101–105}. Anti-hypertensive effects have also been reported for grape seed extract in spontaneously hypertensive rats ^{106,107}, in angiotensin II-induced hypertension ¹⁰⁸, cafeteria-fed rats ^{109,110}. Reduced systolic blood pressure was also observed for chronic consumption of other phenolic-rich products such as grape pomace extract ¹¹¹, grape seed extracts ¹¹², tea extracts ¹¹³, pomegranate juice ¹¹⁴, cranberry juice ¹¹⁵, cocoa powder ¹¹⁶, cinnamon ¹¹⁷ or blueberry ¹¹⁸ in hypertensive animal models. The antihypertensive effect of cinnamon extract also has been reported in a model of L-NAME-induced hypertension in rat ¹¹⁹. Finally, antihypertensive effects have also been reported after treatment of models of hypertension with isolated compounds, including (-)-epicatechin ^{120,121}, quercetin ^{122–127}, chlorogenic acid ¹²⁸, (-)-epigallocatechin-3-*O*-gallate ¹²⁹, genistein ¹³⁰, and trans-resveratrol ¹³¹.

Ageing is another major risk factor of cardiovascular diseases that have been associated with an age-related endothelial dysfunction both in animal models and in human. The chronic intake of a red wine polyphenolic extract by a model of ageing-related endothelial dysfunction was associated with a delay in the onset of the endothelial dysfunction ¹⁸. Subsequent studies further indicated that a treatment with red wine extract in middle-aged rats with an already established ageing-related endothelial dysfunction was associated with an improved endothelial function ^{22,132}.

Finally, beneficial vascular and endothelial effects of polyphenol-rich products have been reported in other models of pathologies associated with endothelial dysfunction. In diabetes, pomegranate juice and extract were able to improve endothelial dysfunction in female Zucker rats ¹¹⁴, while oral intake of (-)-epigallocatechin-3-*O*-gallate, resveratrol and genistein restored the endothelial function in streptozotocin-induced diabetic rats ^{133–135}.

Low dose of chlorogenic acid (0.02 % in the diet) given to diabetic db/db mice for 12 weeks was associated with preserve endothelial function and NO bioavailability, and lower vascular oxidative stress in the aortic tissues exposed *ex vivo* to high glucose concentration ⁸⁷.

In pregnant mice without functional eNOS (eNOS^{-/-} mice), chronic intake of grape-seed extract decreased the systolic blood pressure and improved the endothelium-dependent relaxation of mesenteric and uterine arteries, whereas no effect was seen in aorta ¹³⁶.

In most experimental models of cardiovascular risk factors, the endothelial dysfunction is associated with an increased vascular level of oxidative stress throughout the vascular wall.

This oxidative stress is mainly associated with the formation of superoxide anions by several sources including NADPH oxidase, COXs, xanthine oxidase, cytochrome P450, the mitochondrial respiratory chain and, last but not least, uncoupled eNOS ^{22,105,132,137}. Chronic treatment of middle-aged rats or angiotensin II-induced hypertensive rats with red wine phenolic extract improved the endothelial function in association with a reduced level of vascular oxidative stress and expression of NADPH sub-units ^{18,22,105,132}. Other studies suggest that dietary phenolic compounds can also decrease the level of vascular oxidative stress by inducing the expression of antioxidant enzymes ^{113,138}

Altogether, these studies indicate that dietary phenolic compounds can exert a beneficial effect on the cardiovascular system through several mechanisms including an improved endothelial function and decreased oxidative stress.

d. Clinical studies

Several epidemiological studies and meta-analysis have indicated a link between consumption of diet rich in phenolic compounds, or diet rich in fruits and vegetables such as the Mediterranean diet, and beneficial health effects ^{139–147}. For example, a study indicated that in the USA diet-related cardiometabolic deaths are predominantly observed in a population

characterized by a low intake of vegetables and fruits ⁹. Conversely, a reduced cardiovascular mortality was observed with an increased consumption of fruits and vegetables ^{140,141,144,148}, or with increased adherence of the Mediterranean diet ¹⁴⁶. The effect of increased fruit and vegetables consumption was effective on both the relative risk of stroke ^{141,143} and of coronary heart death ^{140,142}, the two major causes of cardiovascular death. The beneficial effect of fruits and vegetable consumption is due, at least in part, to their high content in phenolic compounds.

In the NIH-AARP study, a statistically significant relationship was found between mortality due to cardiovascular death of older people and intake level of total flavonoids, and this relationship was also found for flavonols, anthocyanidins and flavones ¹⁴⁹.

Besides consumption of general fruits and vegetables, epidemiological studies indicated associations between reduced risk of cardiovascular morbi-mortality and consumption of specific dietary products rich in phenolic compounds. Such beneficial effects have been reported for chronic and moderate consumption of red wine ¹⁵⁰, cocoa products ¹⁵¹, tea ¹⁵² or, to some extent, coffee ¹⁵³.

Besides the cardiovascular mortality, the effects of treatments on the vascular health in Humans is generally assessed through a hypertensive effect, whereas the endothelial function can be assessed using flow-mediated dilatation (FMD) measurement. FMD uses non-invasive ultrasound to measure the percentage of dilatation of the brachial artery in response to the re-establishment of a blood flow after the temporary occlusion of the artery with a cuff, and is due to an increased endothelial formation of NO in response to shear stress. A blunted FMD has been observed in Humans presenting major cardiovascular risk factors, and is known to be an independent predictor of the cardiovascular risk ¹⁶.

In agreement with the studies reporting decreased cardiovascular mortality associated with increasing consumption of phenolic compounds, several clinical studies indicate that products

rich in phenolic compounds, and in some instance isolated compounds, are able to improve the vascular function in Humans.

Following the proposition by Serge Renaud that red wine could be involved in the lower prevalence of cardiovascular diseases in the French population, termed as the French paradox, several studies evaluated the effect of wine consumption on the vascular health ¹⁵⁴. The chronic consumption of moderate dose of red wine (272 ml/day for 4 weeks) by normotensive subjects or patients with grade 1 hypertension was associated with a decreased blood pressure (2.3 and 5.8 mmHg, respectively), whether the red wine was with or without alcohol ¹⁵⁵.

Conversely, another study reported no effect on the blood pressure of chronic consumption of red wine (200 ml/day for up to 20 weeks) in normotensive subjects with documented carotid atherosclerosis ¹⁵⁶. The beneficial effect could be due, at least in part, to the increased FMD observed after consumption of low dose of red wine ^{157–159}. Similar increase in FMD were observed in healthy volunteers following the ingestion during meal of red grape juice during meal, with or without alcohol ¹⁶⁰. Moreover, ingestion of red wine was able to prevent the smoke-induced decrease in FMD ¹⁶¹. To avoid the deleterious effects of alcohol consumption associated with red wine, several studies have focused on other grape-derived products. For instance, the chronic consumption of purple grape juice (about 2 glasses/day for 8 weeks) was associated with a decreased blood pressure in Korean hypertensive patients in a study by Park et al., whereas no such effect was found in the study by Dohadwala et al. in prehypertensive patients ^{162,163}. The chronic intake of grape seed extract (300 mg/day for 6 weeks) by patients with mild hypertension was associated with a reduced blood pressure, and the effect was greater in patients with the highest initial blood pressure ¹⁶⁴. The chronic consumption of Concord purple grape juice (4 or 8 ml/kg/day for 8 weeks) by patients with coronary heart disease was associated with an increased in FMD ¹⁶⁵. Similar effects were reported following the intake of a single dose (600 mg) of a red grape extract by patients with coronary heart

diseases ¹⁶⁶.

Other fruit-derived products rich in phenolic compounds have shown beneficial effect on the vascular health. Indeed, chronic intake of pomegranate juice (50 ml for 2 weeks) by hypertensive patients was associated with a reduction of the systolic blood pressure by 5% ¹⁶⁷. Similarly, a reduction about 6% of systolic blood pressure was reported after chronic intake of 150 ml/day for 2 weeks of pomegranate juice ¹⁶⁸. The chronic consumption of pomegranate juice (50 ml/day for up to 3 years) by patients with carotid artery stenosis was also associated with a 12% reduction of systolic pressure at 1 year, with no modification further seems at 3 years ¹⁶⁹. The chronic consumption of fruit juices rich in phenolic compounds (500 ml/day for 12 weeks) was associated with reduced blood pressure both in normotensive subjects and hypertensive patients, with a greater effect observed for hypertensive patients ¹⁷⁰. Chronic treatment of hypercholesterolemic patients with anthocyanin isolated from berries (320 mg/day for 12 weeks) resulted in increased FMD ¹⁷¹. Also, chronic moderate consumption of berries for 8 weeks by middle-aged subjects with cardiovascular risk factors was associated with reduced systolic blood pressure ¹⁷². Finally, blueberries consumption also improved FMD in healthy volunteers in a time- and dose-dependent manner, and this was associated with an increased levels of circulating metabolites ¹⁷³.

Cocoa, another dietary product rich in phenolic compounds, and dark chocolate also have been reported to exert beneficial effects on the vasculature and the endothelium, and these effects seem to be related to its content in (-)-epicatechin and to the activation of the endothelial NO formation ¹⁷⁴. Indeed, the consumption by healthy volunteers of a single dose of a flavanol-rich cocoa drink increased FMD and was associated with a peak in plasma concentration of flavanols and (-)-epicatechin metabolites, as well as of plasma nitroso species indicating an increased formation of NO ¹⁷⁴. In healthy volunteers, 1 week treatment with cocoa dose-dependently increase FMD and reduce office blood pressure ¹⁷⁵. In addition,

chronic consumption of a flavonoid-rich chocolate bar (46 g/day for 2 weeks), but not of flavonoid-poor placebo, by healthy volunteers was also associated with an improved FMD and an increased plasma catechins concentration ¹⁷⁶. An increased FMD was also observed after a single intake of 22 g of dark chocolate in overweight subjects ¹⁷⁷. Moreover, chronic ingestion of dark chocolate (100 g/day for 2 weeks) was associated with reduced systolic blood pressure in elderly patients with mild hypertension ¹⁷⁸. In type 2 diabetic patients, chronic chocolate consumption (25 g/day for 8 weeks) reduced systolic and diastolic blood pressure ¹⁷⁹. Moreover, chronic consumption of cocoa by elderly patients for 8 weeks significantly reduced blood pressure ¹⁸⁰.

Chronic consumption of black tea (3 cups/day for 6 months) by normotensive subjects, was associated with lower (about 2 to 3 mmHg) systolic and diastolic blood pressure ¹⁸¹. In healthy volunteers, 1 week chronic ingestion of black tea was associated with a dose-dependent increase in FMD and decrease in blood pressure ¹⁸². Increased FMD was also reported after acute consumption of either green or black tea in healthy volunteers ^{183,184}. In patients with coronary artery disease, the consumption of black tea, either as a single dose (450 ml) or as a chronic treatment (900 ml/day for 2 weeks), improved significantly the FMD ¹⁸⁵. The chronic consumption of black tea (5 cup/day for 4 weeks) by patients with mild dyslipidemia was associated with an improved FMD ¹⁸⁶. Meta-analysis also indicated that both green and black tea consumption are associated with reduced systolic and diastolic blood pressure ^{187,188}, and improved FMD ¹⁸⁹.

Furthermore, a meta-analysis of randomized controlled trials indicated that polyphenol-rich food, but not purified food phenolic extract, were significantly associated with reduced systolic and diastolic blood pressure (-3.69 and -1.44 mmHg, respectively) and increased FMD (+1.44%) ¹⁹⁰. In addition, when both polyphenol-rich food and purified extract were considered, a significant reduction in triglyceridemia and total cholesterol was observed ¹⁹⁰.

5. Conclusion

Over the last decades, increasing studies have reported beneficial effects of the consumption of products rich in phenolic compounds. These products are able to improve the endothelial function, and thus the cardiovascular health, in both experimental models of cardiovascular diseases and also in patients with major cardiovascular risk factors. While the information regarding the exact nature of the active compounds or their metabolites/catabolites, these findings suggest that products rich in phenolic compounds are an important part of healthy diets to reduce the burden of cardiovascular diseases.

References

- (1) WHO Fact Sheet - Cardiovascular diseases (CVDs). World Health Organization. [https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)) (accessed 2023-10-20).
- (2) Wilkins, E.; Wilson, L.; Wickramasinghe, K.; Bhatnagar, P.; Leal, J.; Luengo-Fernandez, R.; Burns, R.; Rayner, M.; Townsend, N. *European Cardiovascular Disease Statistics 2017*; European Heart Network: Brussels, 2017.
- (3) Tsao, C. W.; Aday, A. W.; Almarzooq, Z. I.; Anderson, C. A. M.; Arora, P.; Avery, C. L.; Baker-Smith, C. M.; Beaton, A. Z.; Boehme, A. K.; Buxton, A. E.; Commodore-Mensah, Y.; Elkind, M. S. V.; Evenson, K. R.; Eze-Nliam, C.; Fugar, S.; Generoso, G.; Heard, D. G.; Hiremath, S.; Ho, J. E.; Kalani, R.; Kazi, D. S.; Ko, D.; Levine, D. A.; Liu, J.; Ma, J.; Magnani, J. W.; Michos, E. D.; Mussolino, M. E.; Navaneethan, S. D.; Parikh, N. I.; Poudel, R.; Rezk-Hanna, M.; Roth, G. A.; Shah, N. S.; St-Onge, M.-P.; Thacker, E. L.; Virani, S. S.; Voeks, J. H.; Wang, N.-Y.; Wong, N. D.; Wong, S. S.; Yaffe, K.; Martin, S. S.; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association. *Circulation* **2023**, *147* (8). <https://doi.org/10.1161/CIR.0000000000001123>.
- (4) Alfaras, I.; Di Germanio, C.; Bernier, M.; Csiszar, A.; Ungvari, Z.; Lakatta, E. G.; De Cabo, R. Pharmacological Strategies to Retard Cardiovascular Aging. *Circ. Res.* **2016**, *118* (10), 1626–1642. <https://doi.org/10.1161/CIRCRESAHA.116.307475>.
- (5) Chiao, Y. A.; Lakatta, E.; Ungvari, Z.; Dai, D.-F.; Rabinovitch, P. Cardiovascular Disease and Aging. In *Advances in Geroscience*; Sierra, F., Kohanski, R., Eds.; Springer International Publishing: Cham, 2016; pp 121–160. https://doi.org/10.1007/978-3-319-23246-1_5.
- (6) Donato, A. J.; Machin, D. R.; Lesniewski, L. A. Mechanisms of Dysfunction in the Aging Vasculature and Role in Age-Related Disease. *Circ. Res.* **2018**, *123* (7), 825–848. <https://doi.org/10.1161/CIRCRESAHA.118.312563>.
- (7) Seals, D. R.; Jablonski, K. L.; Donato, A. J. Aging and Vascular Endothelial Function in Humans. *Clin. Sci. Lond. Engl.* 1979 **2011**, *120* (9), 357–375. <https://doi.org/10.1042/CS20100476>.
- (8) Tsao, C. W.; Aday, A. W.; Almarzooq, Z. I.; Alonso, A.; Beaton, A. Z.; Bittencourt, M. S.; Boehme, A. K.; Buxton, A. E.; Carson, A. P.; Commodore-Mensah, Y.; Elkind, M. S. V.; Evenson, K. R.; Eze-Nliam, C.; Ferguson, J. F.; Generoso, G.; Ho, J. E.; Kalani, R.; Khan, S. S.; Kissela, B. M.; Knutson, K. L.; Levine, D. A.; Lewis, T. T.; Liu, J.; Loop, M. S.; Ma, J.; Mussolino, M. E.; Navaneethan, S. D.; Perak, A. M.; Poudel, R.; Rezk-Hanna, M.; Roth, G. A.; Schroeder, E. B.; Shah, S. H.; Thacker, E. L.; VanWagner, L. B.; Virani, S. S.; Voeks, J. H.; Wang, N.-Y.; Yaffe, K.; Martin, S. S.; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics—2022 Update: A Report From the American Heart Association. *Circulation* **2022**, *145* (8). <https://doi.org/10.1161/CIR.0000000000001052>.
- (9) Micha, R.; Peñalvo, J. L.; Cudhea, F.; Imamura, F.; Rehm, C. D.; Mozaffarian, D. Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States. *JAMA* **2017**, *317* (9), 912. <https://doi.org/10.1001/jama.2017.0947>.
- (10) Furchgott, R. F.; Zawadzki, J. V. The Obligatory Role of Endothelial Cells in the Relaxation of Arterial Smooth Muscle by Acetylcholine. *Nature* **1980**, *288* (5789), 373–376.
- (11) Vanhoutte, P. M.; Shimokawa, H.; Feletou, M.; Tang, E. H. Endothelial Dysfunction and Vascular Disease - a 30th Anniversary Update. *Acta Physiol.* **2017**, *219* (1), 22–96.

- (12) Herman, A. G.; Moncada, S. Therapeutic Potential of Nitric Oxide Donors in the Prevention and Treatment of Atherosclerosis. *Eur. Heart J.* **2005**, *26* (19), 1945–1955.
- (13) Vita, J. A.; Keaney, J. F. Endothelial Function: A Barometer for Cardiovascular Risk? *Circulation* **2002**, *106* (6), 640–642.
- (14) Moncada, S.; Palmer, R. M.; Higgs, E. A. Nitric Oxide: Physiology, Pathophysiology, and Pharmacology. *Pharmacol. Rev.* **1991**, *43* (2), 109–142.
- (15) Feletou, M.; Vanhoutte, P. M. EDHF: An Update. *Clin. Sci.* **2009**, *117* (4), 139–155.
<https://doi.org/10.1042/CS20090096>.
- (16) Yeboah, J.; Crouse, J. R.; Hsu, F. C.; Burke, G. L.; Herrington, D. M. Brachial Flow-Mediated Dilation Predicts Incident Cardiovascular Events in Older Adults: The Cardiovascular Health Study. *Circulation* **2007**, *115* (18), 2390–2397.
<https://doi.org/10.1161/CIRCULATIONAHA.106.678276>.
- (17) Taddei, S.; Virdis, A.; Ghiadoni, L.; Salvetti, G.; Bernini, G.; Magagna, A.; Salvetti, A. Age-Related Reduction of NO Availability and Oxidative Stress in Humans. *Hypertension* **2001**, *38* (2), 274–279.
- (18) Dal-Ros, S.; Zoll, J.; Lang, A. L.; Auger, C.; Keller, N.; Bronner, C.; Geny, B.; Schini-Kerth, V. B. Chronic Intake of Red Wine Polyphenols by Young Rats Prevents Aging-Induced Endothelial Dysfunction and Decline in Physical Performance: Role of NADPH Oxidase. *Biochem. Biophys. Res. Commun.* **2011**, *404* (2), 743–749.
- (19) Deanfield, J. E.; Halcox, J. P.; Rabelink, T. J. Endothelial Function and Dysfunction: Testing and Clinical Relevance. *Circulation* **2007**, *115* (10), 1285–1295.
<https://doi.org/10.1161/CIRCULATIONAHA.106.652859>.
- (20) Griendling, K. K.; Sorescu, D.; Ushio-Fukai, M. NAD(P)H Oxidase: Role in Cardiovascular Biology and Disease. *Circ. Res.* **2000**, *86* (5), 494–501.
- (21) Griendling, K. K.; FitzGerald, G. A. Oxidative Stress and Cardiovascular Injury: Part II: Animal and Human Studies. *Circulation* **2003**, *108* (17), 2034–2040.
<https://doi.org/10.1161/01.CIR.0000093661.90582.c4>.
- (22) Idris Khodja, N.; Chataigneau, T.; Auger, C.; Schini-Kerth, V. B. Grape-Derived Polyphenols Improve Aging-Related Endothelial Dysfunction in Rat Mesenteric Artery: Role of Oxidative Stress and the Angiotensin System. *PLoS ONE* **2012**, *7* (2), e32039.
<https://doi.org/10.1371/journal.pone.0032039>.
- (23) Lerman, A.; Zeiher, A. M. Endothelial Function: Cardiac Events. *Circulation* **2005**, *111* (3), 363–368.
- (24) Vanhoutte, P. M. Endothelial Dysfunction: The First Step toward Coronary Arteriosclerosis. *Circ J* **2009**, *73* (4), 595–601.
- (25) Minamino, T.; Miyauchi, H.; Yoshida, T.; Ishida, Y.; Yoshida, H.; Komuro, I. Endothelial Cell Senescence in Human Atherosclerosis: Role of Telomere in Endothelial Dysfunction. *Circulation* **2002**, *105* (13), 1541–1544.
- (26) Coppé, J.-P.; Desprez, P.-Y.; Krtolica, A.; Campisi, J. The Senescence-Associated Secretory Phenotype: The Dark Side of Tumor Suppression. *Annu. Rev. Pathol.* **2010**, *5*, 99–118.
<https://doi.org/10.1146/annurev-pathol-121808-102144>.
- (27) Pantsulaia, I.; Ciszewski, W. M.; Niewiarowska, J. Senescent Endothelial Cells: Potential Modulators of Immunosenescence and Ageing. *Ageing Res. Rev.* **2016**, *29*, 13–25.
<https://doi.org/10.1016/j.arr.2016.05.011>.
- (28) Hubackova, S.; Krejcikova, K.; Bartek, J.; Hodny, Z. IL1- and TGF β -Nox4 Signaling, Oxidative Stress and DNA Damage Response Are Shared Features of Replicative, Oncogene-Induced, and Drug-Induced Paracrine ‘Bystander Senescence.’ *Aging* **2012**, *4* (12), 932–951.
<https://doi.org/10.18632/aging.100520>.
- (29) Campisi, J.; Robert, L. Cell Senescence: Role in Aging and Age-Related Diseases. In *Interdisciplinary Topics in Gerontology and Geriatrics*; Robert, L., Fulop, T., Eds.; S. Karger AG, 2014; Vol. 39, pp 45–61. <https://doi.org/10.1159/000358899>.

- (30) Hayflick, L. The Limited in Vitro Lifetime of Human Diploid Cell Strains. *Exp. Cell Res.* **1965**, *37* (3), 614–636. [https://doi.org/10.1016/0014-4827\(65\)90211-9](https://doi.org/10.1016/0014-4827(65)90211-9).
- (31) Shay, J. W.; Wright, W. E. Hayflick, His Limit, and Cellular Ageing. *Nat. Rev. Mol. Cell Biol.* **2000**, *1* (1), 72–76. <https://doi.org/10.1038/35036093>.
- (32) Erusalimsky, J. D. Vascular Endothelial Senescence: From Mechanisms to Pathophysiology. *J. Appl. Physiol.* **2009**, *106* (1), 326–332. <https://doi.org/10.1152/japplphysiol.91353.2008>.
- (33) Abdelgawad, I. Y.; Agostinucci, K.; Ismail, S. G.; Grant, M. K. O.; Zordoky, B. N. EA.Hy926 Cells and HUVECs Share Similar Senescence Phenotypes but Respond Differently to the Senolytic Drug ABT-263. *Cells* **2022**, *11* (13), 1992. <https://doi.org/10.3390/cells11131992>.
- (34) D'Apolito, M.; Colia, A. L.; Lasalvia, M.; Capozzi, V.; Falcone, M. P.; Pettoello-Mantovani, M.; Brownlee, M.; Maffione, A. B.; Giardino, I. Urea-Induced ROS Accelerate Senescence in Endothelial Progenitor Cells. *Atherosclerosis* **2017**, *263*, 127–136. <https://doi.org/10.1016/j.atherosclerosis.2017.06.028>.
- (35) Silva, G. C.; Abbas, M.; Khemais-Benkhiat, S.; Burban, M.; Ribeiro, T. P.; Toti, F.; Idris-Khodja, N.; Côrtes, S. F.; Schini-Kerth, V. B. Replicative Senescence Promotes Prothrombotic Responses in Endothelial Cells: Role of NADPH Oxidase- and Cyclooxygenase-Derived Oxidative Stress. *Exp. Gerontol.* **2017**, *93*, 7–15. <https://doi.org/10.1016/j.exger.2017.04.006>.
- (36) Khemais-Benkhiat, S.; Belcastro, E.; Idris-Khodja, N.; Park, S.-H.; Amoura, L.; Abbas, M.; Auger, C.; Kessler, L.; Mayoux, E.; Toti, F.; Schini-Kerth, V. B. Angiotensin II-Induced Redox-Sensitive SGLT1 and 2 Expression Promotes High Glucose-Induced Endothelial Cell Senescence. *J. Cell. Mol. Med.* **2020**, *24* (3), 2109–2122. <https://doi.org/10.1111/jcmm.14233>.
- (37) Khemais-Benkhiat, S.; Idris-Khodja, N.; Ribeiro, T. P.; Silva, G. C.; Abbas, M.; Kheloufi, M.; Lee, J.-O.; Toti, F.; Auger, C.; Schini-Kerth, V. B. The Redox-Sensitive Induction of the Local Angiotensin System Promotes Both Premature and Replicative Endothelial Senescence: Preventive Effect of a Standardized Crataegus Extract. *J. Gerontol. A. Biol. Sci. Med. Sci.* **2016**, *71* (12), 1581–1590. <https://doi.org/10.1093/gerona/glv213>.
- (38) Park, S.-H.; Belcastro, E.; Hasan, H.; Matsushita, K.; Marchandot, B.; Abbas, M.; Toti, F.; Auger, C.; Jesel, L.; Ohlmann, P.; Morel, O.; Schini-Kerth, V. B. Angiotensin II-Induced Upregulation of SGLT1 and 2 Contributes to Human Microparticle-Stimulated Endothelial Senescence and Dysfunction: Protective Effect of Gliflozins. *Cardiovasc. Diabetol.* **2021**, *20* (1), 65. <https://doi.org/10.1186/s12933-021-01252-3>.
- (39) Park, S.-H.; Farooq, M. A.; Gaertner, S.; Bruckert, C.; Qureshi, A. W.; Lee, H.-H.; Benrahla, D.; Pollet, B.; Stephan, D.; Ohlmann, P.; Lessinger, J.-M.; Mayoux, E.; Auger, C.; Morel, O.; Schini-Kerth, V. B. Empagliflozin Improved Systolic Blood Pressure, Endothelial Dysfunction and Heart Remodeling in the Metabolic Syndrome ZSF1 Rat. *Cardiovasc. Diabetol.* **2020**, *19* (1), 19. <https://doi.org/10.1186/s12933-020-00997-7>.
- (40) Urata, R.; Ikeda, K.; Yamazaki, E.; Ueno, D.; Katayama, A.; Shin-Ya, M.; Ohgitani, E.; Mazda, O.; Matoba, S. Senescent Endothelial Cells Are Predisposed to SARS-CoV-2 Infection and Subsequent Endothelial Dysfunction. *Sci. Rep.* **2022**, *12* (1), 11855. <https://doi.org/10.1038/s41598-022-15976-z>.
- (41) Mroueh, A.; Fakih, W.; Carmona, A.; Trimaille, A.; Matsushita, K.; Marchandot, B.; Qureshi, A. W.; Gong, D.-S.; Auger, C.; Sattler, L.; Reydel, A.; Hess, S.; Oulehri, W.; Vollmer, O.; Lessinger, J.-M.; Meyer, N.; Pieper, M. P.; Jesel, L.; Bäck, M.; Schini-Kerth, V.; Morel, O. COVID-19 Promotes Endothelial Dysfunction and Thrombogenicity: Role of Proinflammatory Cytokines/SGLT2 Prooxidant Pathway. *J. Thromb. Haemost. JTH* **2023**, S1538-7836(23)00724-9. <https://doi.org/10.1016/j.jtha.2023.09.022>.
- (42) Kim, E.-C.; Kim, J.-R. Senotherapeutics: Emerging Strategy for Healthy Aging and Age-Related Disease. *BMB Rep.* **2019**, *52* (1), 47–55. <https://doi.org/10.5483/BMBRep.2019.52.1.293>.
- (43) Du, H.; Li, L.; Bennett, D.; Guo, Y.; Key, T. J.; Bian, Z.; Sherliker, P.; Gao, H.; Chen, Y.; Yang, L.; Chen, J.; Wang, S.; Du, R.; Su, H.; Collins, R.; Peto, R.; Chen, Z. Fresh Fruit Consumption and Major Cardiovascular Disease in China. *N. Engl. J. Med.* **2016**, *374* (14), 1332–1343. <https://doi.org/10.1056/NEJMoa1501451>.

- (44) Crozier, A.; Jaganath, I. B.; Clifford, M. N. Dietary Phenolics: Chemistry, Bioavailability and Effects on Health. *Nat. Prod. Rep.* **2009**, *26* (8), 1001–1043. <https://doi.org/10.1039/b802662a>.
- (45) Iqbal, I.; Wilairatana, P.; Saqib, F.; Nasir, B.; Wahid, M.; Latif, M. F.; Iqbal, A.; Naz, R.; Mubarak, M. S. Plant Polyphenols and Their Potential Benefits on Cardiovascular Health: A Review. *Molecules* **2023**, *28* (17), 6403. <https://doi.org/10.3390/molecules28176403>.
- (46) Crozier, A. Classification and Biosynthesis of Secondary Plant Products: An Overview. In *Plants: Diet and Health*; Blackwell Science Ltd, 2008; pp 27–48.
- (47) Del Rio, D.; Rodriguez-Mateos, A.; Spencer, J. P.; Tognolini, M.; Borges, G.; Crozier, A. Dietary (Poly)Phenolics in Human Health: Structures, Bioavailability, and Evidence of Protective Effects Against Chronic Diseases. *Antioxid Redox Signal* **2012**. <https://doi.org/10.1089/ars.2012.4581>.
- (48) Zaheer, K.; Humayoun Akhtar, M. An Updated Review of Dietary Isoflavones: Nutrition, Processing, Bioavailability and Impacts on Human Health. *Crit. Rev. Food Sci. Nutr.* **2017**, *57* (6), 1280–1293. <https://doi.org/10.1080/10408398.2014.989958>.
- (49) Carnauba, R. A.; Hassimotto, N. M. A.; Lajolo, F. M. Estimated Dietary Polyphenol Intake and Major Food Sources of the Brazilian Population. *Br. J. Nutr.* **2021**, *126* (3), 441–448. <https://doi.org/10.1017/S0007114520004237>.
- (50) Huang, Q.; Braffett, B. H.; Simmens, S. J.; Young, H. A.; Ogden, C. L. Dietary Polyphenol Intake in US Adults and 10-Year Trends: 2007–2016. *J. Acad. Nutr. Diet.* **2020**, *120* (11), 1821–1833. <https://doi.org/10.1016/j.jand.2020.06.016>.
- (51) Lin, X.; Zhao, J.; Ge, S.; Lu, H.; Xiong, Q.; Guo, X.; Li, L.; He, S.; Wang, J.; Peng, F.; Fan, Y.; Zuo, X.; Tian, C.; Ying, C. Dietary Polyphenol Intake and Risk of Hypertension: An 18-y Nationwide Cohort Study in China. *Am. J. Clin. Nutr.* **2023**, *118* (1), 264–272. <https://doi.org/10.1016/j.ajcnut.2023.05.001>.
- (52) Zamora-Ros, R.; Knaze, V.; Rothwell, J. A.; Hémon, B.; Moskal, A.; Overvad, K.; Tjønneland, A.; Kyrø, C.; Fagherazzi, G.; Boutron-Ruault, M.-C.; Touillaud, M.; Katzke, V.; Kühn, T.; Boeing, H.; Förster, J.; Trichopoulou, A.; Valanou, E.; Peppas, E.; Palli, D.; Agnoli, C.; Ricceri, F.; Tumino, R.; De Magistris, M. S.; Peeters, P. H. M.; Bueno-de-Mesquita, H. B.; Engeset, D.; Skeie, G.; Hjartåker, A.; Menéndez, V.; Agudo, A.; Molina-Montes, E.; Huerta, J. M.; Barricarte, A.; Amiano, P.; Sonestedt, E.; Nilsson, L. M.; Landberg, R.; Key, T. J.; Khaw, K.-T.; Wareham, N. J.; Lu, Y.; Slimani, N.; Romieu, I.; Riboli, E.; Scalbert, A. Dietary Polyphenol Intake in Europe: The European Prospective Investigation into Cancer and Nutrition (EPIC) Study. *Eur. J. Nutr.* **2016**, *55* (4), 1359–1375. <https://doi.org/10.1007/s00394-015-0950-x>.
- (53) Auger, C.; Mullen, W.; Hara, Y.; Crozier, A. Bioavailability of Polyphenon E Flavan-3-Ols in Humans with an Ileostomy. *J. Nutr.* **2008**, *138* (8), 1535S–1542S.
- (54) Chow, H. H.; Cai, Y.; Alberts, D. S.; Hakim, I.; Dorr, R.; Shahi, F.; Crowell, J. A.; Yang, C. S.; Hara, Y. Phase I Pharmacokinetic Study of Tea Polyphenols Following Single-Dose Administration of Epigallocatechin Gallate and Polyphenon E. *Cancer Epidemiol Biomark. Prev* **2001**, *10* (1), 53–58.
- (55) Stalmach, A.; Troufflard, S.; Serafini, M.; Crozier, A. Absorption, Metabolism and Excretion of Choleadi Green Tea Flavan-3-Ols by Humans. *Mol. Nutr. Food Res.* **2009**, *53 Suppl 1*, S44–53. <https://doi.org/10.1002/mnfr.200800169>.
- (56) Ishisaka, A.; Ichikawa, S.; Sakakibara, H.; Piskula, M. K.; Nakamura, T.; Kato, Y.; Ito, M.; Miyamoto, K.; Tsuji, A.; Kawai, Y.; Terao, J. Accumulation of Orally Administered Quercetin in Brain Tissue and Its Antioxidative Effects in Rats. *Free Radic Biol Med* **2011**, *51* (7), 1329–1336. <https://doi.org/10.1016/j.freeradbiomed.2011.06.017>.
- (57) Kawai, Y.; Ishisaka, A.; Saito, S.; Uchida, K.; Shibata, N.; Kobayashi, M.; Fukuchi, Y.; Naito, M.; Terao, J. Immunochemical Detection of Flavonoid Glycosides: Development, Specificity, and Application of Novel Monoclonal Antibodies. *Arch. Biochem. Biophys.* **2008**, *476* (2), 124–132. <https://doi.org/10.1016/j.abb.2008.01.022>.
- (58) Kawai, Y.; Nishikawa, T.; Shiba, Y.; Saito, S.; Murota, K.; Shibata, N.; Kobayashi, M.; Kanayama, M.; Uchida, K.; Terao, J. Macrophage as a Target of Quercetin Glucuronides in Human

- Atherosclerotic Arteries: Implication in the Anti-Atherosclerotic Mechanism of Dietary Flavonoids. *J Biol Chem* **2008**, 283 (14), 9424–9434. <https://doi.org/10.1074/jbc.M706571200>.
- (59) Kawai, Y.; Tanaka, H.; Murota, K.; Naito, M.; Terao, J. (-)-Epicatechin Gallate Accumulates in Foamy Macrophages in Human Atherosclerotic Aorta: Implication in the Anti-Atherosclerotic Actions of Tea Catechins. *Biochem. Biophys. Res. Commun.* **2008**, 374 (3), 527–532. <https://doi.org/10.1016/j.bbrc.2008.07.086>.
 - (60) Andriantsitohaina, R.; Auger, C.; Chataigneau, T.; Etienne-Selloum, N.; Li, H.; Martinez, M. C.; Schini-Kerth, V. B.; Laher, I. Molecular Mechanisms of the Cardiovascular Protective Effects of Polyphenols. *Br J Nutr* **2012**, 108 (9), 1532–1549. <https://doi.org/10.1017/S0007114512003406>.
 - (61) Auger, C.; Said, A.; Nguyen, P. N.; Chabert, P.; Idris-Khodja, N.; Schini-Kerth, V. B. Potential of Food and Natural Products to Promote Endothelial and Vascular Health: *J. Cardiovasc. Pharmacol.* **2016**, 68 (1), 11–18. <https://doi.org/10.1097/FJC.0000000000000382>.
 - (62) Auger, C.; Chataigneau, T.; Schini-Kerth, V. B. Vascular Protection by Grape-Derived Polyphenols. *Agro Food Ind. Hi-Tech* **2009**, 20 (1), 38–40.
 - (63) Oak, M.-H.; Auger, C.; Belcastro, E.; Park, S.-H.; Lee, H.-H.; Schini-Kerth, V. B. Potential Mechanisms Underlying Cardiovascular Protection by Polyphenols: Role of the Endothelium. *Free Radic. Biol. Med.* **2018**, 122, 161–170. <https://doi.org/10.1016/j.freeradbiomed.2018.03.018>.
 - (64) Fitzpatrick, D. F.; Hirschfield, S. L.; Coffey, R. G. Endothelium-Dependent Vasorelaxing Activity of Wine and Other Grape Products. *Am J Physiol* **1993**, 265 (2 Pt 2), H774–8.
 - (65) Fitzpatrick, D. F.; Hirschfield, S. L.; Ricci, T.; Jantzen, P.; Coffey, R. G. Endothelium-Dependent Vasorelaxation Caused by Various Plant Extracts. *J. Cardiovasc. Pharmacol.* **1995**, 26 (1), 90–95.
 - (66) Anselm, E.; Chataigneau, M.; Ndiaye, M.; Chataigneau, T.; Schini-Kerth, V. B. Grape Juice Causes Endothelium-Dependent Relaxation via a Redox-Sensitive Src- and Akt-Dependent Activation of eNOS. *Cardiovasc Res* **2007**, 73 (2), 404–413. [https://doi.org/S0008-6363\(06\)00356-7](https://doi.org/S0008-6363(06)00356-7) [pii] 10.1016/j.cardiores.2006.08.004.
 - (67) Ndiaye, M.; Chataigneau, T.; Andriantsitohaina, R.; Stoclet, J. C.; Schini-Kerth, V. B. Red Wine Polyphenols Cause Endothelium-Dependent EDHF-Mediated Relaxations in Porcine Coronary Arteries via a Redox-Sensitive Mechanism. *Biochem Biophys Res Commun* **2003**, 310 (2), 371–377. <https://doi.org/S0006291X03018151> [pii].
 - (68) D’Agostino, R.; Barberio, L.; Gatto, M.; Muzzalupo, I.; Mandalà, M. Extra Virgin Olive Oil Phenols Dilate the Rat Mesenteric Artery by Activation of BKCa²⁺ Channels in Smooth Muscle Cells. *Molecules* **2020**, 25 (11), 2601. <https://doi.org/10.3390/molecules25112601>.
 - (69) Auger, C.; Kim, J. H.; Chabert, P.; Chaabi, M.; Anselm, E.; Lanciaux, X.; Lobstein, A.; Schini-Kerth, V. B. The EGCg-Induced Redox-Sensitive Activation of Endothelial Nitric Oxide Synthase and Relaxation Are Critically Dependent on Hydroxyl Moieties. *Biochem. Biophys. Res. Commun.* **2010**, 393 (1), 162–167. <https://doi.org/10.1016/j.bbrc.2010.01.112>.
 - (70) Madeira, S. V.; Auger, C.; Anselm, E.; Chataigneau, M.; Chataigneau, T.; Soares de Moura, R.; Schini-Kerth, V. B. eNOS Activation Induced by a Polyphenol-Rich Grape Skin Extract in Porcine Coronary Arteries. *J Vasc Res* **2009**, 46 (5), 406–416. <https://doi.org/000194271> [pii] 10.1159/000194271.
 - (71) Ndiaye, M.; Chataigneau, M.; Lobysheva, I.; Chataigneau, T.; Schini-Kerth, V. B. Red Wine Polyphenol-Induced, Endothelium-Dependent NO-Mediated Relaxation Is Due to the Redox-Sensitive PI3-Kinase/Akt-Dependent Phosphorylation of Endothelial NO-Synthase in the Isolated Porcine Coronary Artery. *FASEB J* **2005**, 19 (3), 455–457. <https://doi.org/04-2146fje> [pii] 10.1096/fj.04-2146fje.
 - (72) Alhosin, M.; Anselm, E.; Rashid, S.; Kim, J. H.; Frota Madeira, S. V.; Bronner, C.; Schini-Kerth, V. B. Redox-Sensitive Up-Regulation of eNOS by Purple Grape Juice in Endothelial Cells: Role of PI3-Kinase/Akt, P38 MAPK, JNK, FoxO1 and FoxO3a. *PLoS ONE* **2013**, 8 (3), e57883. <https://doi.org/10.1371/journal.pone.0057883>.

- (73) Auger, C.; Chaabi, M.; Anselm, E.; Lobstein, A.; Schini-Kerth, V. B. The Red Wine Extract-Induced Activation of Endothelial Nitric Oxide Synthase Is Mediated by a Great Variety of Polyphenolic Compounds. *Mol. Nutr. Food Res.* **2010**, *54 Suppl 2*, S171–83. <https://doi.org/10.1002/mnfr.200900602>.
- (74) Kim, J. A.; Formoso, G.; Li, Y.; Potenza, M. A.; Marasciulo, F. L.; Montagnani, M.; Quon, M. J. Epigallocatechin Gallate, a Green Tea Polyphenol, Mediates NO-Dependent Vasodilation Using Signaling Pathways in Vascular Endothelium Requiring Reactive Oxygen Species and Fyn. *J Biol Chem* **2007**, *282* (18), 13736–13745. <https://doi.org/10.1074/jbc.M609725200>.
- (75) Kim, J. H.; Auger, C.; Kurita, I.; Anselm, E.; Rivoarilala, L. O.; Lee, H. J.; Lee, K. W.; Schini-Kerth, V. B. Aronia Melanocarpa Juice, a Rich Source of Polyphenols, Induces Endothelium-Dependent Relaxations in Porcine Coronary Arteries via the Redox-Sensitive Activation of Endothelial Nitric Oxide Synthase. *Nitric Oxide* **2013**, *35*, 54–64. <https://doi.org/10.1016/j.niox.2013.08.002>.
- (76) Chalopin, M.; Tesse, A.; Martinez, M. C.; Rognan, D.; Arnal, J. F.; Andriantsitohaina, R. Estrogen Receptor Alpha as a Key Target of Red Wine Polyphenols Action on the Endothelium. *PLoS ONE* **2010**, *5* (1), e8554. <https://doi.org/10.1371/journal.pone.0008554>.
- (77) Kane, M. O.; Anselm, E.; Rattmann, Y. D.; Auger, C.; Schini-Kerth, V. B. Role of Gender and Estrogen Receptors in the Rat Aorta Endothelium-Dependent Relaxation to Red Wine Polyphenols. *Vascul. Pharmacol.* **2009**, *51* (2–3), 140–146. <https://doi.org/10.1016/j.vph.2009.05.002>.
- (78) Leonetti, D.; Soleti, R.; Clere, N.; Vergori, L.; Jacques, C.; Duluc, L.; Dourguia, C.; Martínez, M. C.; Andriantsitohaina, R. Estrogen Receptor α Participates to the Beneficial Effect of Red Wine Polyphenols in a Mouse Model of Obesity-Related Disorders. *Front. Pharmacol.* **2017**, *7*. <https://doi.org/10.3389/fphar.2016.00529>.
- (79) Cui, X.; Liu, X.; Feng, H.; Zhao, S.; Gao, H. Grape Seed Proanthocyanidin Extracts Enhance Endothelial Nitric Oxide Synthase Expression through 5'-AMP Activated Protein Kinase/Sirtuin 1-Kruppel like Factor 2 Pathway and Modulate Blood Pressure in Ouabain Induced Hypertensive Rats. *Biol. Pharm. Bull.* **2012**, *35* (12), 2192–2197.
- (80) Kane, M. O.; Sene, M.; Anselm, E.; Dal, S.; Schini-Kerth, V. B.; Augier, C. Role of AMP-Activated Protein Kinase in NO- and EDHF-Mediated Endothelium-Dependent Relaxations to Red Wine Polyphenols. *Indian J. Physiol. Pharmacol.* **2015**, *59* (4), 369–379.
- (81) Martin, S.; Andriambeloson, E.; Takeda, K.; Andriantsitohaina, R. Red Wine Polyphenols Increase Calcium in Bovine Aortic Endothelial Cells: A Basis to Elucidate Signalling Pathways Leading to Nitric Oxide Production. *Br. J. Pharmacol.* **2002**, *135* (6), 1579–1587. <https://doi.org/10.1038/sj.bjp.0704603>.
- (82) Auger, C.; Pollet, B.; Arnold, C.; Marx, C.; Schini-Kerth, V. B. Great Heterogeneity of Commercial Fruit Juices to Induce Endothelium-Dependent Relaxations in Isolated Porcine Coronary Arteries: Role of the Phenolic Content and Composition. *J. Med. Food* **2015**, *18* (1), 128–136.
- (83) Matute, A.; Tabart, J.; Cheramy-Bien, J.-P.; Pirotte, B.; Kevers, C.; Auger, C.; Schini-Kerth, V.; Dommes, J.; Defraigne, J.-O.; Pincemail, J. Compared Phenolic Compound Contents of 22 Commercial Fruit and Vegetable Juices: Relationship to Ex-Vivo Vascular Reactivity and Potential in Vivo Projection. *Antioxid. Basel Switz.* **2020**, *9* (2), E92. <https://doi.org/10.3390/antiox9020092>.
- (84) Auger, C.; Kim, J. H.; Trinh, S.; Chataigneau, T.; Popken, A. M.; Schini-Kerth, V. B. Fruit Juice-Induced Endothelium-Dependent Relaxations in Isolated Porcine Coronary Arteries: Evaluation of Different Fruit Juices and Purees and Optimization of a Red Fruit Juice Blend. *Food Funct.* **2011**, *2* (5), 245–250. <https://doi.org/10.1039/c1fo10040h>.
- (85) Franceschelli, S.; De Cecco, F.; Pesce, M.; Ripari, P.; Guagnano, M. T.; Nuevo, A. B.; Grilli, A.; Sancilio, S.; Speranza, L. Hydroxytyrosol Reduces Foam Cell Formation and Endothelial Inflammation Regulating the PPAR γ /LXR α /ABCA1 Pathway. *Int. J. Mol. Sci.* **2023**, *24* (3), 2057. <https://doi.org/10.3390/ijms24032057>.

- (86) Joo, H.; Choi, S.; Lee, Y.; Lee, E.; Park, M.; Park, K.; Kim, C.-S.; Lim, Y.; Park, J.-T.; Jeon, B. Anthocyanin-Rich Extract from Red Chinese Cabbage Alleviates Vascular Inflammation in Endothelial Cells and Apo E^{-/-} Mice. *Int. J. Mol. Sci.* **2018**, *19* (3), 816. <https://doi.org/10.3390/ijms19030816>.
- (87) Wang, D.; Hou, J.; Wan, J.; Yang, Y.; Liu, S.; Li, X.; Li, W.; Dai, X.; Zhou, P.; Liu, W.; Wang, P. Dietary Chlorogenic Acid Ameliorates Oxidative Stress and Improves Endothelial Function in Diabetic Mice via Nrf2 Activation. *J. Int. Med. Res.* **2021**, *49* (1), 030006052098536. <https://doi.org/10.1177/0300060520985363>.
- (88) Zhu, Y.; Tchkonina, T.; Pirtskhalava, T.; Gower, A. C.; Ding, H.; Giorgadze, N.; Palmer, A. K.; Ikeno, Y.; Hubbard, G. B.; Lenburg, M.; O'Hara, S. P.; LaRusso, N. F.; Miller, J. D.; Roos, C. M.; Verzosa, G. C.; LeBrasseur, N. K.; Wren, J. D.; Farr, J. N.; Khosla, S.; Stout, M. B.; McGowan, S. J.; Fuhrmann-Stroissnigg, H.; Gurkar, A. U.; Zhao, J.; Colangelo, D.; Dorronsoro, A.; Ling, Y. Y.; Barghouthy, A. S.; Navarro, D. C.; Sano, T.; Robbins, P. D.; Niedernhofer, L. J.; Kirkland, J. L. The Achilles' Heel of Senescent Cells: From Transcriptome to Senolytic Drugs. *Aging Cell* **2015**, *14* (4), 644–658. <https://doi.org/10.1111/acer.12344>.
- (89) Li, W.; Qin, L.; Feng, R.; Hu, G.; Sun, H.; He, Y.; Zhang, R. Emerging Senolytic Agents Derived from Natural Products. *Mech. Ageing Dev.* **2019**, *181*, 1–6. <https://doi.org/10.1016/j.mad.2019.05.001>.
- (90) Sun, Y.; Hu, X.; Hu, G.; Xu, C.; Jiang, H. Curcumin Attenuates Hydrogen Peroxide-Induced Premature Senescence via the Activation of SIRT1 in Human Umbilical Vein Endothelial Cells. *Biol. Pharm. Bull.* **2015**, *38* (8), 1134–1141. <https://doi.org/10.1248/bpb.b15-00012>.
- (91) Zhang, E.; Guo, Q.; Gao, H.; Xu, R.; Teng, S.; Wu, Y. Metformin and Resveratrol Inhibited High Glucose-Induced Metabolic Memory of Endothelial Senescence through SIRT1/P300/P53/P21 Pathway. *PLOS ONE* **2015**, *10* (12), e0143814. <https://doi.org/10.1371/journal.pone.0143814>.
- (92) Shen, X.; Wang, M.; Bi, X.; Zhang, J.; Wen, S.; Fu, G.; Xia, L. Resveratrol Prevents Endothelial Progenitor Cells from Senescence and Reduces the Oxidative Reaction via PPAR- γ /HO-1 Pathways. *Mol. Med. Rep.* **2016**, *14* (6), 5528–5534. <https://doi.org/10.3892/mmr.2016.5929>.
- (93) Zhang, L.; Zheng, J.; Tie, X.; Lin, T.; Yang, W.; Li, Z.; Zou, Y.; Guan, G.; Liu, P.; Luo, W.; Li, Z. Pterostilbene and Its Nicotinate Derivative Ameliorated Vascular Endothelial Senescence and Elicited Endothelium-Dependent Relaxations via Activation of Sirtuin 1. *Can. J. Physiol. Pharmacol.* **2021**, *99* (9), 900–909. <https://doi.org/10.1139/cjpp-2020-0583>.
- (94) Alves-Santos, A. M.; Sugizaki, C. S. A.; Lima, G. C.; Naves, M. M. V. Prebiotic Effect of Dietary Polyphenols: A Systematic Review. *J. Funct. Foods* **2020**, *74*, 104169. <https://doi.org/10.1016/j.jff.2020.104169>.
- (95) Reagan-Shaw, S.; Nihal, M.; Ahmad, N. Dose Translation from Animal to Human Studies Revisited. *FASEB J* **2008**, *22* (3), 659–661. <https://doi.org/10.1096/fj.07-9574LSF>.
- (96) Bleakley, C.; Hamilton, P. K.; Pumb, R.; Harbinson, M.; McVeigh, G. E. Endothelial Function in Hypertension: Victim or Culprit? *J Clin Hypertens Greenwich* **2015**, *17* (8), 651–654.
- (97) Chan, S.-L.; Capdeville-Atkinson, C.; Atkinson, J. Red Wine Polyphenols Improve Endothelium-Dependent Dilation in Rat Cerebral Arterioles. *J. Cardiovasc. Pharmacol.* **2008**, *51* (6), 553–558. <https://doi.org/10.1097/FJC.0b013e3181760fa5>.
- (98) Chan, S. L.; Tabellion, A.; Bagrel, D.; Perrin-Sarrado, C.; Capdeville-Atkinson, C.; Atkinson, J. Impact of Chronic Treatment with Red Wine Polyphenols (RWP) on Cerebral Arterioles in the Spontaneous Hypertensive Rat. *J. Cardiovasc. Pharmacol.* **2008**, *51* (3), 304–310. <https://doi.org/10.1097/FJC.0b013e318163a946>.
- (99) Lopez-Sepulveda, R.; Jimenez, R.; Romero, M.; Zarzuelo, M. J.; Sanchez, M.; Gomez-Guzman, M.; Vargas, F.; O'Valle, F.; Zarzuelo, A.; Perez-Vizcaino, F.; Duarte, J. Wine Polyphenols Improve Endothelial Function in Large Vessels of Female Spontaneously Hypertensive Rats. *Hypertension* **2008**, *51* (4), 1088–1095. <https://doi.org/10.1161/HYPERTENSIONAHA.107.107672>.

- (100) Mizutani, K.; Ikeda, K.; Kawai, Y.; Yamori, Y. Extract of Wine Phenolics Improves Aortic Biomechanical Properties in Stroke-Prone Spontaneously Hypertensive Rats (SHRSP). *J. Nutr. Sci. Vitaminol. (Tokyo)* **1999**, *45* (1), 95–106.
- (101) Bernatova, I.; Pechanova, O.; Babal, P.; Kysela, S.; Stvrtina, S.; Andriantsitohaina, R. Wine Polyphenols Improve Cardiovascular Remodeling and Vascular Function in NO-Deficient Hypertension. *Am. J. Physiol. Heart Circ. Physiol.* **2002**, *282* (3), H942-8. <https://doi.org/10.1152/ajpheart.00724.2001>.
- (102) de Moura, R. S.; Miranda, D. Z.; Pinto, A. C.; Sicca, R. F.; Souza, M. A.; Rubenich, L. M.; Carvalho, L. C.; Rangel, B. M.; Tano, T.; Madeira, S. V.; Resende, A. C. Mechanism of the Endothelium-Dependent Vasodilation and the Antihypertensive Effect of Brazilian Red Wine. *J. Cardiovasc. Pharmacol.* **2004**, *44* (3), 302–309.
- (103) Jimenez, R.; Lopez-Sepulveda, R.; Kadmiri, M.; Romero, M.; Vera, R.; Sanchez, M.; Vargas, F.; O'Valle, F.; Zarzuelo, A.; Duenas, M.; Santos-Buelga, C.; Duarte, J. Polyphenols Restore Endothelial Function in DOCA-Salt Hypertension: Role of Endothelin-1 and NADPH Oxidase. *Free Radic Biol Med* **2007**, *43* (3), 462–473. <https://doi.org/10.1016/j.freeradbiomed.2007.05.007>.
- (104) Pechanova, O.; Bernatova, I.; Babal, P.; Martinez, M. C.; Kysela, S.; Stvrtina, S.; Andriantsitohaina, R. Red Wine Polyphenols Prevent Cardiovascular Alterations in L-NAME-Induced Hypertension. *J. Hypertens.* **2004**, *22* (8), 1551–1559.
- (105) Sarr, M.; Chataigneau, M.; Martins, S.; Schott, C.; El Bedoui, J.; Oak, M. H.; Muller, B.; Chataigneau, T.; Schini-Kerth, V. B. Red Wine Polyphenols Prevent Angiotensin II-Induced Hypertension and Endothelial Dysfunction in Rats: Role of NADPH Oxidase. *Cardiovasc. Res.* **2006**, *71* (4), 794–802. <https://doi.org/10.1016/j.cardiores.2006.05.022>.
- (106) Liang, Y.; Wang, J.; Gao, H.; Wang, Q.; Zhang, J.; Qiu, J. Beneficial Effects of Grape Seed Proanthocyanidin Extract on Arterial Remodeling in Spontaneously Hypertensive Rats via Protecting against Oxidative Stress. *Mol. Med. Rep.* **2016**, *14* (4), 3711–3718. <https://doi.org/10.3892/mmr.2016.5699>.
- (107) Peng, N.; Clark, J. T.; Prasain, J.; Kim, H.; White, C. R.; Wyss, J. M. Antihypertensive and Cognitive Effects of Grape Polyphenols in Estrogen-Depleted, Female, Spontaneously Hypertensive Rats. *Am J Physiol Regul Integr Comp Physiol* **2005**, *289* (3), R771-5. <https://doi.org/10.1152/ajpregu.00147.2005>.
- (108) Patil, P. D.; Melo, A. C.; Westwood, B. M.; Tallant, E. A.; Gallagher, P. E. A Polyphenol-Rich Extract from Muscadine Grapes Prevents Hypertension-Induced Diastolic Dysfunction and Oxidative Stress. *Antioxidants* **2022**, *11* (10), 2026. <https://doi.org/10.3390/antiox11102026>.
- (109) Mas-Capdevila, A.; Iglesias-Carres, L.; Arola-Arnal, A.; Suárez, M.; Bravo, F. I.; Muguerza, B. Changes in Arterial Blood Pressure Caused by Long-Term Administration of Grape Seed Proanthocyanidins in Rats with Established Hypertension. *Food Funct.* **2020**, *11* (10), 8735–8742. <https://doi.org/10.1039/D0FO00981D>.
- (110) Pons, Z.; Margalef, M.; Bravo, F. I.; Arola-Arnal, A.; Muguerza, B. Chronic Administration of Grape-Seed Polyphenols Attenuates the Development of Hypertension and Improves Other Cardiometabolic Risk Factors Associated with the Metabolic Syndrome in Cafeteria Diet-Fed Rats. *Br. J. Nutr.* **2017**, *117* (2), 200–208. <https://doi.org/10.1017/S0007114516004426>.
- (111) Rasines-Perea, Z.; Ky, I.; Cros, G.; Crozier, A.; Teissedre, P.-L. Grape Pomace: Antioxidant Activity, Potential Effect Against Hypertension and Metabolites Characterization after Intake. *Diseases* **2018**, *6* (3), 60. <https://doi.org/10.3390/diseases6030060>.
- (112) Al-Awwadi, N. A.; Araiz, C.; Bornet, A.; Delbosc, S.; Cristol, J. P.; Linck, N.; Azay, J.; Teissedre, P. L.; Cros, G. Extracts Enriched in Different Polyphenolic Families Normalize Increased Cardiac NADPH Oxidase Expression While Having Differential Effects on Insulin Resistance, Hypertension, and Cardiac Hypertrophy in High-Fructose-Fed Rats. *J. Agric. Food Chem.* **2005**, *53* (1), 151–157. <https://doi.org/10.1021/jf048919f>.

- (113) Negishi, H.; Xu, J. W.; Ikeda, K.; Njelekela, M.; Nara, Y.; Yamori, Y. Black and Green Tea Polyphenols Attenuate Blood Pressure Increases in Stroke-Prone Spontaneously Hypertensive Rats. *J. Nutr.* **2004**, *134* (1), 38–42.
- (114) de Nigris, F.; Balestrieri, M. L.; Williams-Ignarro, S.; D'Armiento, F. P.; Fiorito, C.; Ignarro, L. J.; Napoli, C. The Influence of Pomegranate Fruit Extract in Comparison to Regular Pomegranate Juice and Seed Oil on Nitric Oxide and Arterial Function in Obese Zucker Rats. *Nitric Oxide* **2007**, *17* (1), 50–54. <https://doi.org/10.1016/j.niox.2007.04.005>.
- (115) Maher, M. A.; Mataczynski, H.; Stefaniak, H. M.; Wilson, T. Cranberry Juice Induces Nitric Oxide-Dependent Vasodilation in Vitro and Its Infusion Transiently Reduces Blood Pressure in Anesthetized Rats. *J. Med. Food* **2000**, *3* (3), 141–147.
- (116) Cienfuegos-Jovellanos, E.; Quinones Mdel, M.; Muguerza, B.; Moulay, L.; Miguel, M.; Aleixandre, A. Antihypertensive Effect of a Polyphenol-Rich Cocoa Powder Industrially Processed to Preserve the Original Flavonoids of the Cocoa Beans. *J. Agric. Food Chem.* **2009**, *57* (14), 6156–6162. <https://doi.org/10.1021/jf804045b>.
- (117) Preuss, H. G.; Echard, B.; Polansky, M. M.; Anderson, R. Whole Cinnamon and Aqueous Extracts Ameliorate Sucrose-Induced Blood Pressure Elevations in Spontaneously Hypertensive Rats. *J. Am. Coll. Nutr.* **2006**, *25* (2), 144–150.
- (118) Shaughnessy, K. S.; Boswall, I. A.; Scanlan, A. P.; Gottschall-Pass, K. T.; Sweeney, M. I. Diets Containing Blueberry Extract Lower Blood Pressure in Spontaneously Hypertensive Stroke-Prone Rats. *Nutr. Res.* **2009**, *29* (2), 130–138. <https://doi.org/10.1016/j.nutres.2009.01.001>.
- (119) Nyadjeu, P.; Nguelefack-Mbuyo, E. P.; Atsamo, A. D.; Nguelefack, T. B.; Dongmo, A. B.; Kamanyi, A. Acute and Chronic Antihypertensive Effects of Cinnamomum Zeylanicum Stem Bark Methanol Extract in L-NAME-Induced Hypertensive Rats. *BMC Complement. Altern. Med.* **2013**, *13*, 27.
- (120) Galleano, M.; Bernatova, I.; Puzserova, A.; Balis, P.; Sestakova, N.; Pechanova, O.; Fraga, C. G. (-)-Epicatechin Reduces Blood Pressure and Improves Vasorelaxation in Spontaneously Hypertensive Rats by NO-Mediated Mechanism. *IUBMB Life* **2013**, *65* (8), 710–715.
- (121) Gomez-Guzman, M.; Jimenez, R.; Sanchez, M.; Zarzuelo, M. J.; Galindo, P.; Quintela, A. M.; Lopez-Sepulveda, R.; Romero, M.; Tamargo, J.; Vargas, F.; Perez-Vizcaino, F.; Duarte, J. Epicatechin Lowers Blood Pressure, Restores Endothelial Function, and Decreases Oxidative Stress and Endothelin-1 and NADPH Oxidase Activity in DOCA-Salt Hypertension. *Free Radic Biol Med* **2012**, *52* (1), 70–79. <https://doi.org/10.1016/j.freeradbiomed.2011.09.015>.
- (122) Duarte, J.; Jimenez, R.; O'Valle, F.; Galisteo, M.; Perez-Palencia, R.; Vargas, F.; Perez-Vizcaino, F.; Zarzuelo, A.; Tamargo, J. Protective Effects of the Flavonoid Quercetin in Chronic Nitric Oxide Deficient Rats. *J. Hypertens.* **2002**, *20* (9), 1843–1854.
- (123) Duarte, J.; Perez-Palencia, R.; Vargas, F.; Ocete, M. A.; Perez-Vizcaino, F.; Zarzuelo, A.; Tamargo, J. Antihypertensive Effects of the Flavonoid Quercetin in Spontaneously Hypertensive Rats. *Br. J. Pharmacol.* **2001**, *133* (1), 117–124. <https://doi.org/10.1038/sj.bjp.0704064>.
- (124) Galisteo, M.; Garcia-Saura, M. F.; Jimenez, R.; Villar, I. C.; Wangenstein, R.; Zarzuelo, A.; Vargas, F.; Duarte, J. Effects of Quercetin Treatment on Vascular Function in Deoxycorticosterone Acetate-Salt Hypertensive Rats. Comparative Study with Verapamil. *Planta Med.* **2004**, *70* (4), 334–341. <https://doi.org/10.1055/s-2004-818945>.
- (125) Garcia-Saura, M. F.; Galisteo, M.; Villar, I. C.; Bermejo, A.; Zarzuelo, A.; Vargas, F.; Duarte, J. Effects of Chronic Quercetin Treatment in Experimental Renovascular Hypertension. *Mol. Cell. Biochem.* **2005**, *270* (1–2), 147–155.
- (126) Machha, A.; Mustafa, M. R. Chronic Treatment with Flavonoids Prevents Endothelial Dysfunction in Spontaneously Hypertensive Rat Aorta. *J. Cardiovasc. Pharmacol.* **2005**, *46* (1), 36–40.
- (127) Sanchez, M.; Galisteo, M.; Vera, R.; Villar, I. C.; Zarzuelo, A.; Tamargo, J.; Perez-Vizcaino, F.; Duarte, J. Quercetin Downregulates NADPH Oxidase, Increases eNOS Activity and Prevents

- Endothelial Dysfunction in Spontaneously Hypertensive Rats. *J. Hypertens.* **2006**, *24* (1), 75–84.
- (128) Suzuki, A.; Yamamoto, N.; Jokura, H.; Yamamoto, M.; Fujii, A.; Tokimitsu, I.; Saito, I. Chlorogenic Acid Attenuates Hypertension and Improves Endothelial Function in Spontaneously Hypertensive Rats. *J. Hypertens.* **2006**, *24* (6), 1065–1073. <https://doi.org/10.1097/01.hjh.0000226196.67052.c0>.
- (129) Potenza, M. A.; Marasciulo, F. L.; Tarquinio, M.; Tiravanti, E.; Colantuono, G.; Federici, A.; Kim, J. A.; Quon, M. J.; Montagnani, M. EGCG, a Green Tea Polyphenol, Improves Endothelial Function and Insulin Sensitivity, Reduces Blood Pressure, and Protects against Myocardial I/R Injury in SHR. *Am J Physiol Endocrinol Metab* **2007**, *292* (5), E1378–87. <https://doi.org/10.1152/ajpendo.00698.2006>.
- (130) Vera, R.; Galisteo, M.; Villar, I. C.; Sanchez, M.; Zarzuelo, A.; Perez-Vizcaino, F.; Duarte, J. Soy Isoflavones Improve Endothelial Function in Spontaneously Hypertensive Rats in an Estrogen-Independent Manner: Role of Nitric-Oxide Synthase, Superoxide, and Cyclooxygenase Metabolites. *J Pharmacol Exp Ther* **2005**, *314* (3), 1300–1309. <https://doi.org/10.1124/jpet.105.085530>.
- (131) Rivera, L.; Moron, R.; Zarzuelo, A.; Galisteo, M. Long-Term Resveratrol Administration Reduces Metabolic Disturbances and Lowers Blood Pressure in Obese Zucker Rats. *Biochem. Pharmacol.* **2009**, *77* (6), 1053–1063. <https://doi.org/10.1016/j.bcp.2008.11.027>.
- (132) Dal-Ros, S.; Bronner, C.; Auger, C.; Schini-Kerth, V. B. Red Wine Polyphenols Improve an Established Aging-Related Endothelial Dysfunction in the Mesenteric Artery of Middle-Aged Rats: Role of Oxidative Stress. *Biochem. Biophys. Res. Commun.* **2012**, *419* (2), 381–387. <https://doi.org/10.1016/j.bbrc.2012.02.031>.
- (133) Baluchnejadmojarad, T.; Roghani, M. Chronic Administration of Genistein Improves Aortic Reactivity of Streptozotocin-Diabetic Rats: Mode of Action. *Vascul. Pharmacol.* **2008**, *49* (1), 1–5.
- (134) Roghani, M.; Baluchnejadmojarad, T. Mechanisms Underlying Vascular Effect of Chronic Resveratrol in Streptozotocin-Diabetic Rats. *Phytother Res* **2010**, *24* Suppl 2, S148–54. <https://doi.org/10.1002/ptr.3032>.
- (135) Roghani, M.; Baluchnejadmojarad, T. Chronic Epigallocatechin-Gallate Improves Aortic Reactivity of Diabetic Rats: Underlying Mechanisms. *Vascul. Pharmacol.* **2009**, *51* (2–3), 84–89. <https://doi.org/10.1016/j.vph.2009.04.003>.
- (136) Tropea, T.; Greenwood, S. L.; Sibley, C. P.; Cottrell, E. C. Grape Seed Extract Polyphenols Improve Resistance Artery Function in Pregnant eNOS^{−/−} Mice. *Front. Physiol.* **2020**, *11*, 588000. <https://doi.org/10.3389/fphys.2020.588000>.
- (137) Kane, M. O.; Etienne-Selloum, N.; Madeira, S. V.; Sarr, M.; Walter, A.; Dal-Ros, S.; Schott, C.; Chataigneau, T.; Schini-Kerth, V. B. Endothelium-Derived Contracting Factors Mediate the Ang II-Induced Endothelial Dysfunction in the Rat Aorta: Preventive Effect of Red Wine Polyphenols. *Pflugers Arch* **2010**, *459* (5), 671–679. <https://doi.org/10.1007/s00424-009-0759-7>.
- (138) Mladenka, P.; Zatloukalova, L.; Filipisky, T.; Hrdina, R. Cardiovascular Effects of Flavonoids Are Not Caused Only by Direct Antioxidant Activity. *Free Radic Biol Med* **2010**, *49* (6), 963–975. <https://doi.org/10.1016/j.freeradbiomed.2010.06.010>.
- (139) Dauchet, L.; Kesse-Guyot, E.; Czernichow, S.; Bertrais, S.; Estaquio, C.; Peneau, S.; Vergnaud, A. C.; Chat-Yung, S.; Castetbon, K.; Deschamps, V.; Brindel, P.; Hercberg, S. Dietary Patterns and Blood Pressure Change over 5-y Follow-up in the SU.VI.MAX Cohort. *Am. J. Clin. Nutr.* **2007**, *85* (6), 1650–1656.
- (140) Dauchet, L.; Amouyel, P.; Hercberg, S.; Dallongeville, J. Fruit and Vegetable Consumption and Risk of Coronary Heart Disease: A Meta-Analysis of Cohort Studies. *J. Nutr.* **2006**, *136* (10), 2588–2593.
- (141) Dauchet, L.; Amouyel, P.; Dallongeville, J. Fruit and Vegetable Consumption and Risk of Stroke: A Meta-Analysis of Cohort Studies. *Neurology* **2005**, *65* (8), 1193–1197.


- (142) He, F. J.; Nowson, C. A.; Lucas, M.; MacGregor, G. A. Increased Consumption of Fruit and Vegetables Is Related to a Reduced Risk of Coronary Heart Disease: Meta-Analysis of Cohort Studies. *J. Hum. Hypertens.* **2007**, *21* (9), 717–728.
- (143) He, F. J.; Nowson, C. A.; MacGregor, G. A. Fruit and Vegetable Consumption and Stroke: Meta-Analysis of Cohort Studies. *Lancet* **2006**, *367* (9507), 320–326. [https://doi.org/10.1016/S0140-6736\(06\)68069-0](https://doi.org/10.1016/S0140-6736(06)68069-0).
- (144) Oude Griep, L. M.; Geleijnse, J. M.; Kromhout, D.; Ocké, M. C.; Verschuren, W. M. M. Raw and Processed Fruit and Vegetable Consumption and 10-Year Coronary Heart Disease Incidence in a Population-Based Cohort Study in the Netherlands. *PLoS ONE* **2010**, *5* (10), e13609.
- (145) Rienks, J.; Barbaresko, J.; Nöthlings, U. Association of Polyphenol Biomarkers with Cardiovascular Disease and Mortality Risk: A Systematic Review and Meta-Analysis of Observational Studies. *Nutrients* **2017**, *9* (4), 415. <https://doi.org/10.3390/nu9040415>.
- (146) Sofi, F.; Macchi, C.; Abbate, R.; Gensini, G. F.; Casini, A. Mediterranean Diet and Health Status: An Updated Meta-Analysis and a Proposal for a Literature-Based Adherence Score. *Public Health Nutr.* **2014**, *17* (12), 2769–2782. <https://doi.org/10.1017/S1368980013003169>.
- (147) Sofi, F.; Cesari, F.; Abbate, R.; Gensini, G. F.; Casini, A. Adherence to Mediterranean Diet and Health Status: Meta-Analysis. *BMJ* **2008**, *337*, a1344. <https://doi.org/10.1136/bmj.a1344>.
- (148) Yang, Y.; Dong, J.-Y.; Cui, R.; Muraki, I.; Yamagishi, K.; Sawada, N.; Iso, H.; Tsugane, S.; for the Japan Public Health Center-based Prospective Study Group. Consumption of Flavonoid-Rich Fruits and Risk of CHD: A Prospective Cohort Study. *Br. J. Nutr.* **2020**, *124* (9), 952–959. <https://doi.org/10.1017/S0007114520001993>.
- (149) Zhao, Y.; Li, D.; Huang, T. Associations of Dietary Flavonoids and Subclasses with Total and Cardiovascular Mortality among 369,827 Older People: The NIH-AARP Diet and Health Study. *Atherosclerosis* **2023**, *365*, 1–8. <https://doi.org/10.1016/j.atherosclerosis.2022.12.006>.
- (150) Chiva-Blanch, G.; Arranz, S.; Lamuela-Raventos, R. M.; Estruch, R. Effects of Wine, Alcohol and Polyphenols on Cardiovascular Disease Risk Factors: Evidences from Human Studies. *Alcohol Alcohol* **2013**, *48* (3), 270–277. <https://doi.org/10.1093/alcalc/agt007>.
- (151) Zhao, B.; Gan, L.; Yu, K.; Männistö, S.; Huang, J.; Albanes, D. Relationship between Chocolate Consumption and Overall and Cause-Specific Mortality, Systematic Review and Updated Meta-Analysis. *Eur. J. Epidemiol.* **2022**, *37* (4), 321–333. <https://doi.org/10.1007/s10654-022-00858-5>.
- (152) Stensvold, I.; Tverdal, A.; Solvoll, K.; Foss, O. P. Tea Consumption. Relationship to Cholesterol, Blood Pressure, and Coronary and Total Mortality. *Prev. Med.* **1992**, *21* (4), 546–553.
- (153) Di Castelnuovo, A.; Di Giuseppe, R.; Iacoviello, L.; De Gaetano, G. Consumption of Cocoa, Tea and Coffee and Risk of Cardiovascular Disease. *Eur. J. Intern. Med.* **2012**, *23* (1), 15–25. <https://doi.org/10.1016/j.ejim.2011.07.014>.
- (154) Renaud, S.; de Lorgeril, M. Wine, Alcohol, Platelets, and the French Paradox for Coronary Heart Disease. *Lancet* **1992**, *339* (8808), 1523–1526.
- (155) Chiva-Blanch, G.; Urpi-Sarda, M.; Ros, E.; Arranz, S.; Valderas-Martinez, P.; Casas, R.; Sacanella, E.; Llorach, R.; Lamuela-Raventos, R. M.; Andres-Lacueva, C.; Estruch, R. Dealcoholized Red Wine Decreases Systolic and Diastolic Blood Pressure and Increases Plasma Nitric Oxide: Short Communication. *Circ. Res.* **2012**, *111* (8), 1065–1068. <https://doi.org/10.1161/CIRCRESAHA.112.275636>.
- (156) Droste, D. W.; Iliescu, C.; Vaillant, M.; Gantenbein, M.; De Bremaeker, N.; Lieunard, C.; Velez, T.; Meyer, M.; Guth, T.; Kuemmerle, A.; Chioti, A. A Daily Glass of Red Wine and Lifestyle Changes Do Not Affect Arterial Blood Pressure and Heart Rate in Patients with Carotid Arteriosclerosis after 4 and 20 Weeks. *Cerebrovasc Extra* **2013**, *3* (1), 121–129.
- (157) Agewall, S.; Wright, S.; Doughty, R. N.; Whalley, G. A.; Duxbury, M.; Sharpe, N. Does a Glass of Red Wine Improve Endothelial Function? *Eur. Heart J.* **2000**, *21* (1), 74–78.
- (158) Boban, M.; Modun, D.; Music, I.; Vukovic, J.; Brizic, I.; Salamunic, I.; Obad, A.; Palada, I.; Dujic, Z. Red Wine Induced Modulation of Vascular Function: Separating the Role of Polyphenols,

- Ethanol, and Urates. *J. Cardiovasc. Pharmacol.* **2006**, *47* (5), 695–701.
<https://doi.org/10.1097/01.fjc.0000211762.06271.ce>.
- (159) Hashimoto, M.; Kim, S.; Eto, M.; Iijima, K.; Ako, J.; Yoshizumi, M.; Akishita, M.; Kondo, K.; Itakura, H.; Hosoda, K.; Toba, K.; Ouchi, Y. Effect of Acute Intake of Red Wine on Flow-Mediated Vasodilatation of the Brachial Artery. *Am J Cardiol* **2001**, *88* (12), 1457–1460, A9.
 - (160) Hampton, S. M.; Isherwood, C.; Kirkpatrick, V. J.; Lynne-Smith, A. C.; Griffin, B. A. The Influence of Alcohol Consumed with a Meal on Endothelial Function in Healthy Individuals. *J Hum Nutr Diet* **2010**, *23* (2), 120–125.
 - (161) Papamichael, C.; Karatzi, K.; Karatzis, E.; Papaioannou, T. G.; Katsichti, P.; Zampelas, A.; Lekakis, J. Combined Acute Effects of Red Wine Consumption and Cigarette Smoking on Haemodynamics of Young Smokers. *J. Hypertens.* **2006**, *24* (7), 1287–1292.
<https://doi.org/10.1097/01.hjh.0000234108.08368.01>.
 - (162) Dohadwala, M. M.; Hamburg, N. M.; Holbrook, M.; Kim, B. H.; Duess, M. A.; Levit, A.; Titas, M.; Chung, W. B.; Vincent, F. B.; Caiano, T. L.; Frame, A. A.; Keaney, J. F.; Vita, J. A. Effects of Concord Grape Juice on Ambulatory Blood Pressure in Prehypertension and Stage 1 Hypertension. *Am. J. Clin. Nutr.* **2011**, *93*, 934–940.
 - (163) Park, Y. K.; Kim, J. S.; Kang, M. H. Concord Grape Juice Supplementation Reduces Blood Pressure in Korean Hypertensive Men: Double-Blind, Placebo Controlled Intervention Trial. *BioFactors* **2004**, *22* (1–4), 145–147.
 - (164) Park, E.; Edirisinghe, I.; Choy, Y. Y.; Waterhouse, A.; Burton-Freeman, B. Effects of Grape Seed Extract Beverage on Blood Pressure and Metabolic Indices in Individuals with Pre-Hypertension: A Randomised, Double-Blinded, Two-Arm, Parallel, Placebo-Controlled Trial. *Br. J. Nutr.* **2016**, *115* (2), 226–238. <https://doi.org/10.1017/S0007114515004328>.
 - (165) Chou, E. J.; Keevil, J. G.; Aeschlimann, S.; Wiebe, D. A.; Folts, J. D.; Stein, J. H. Effect of Ingestion of Purple Grape Juice on Endothelial Function in Patients with Coronary Heart Disease. *Am J Cardiol* **2001**, *88* (5), 553–555.
 - (166) Lekakis, J.; Rallidis, L. S.; Andreadou, I.; Vamvakou, G.; Kazantzoglou, G.; Magiatis, P.; Skaltsounis, A. L.; Kremastinos, D. T. Polyphenolic Compounds from Red Grapes Acutely Improve Endothelial Function in Patients with Coronary Heart Disease. *Eur J Cardiovasc Prev Rehabil* **2005**, *12* (6), 596–600.
 - (167) Aviram, M.; Dornfeld, L. Pomegranate Juice Consumption Inhibits Serum Angiotensin Converting Enzyme Activity and Reduces Systolic Blood Pressure. *Atherosclerosis* **2001**, *158* (1), 195–198.
 - (168) Asgary, S.; Sahebkar, A.; Afshani, M. R.; Keshvari, M.; Haghjooyjavanmard, S.; Rafieian-Kopaei, M. Clinical Evaluation of Blood Pressure Lowering, Endothelial Function Improving, Hypolipidemic and Anti-Inflammatory Effects of Pomegranate Juice in Hypertensive Subjects. *Phytother. Res.* **2014**, *28* (2), 193–199. <https://doi.org/10.1002/ptr.4977>.
 - (169) Aviram, M.; Rosenblat, M.; Gaitini, D.; Nitecki, S.; Hoffman, A.; Dornfeld, L.; Volkova, N.; Presser, D.; Attias, J.; Liker, H.; Hayek, T. Pomegranate Juice Consumption for 3 Years by Patients with Carotid Artery Stenosis Reduces Common Carotid Intima-Media Thickness, Blood Pressure and LDL Oxidation. *Clin. Nutr.* **2004**, *23* (3), 423–433.
<https://doi.org/10.1016/j.clnu.2003.10.002>.
 - (170) Tjelle, T. E.; Holtung, L.; Bohn, S. K.; Aaby, K.; Thoresen, M.; Wiik, S. A.; Paur, I.; Karlsen, A. S.; Retterstol, K.; Iversen, P. O.; Blomhoff, R. Polyphenol-Rich Juices Reduce Blood Pressure Measures in a Randomised Controlled Trial in High Normal and Hypertensive Volunteers. *Br J Nutr* **2015**, *114* (7), 1054–1063.
 - (171) Zhu, Y.; Xia, M.; Yang, Y.; Liu, F.; Li, Z.; Hao, Y.; Mi, M.; Jin, T.; Ling, W. Purified Anthocyanin Supplementation Improves Endothelial Function via NO-cGMP Activation in Hypercholesterolemic Individuals. *Clin. Chem.* **2011**, *57* (11), 1524–1533.
<https://doi.org/10.1373/clinchem.2011.167361>.

- (172) Erlund, I.; Koli, R.; Alfthan, G.; Marniemi, J.; Puukka, P.; Mustonen, P.; Mattila, P.; Jula, A. Favorable Effects of Berry Consumption on Platelet Function, Blood Pressure, and HDL Cholesterol. *Am. J. Clin. Nutr.* **2008**, *87* (2), 323–331.
- (173) Rodriguez-Mateos, A.; Rendeiro, C.; Bergillos-Meca, T.; Tabatabaee, S.; George, T. W.; Heiss, C.; Spencer, J. P. 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**, *98* (5), 1179–1191. <https://doi.org/10.3945/ajcn.113.066639>.
- (174) Schroeter, H.; Heiss, C.; Balzer, J.; Kleinbongard, P.; Keen, C. L.; Hollenberg, N. K.; Sies, H.; Kwik-Urbe, C.; Schmitz, H. H.; Kelm, M. (–)-Epicatechin Mediates Beneficial Effects of Flavanol-Rich Cocoa on Vascular Function in Humans. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103* (4), 1024–1029. <https://doi.org/10.1073/pnas.0510168103>.
- (175) Grassi, D.; Desideri, G.; Necozione, S.; di Giosia, P.; Barnabei, R.; Allegaert, L.; Bernaert, H.; Ferri, C. Cocoa Consumption Dose-Dependently Improves Flow-Mediated Dilation and Arterial Stiffness Decreasing Blood Pressure in Healthy Individuals. *J. Hypertens.* **2015**, *33* (2), 294–303.
- (176) Engler, M. B.; Engler, M. M.; Chen, C. Y.; Malloy, M. J.; Browne, A.; Chiu, E. Y.; Kwak, H. K.; Milbury, P.; Paul, S. M.; Blumberg, J.; Mietus-Snyder, M. L. Flavonoid-Rich Dark Chocolate Improves Endothelial Function and Increases Plasma Epicatechin Concentrations in Healthy Adults. *J. Am. Coll. Nutr.* **2004**, *23* (3), 197–204.
- (177) Faridi, Z.; Njike, V. Y.; Dutta, S.; Ali, A.; Katz, D. L. Acute Dark Chocolate and Cocoa Ingestion and Endothelial Function: A Randomized Controlled Crossover Trial. *Am J Clin Nutr* **2008**, *88* (1), 58–63. <https://doi.org/88/1/58> [pii].
- (178) Taubert, D.; Berkels, R.; Roesen, R.; Klaus, W. Chocolate and Blood Pressure in Elderly Individuals with Isolated Systolic Hypertension. *JAMA* **2003**, *290* (8), 1029–1030. <https://doi.org/10.1001/jama.290.8.1029>.
- (179) Rostami, A.; Khalili, M.; Haghighat, N.; Eghtesadi, S.; Shidfar, F.; Heidari, I.; Ebrahimpour-Koujan, S.; Eghtesadi, M. High-Cocoa Polyphenol-Rich Chocolate Improves Blood Pressure in Patients with Diabetes and Hypertension. *ARYA Atheroscler.* **2015**, *11* (1), 21–29.
- (180) Mastroiacovo, D.; Kwik-Urbe, C.; Grassi, D.; Necozione, S.; Raffaele, A.; Pistacchio, L.; Righetti, R.; Bocale, R.; Lechiara, M. C.; Marini, C.; Ferri, C.; Desideri, G. 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.* **2015**, *101* (3), 538–548. <https://doi.org/10.3945/ajcn.114.092189>.
- (181) Hodgson, J. M.; Puddey, I. B.; Woodman, R. J.; et al. Effects of Black Tea on Blood Pressure: A Randomized Controlled Trial. *Arch. Intern. Med.* **2012**, *172* (2), 186–188.
- (182) Grassi, D.; Mulder, T. P.; Draijer, R.; Desideri, G.; Molhuizen, H. O.; Ferri, C. Black Tea Consumption Dose-Dependently Improves Flow-Mediated Dilation in Healthy Males. *J. Hypertens.* **2009**, *27* (4), 774–781.
- (183) Alexopoulos, N.; Vlachopoulos, C.; Aznaouridis, K.; Baou, K.; Vasiliadou, C.; Pietri, P.; Xaplanteris, P.; Stefanadi, E.; Stefanadis, C. The Acute Effect of Green Tea Consumption on Endothelial Function in Healthy Individuals. *Eur J Cardiovasc Prev Rehabil* **2008**, *15* (3), 300–305. <https://doi.org/10.1097/HJR.0b013e3282f4832f>.
- (184) Jochmann, N.; Lorenz, M.; Krosigk, A.; Martus, P.; Bohm, V.; Baumann, G.; Stangl, K.; Stangl, V. The Efficacy of Black Tea in Ameliorating Endothelial Function Is Equivalent to That of Green Tea. *Br J Nutr* **2008**, *99* (4), 863–868. <https://doi.org/10.1017/S0007114507838992>.
- (185) Duffy, S. J.; Keaney, J. F.; Holbrook, M.; Gokce, N.; Swerdloff, P. L.; Frei, B.; Vita, J. A. Short- and Long-Term Black Tea Consumption Reverses Endothelial Dysfunction in Patients with Coronary Artery Disease. *Circulation* **2001**, *104* (2), 151–156.
- (186) Hodgson, J. M.; Puddey, I. B.; Burke, V.; Watts, G. F.; Beilin, L. J. Regular Ingestion of Black Tea Improves Brachial Artery Vasodilator Function. *Clin. Sci.* **2002**, *102* (2), 195–201.

- (187) Greyling, A.; Ras, R. T.; Zock, P. L.; Lorenz, M.; Hopman, M. T.; Thijssen, D. H.; Draijer, R. The Effect of Black Tea on Blood Pressure: A Systematic Review with Meta-Analysis of Randomized Controlled Trials. *PLoS ONE* **2014**, *9* (7), e103247.
- (188) Onakpoya, I.; Spencer, E.; Heneghan, C.; Thompson, M. The Effect of Green Tea on Blood Pressure and Lipid Profile: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Nutr Metab Cardiovasc Dis* **2014**, *24* (8), 823–836.
- (189) Ras, R. T.; Zock, P. L.; Draijer, R. Tea Consumption Enhances Endothelial-Dependent Vasodilation; a Meta-Analysis. *PLoS ONE* **2011**, *6* (3), e16974.
<https://doi.org/10.1371/journal.pone.0016974>.
- (190) Kiyimba, T.; Yiga, P.; Bamuwanye, M.; Ogwok, P.; Van der Schueren, B.; Matthys, C. Efficacy of Dietary Polyphenols from Whole Foods and Purified Food Polyphenol Extracts in Optimizing Cardiometabolic Health: A Meta-Analysis of Randomized Controlled Trials. *Adv. Nutr.* **2023**, *14* (2), 270–282. <https://doi.org/10.1016/j.advnut.2023.01.002>.

Figures legends

Figure 1: Schematic showing endothelium-derived vasorelaxing mechanisms controlling the vascular tone in physiological context. Endothelial nitric oxide synthase (eNOS) generates nitric oxide (NO) from L-arginine (L-Arg) after its activation by shear stress via the Src/PI3-kinase/Akt pathway, and by a variety of agonists (Ach, acetylcholine; -HT, serotonin; BK, bradykinin; ADP, adenosine diphosphate) via the calcium/calmodulin pathway ($\text{Ca}^{2+}/\text{CaM}$). NO induces relaxation of the vascular smooth muscle by the activation of soluble guanylyl cyclase (sGC). Endothelium-dependent hyperpolarization (EDH) often involves the activation of endothelial SK_{Ca} and IK_{Ca} channels (small and intermediate conductance Ca^{2+} -activated K^{+} channels, respectively) inducing hyperpolarization () of the endothelium, which is, thereafter, transmitted, in part, to the underlying vascular smooth cells via myo-endothelial gap junctions with subsequent relaxation. Prostacyclin (PGI_2) is also a vasodilator, which has also potent platelet inhibitory effects. In addition, endothelial cells release vasoconstricting factors such as endothelin-1 (ET-1) and vasoactive prostanoids termed ECDF (endothelium-derived contracting factors), that include thromboxane A_2 , acting through their respective receptors, the endothelin receptors (ETRs) and the thromboxane receptor (TPR).

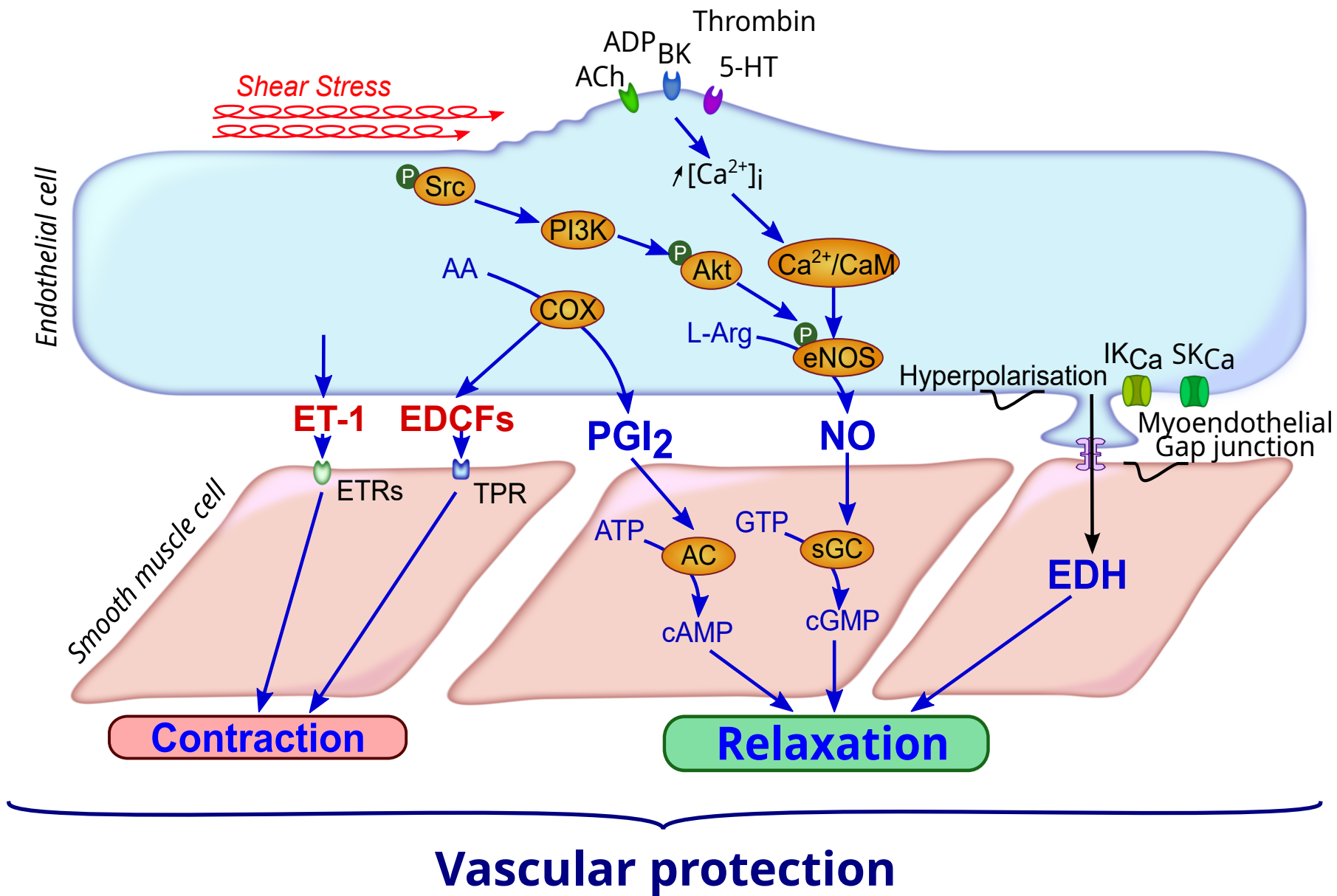
Abbreviations: COX, cyclooxygenases; CaM, calmodulin; Src, Src family kinase; PI3K, phosphatidylinositol 3-kinase; ATP, adenosine triphosphate; cAMP, 3',5' cyclic adenosine monophosphate; GTP, guanosine triphosphate; sGC, soluble guanylyl cyclase; cGMP, 3',5' cyclic guanosine monophosphate; AC, adenylyl cyclase; AA, arachidonic acid.

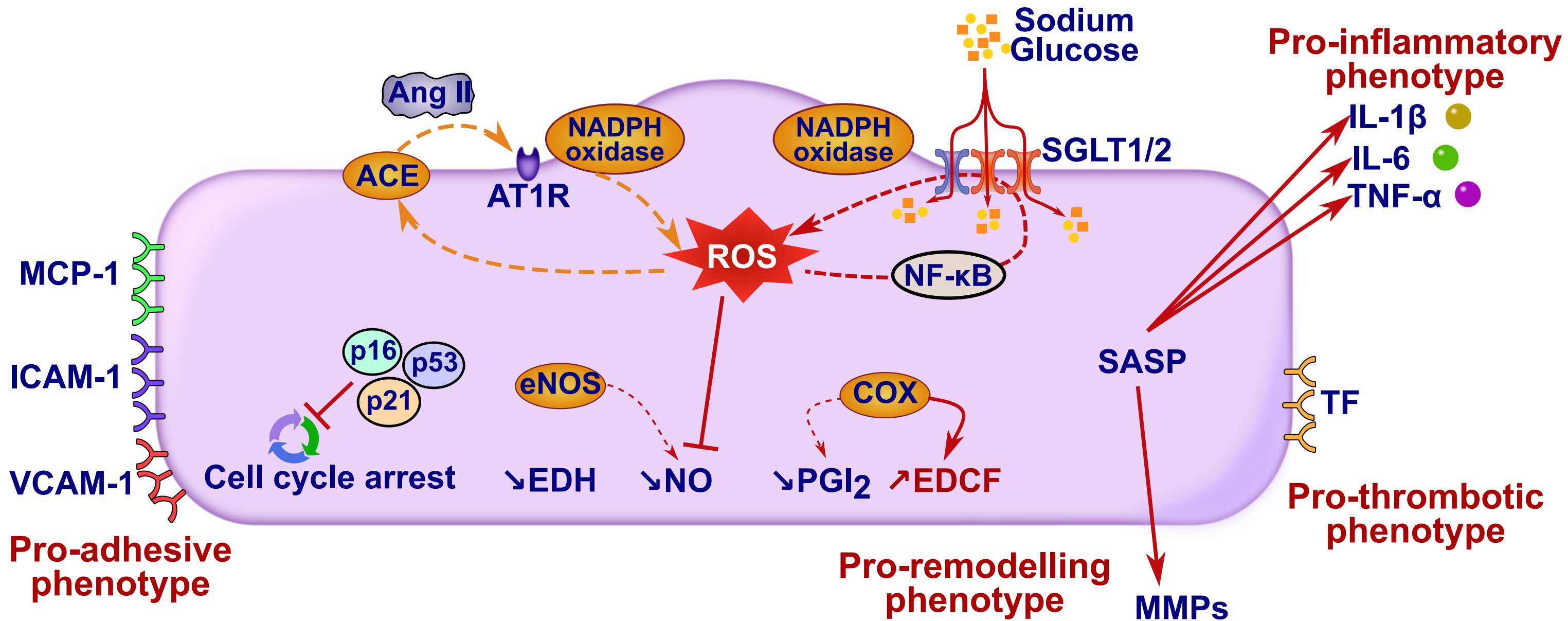
Figure 2: Schematic showing mechanisms involved in the endothelium senescence and dysfunction. Endothelial dysfunction is characterized by a loss of balance between the formation of vasorelaxing and vasoconstricting factors. Endothelial senescence is associated with cell cycle arrest and a senescence-associated secretory phenotype (SASP) leading to pro-

adhesive, pro-inflammatory, pro-thrombotic and pro-remodelling phenotype in the endothelial cells.

Abbreviations: NO, nitric oxide; EDH, endothelium-dependent hyperpolarization; COX, cyclooxygenases; PGI₂, Prostacyclin; EDCF, endothelium-derived contracting factors; SASP, senescence-associated secretory phenotype; MMPs, matrix-metalloproteinases; TF, Tissue factor; SGLT1/2, sodium-glucose co-transporter 1 and 2; AT1R, Angiotensin II type I receptor; Ang II, angiotensin II; ACE, angiotensin converting enzyme;

Figure 3: Effects of phenolic compounds on the endothelium reported using *in vitro* and *ex vivo* studies. The stimulation of the endothelial formation of NO and EDH is mainly due to the redox-sensitive activation of the PI3-kinase/Akt pathway, the Ca²⁺/CaM signaling pathway, and several other additional pathways as indicated. Abbreviations: Ca²⁺/CaM, calcium/calmodulin complex; [Ca²⁺]_i, free intracellular calcium concentration; D3G, Delphinidin-3-*O*-glucoside; EDH, endothelium-dependent hyperpolarization; eNOS, endothelial NO synthase; sGC, soluble guanylyl cyclase; cGMP, cyclic guanosine 3',5' monophosphate; GTP, guanosine triphosphate; NO, nitric oxide; ROS, reactive oxygen species; ER, estrogen receptor; AMPK, AMP-activated protein kinase; Sirt1, sirtuin 1.





Endothelial senescence and dysfunction
Cardiovascular risk

