Review

Cellular and Molecular Bases for the Application of Polyphenols to the Prevention and Treatment of Cardiovascular Disease

Carlo Caiati * and Emilio Jirillo

Posted Date: 26 May 2025

doi: 10.20944/preprints202505.1911.v1

Keywords: Cytokines; Dendritic Cells; Immunotherapy; Macrophages; Myocardial Infarction; T Lymphocytes

 doi:10.20944/preprints202505.1911.v1

Review

Cellular and Molecular Bases for the Application of Polyphenols to the Prevention and Treatment of Cardiovascular Disease

Carlo Caiati * and Emilio Jirillo

Unit of Cardiovascular Diseases, Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", Bari, Italy

* Correspondence: carlo.caiati@uniba.it; Tel.: +39-080-5592117; Fax +39-080-5478796

Abstract: Background: Cardiovascular disease (CVD) is very spread in countries with a Western style diet, representing one of the major causes of morbidity. Genetic factors, obesity, diabetes, dyslipidemia, smoking, and ageing are risk factors for CVD outcome. From a pathogenic point of view, the condition of low-grade inflammation of the arteries leads to endothelial damage, and atherosclerosis development. Nowadays, a broad range of drugs is available to treat CVD, but many of them are associated with side effects. Therefore, alternative therapeutic remedies need to be discovered even in combination with conventional drugs. A balanced diet rich in fruits and vegetables, *e.g.*, the Mediterranean diet, has been shown to lower the incidence of CVD. Plant-derived polyphenols are ingested with food, and these compounds can exert beneficial effects on human health, such as antioxidant, and anti-inflammatory activities. **Objective:** In the present review, the cellular and molecular bases of the beneficial effects of polyphenols on the prevention and treatment of CVD will be pointed out. **Methods**: This review has been accomplished on the basis of literature review spanning mainly in the last 2 decades. **Results**: We found in this respect, that an increased dietary intake of polyphenols is associated with a parallel decrease in chronic disease incidence, even including CVD. **Conclusion:** Despite a plethora of preclinical studies, more clinical trials are needed for a more appropriate treatment of CVD with polyphenols.

Keywords: cytokines; dendritic cells; immunotherapy; macrophages; myocardial infarction; T lymphocytes

Introduction

Cardiovascular disease represents one of the major causes of morbidity in countries adopting Western lifestyles with an annual expectation of deaths by 2030 that exceeds 23.6 million [1]**.** The term CVD encompasses a variety of conditions, such as coronary artery disease (CAD), stroke, peripheral artery disease, hypertension, cerebrovascular disease, and heart failure (HF)**.** Among risk factors of CVD, genetic factors, obesity, diabetes, dyslipidemia, smoking, and ageing account for the occurrence of CVD [2,3]. The above conditions lead to endothelial cell dysfunction, oxidative stress, proliferation of smooth muscle cells, and fibroblasts, with conversion of macrophages to foam cells within the artery walls [4]. Furthermore, the condition of vascular low-grade inflammation promotes atherosclerotic plaque formation, ultimately, causing HF [5] **.** Therapeutically, a broad range of drugs is available for the treatment of CVD, *i.e.*, statins, angiotensin- converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, fibrates, and beta-blockers, however, many of them are associated with side effects[6]**.** Therefore, there is a need to discover and apply innovative therapies even in combination with conventional ones for a more appropriate management of CVD [7,8]**.** It is known that a balanced diet is beneficial for preventing CVD. In fact, consumption of fruits and vegetables has been shown to decrease the incidence of CVD**.** In this respect, Mediterranean diet (MD) decreases inflammatory biomarkers, *e.g.*, interleukin (IL)-1 beta, IL-5 and C-Reactive Protein

 doi:10.20944/preprints202505.1911.v1

(CRP), thus, preventing chronic disease outcome[7,9-11]. In this framework. PREDIMED study demonstrated that MD based on the high consumption of fruits, vegetables, whole grains, and extra virgin olive oil (EVOO) was associated with a reduced risk of CVD[12]. Of note, dietary interventions aimed at reducing low-grade inflammation, have led to divergent results due to differences in tested dietary compounds and chosen inflammatory markers [13,14]. Plant-derived compounds contained in food possess beneficial effects to human health. Among these natural products, polyphenols can be found in fruits, vegetables, seeds, nuts, as well as in red wine, tea, coffee, extra virgin EVOO, and chocolate [15-19]. Nowadays, the human population is more aware about the beneficial effects of polyphenols, and their dietary intake has increased, with a parallel decrease in chronic disease, even including CVD[20]. In the present review, classification, pharmacological activities, and main mechanisms of action of polyphenols will be described. Experimental and clinical evidence of the beneficial effects of these natural compounds on CVD will be discussed..

Classification and General Properties of Polyphenols

Polyphenols are classified according to the number of phenolic rings, and the structural elements they bind [16]. They can be divided into four main classes: flavonoids; non-flavonoids stilbenes; phenolic acids; and lignans (**Error! Reference source not found.**) [21]. Flavonoids are naturally occurring compounds, which encompass six categories: flavanones, flavones, flavanols, isoflavones, flavan-3ols, and anthocyanidins (**Error! Reference source not found.**) [22] . Structurally, they possess two aromatic rings and a heterocyclic ring with a C6-C3-C6 configuration (**Error! Reference source not found.**). They are contained in plants as glycoside and non-glycosylated conjugate compounds, and their type of structure influences bioavailability[23]. Stilbenes, *e.g.,* resveratrol (RES), are composed of two phenyl residues linked by a two-carbon methylene bridge, which can be glycosylated, methylated, or prenylated by specific enzymes (**Error! Reference source not found.**) [24]. Among flavonoids, flavonols, and flavan-3- ols have been object of intensive research. The flavonol quercetin exhibits antihypertensive effects by acting on the contraction of smooth muscles in renal blood vessels, producing vasodilation[25]. Among flavan-3-ols, epigallocatechin-3-gallate (EGCG) is mostly present in green tea, and is endowed with antioxidant, anti-inflammatory, and antiatherogenic properties[26]. Among stilbenes, RES is the most studied compound for its anti-inflammatory, antioxidant, anti-proliferative, anti-apoptotic, and mitochondrial protective effects[27].

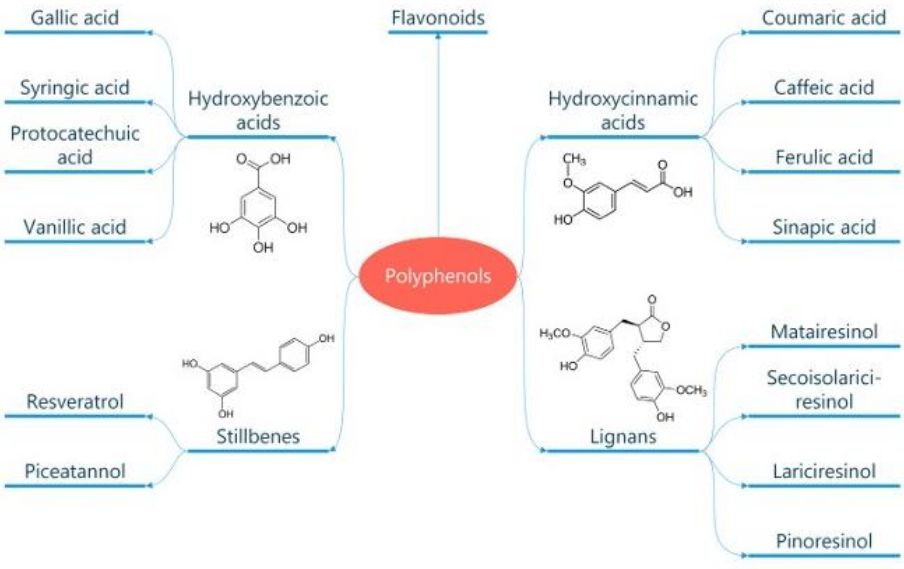

Figure 1. Classification of polyphenols. Polyphenols are natural compounds found in plant-based foods and beverages. Their classification into different subclasses like phenolic acids, flavonoids, stilbenes and lignans is

 doi:10.20944/preprints202505.1911.v1

reported. The chemical formula of these molecules is also reported. Reproduced with permission from Caiati et al. [7].

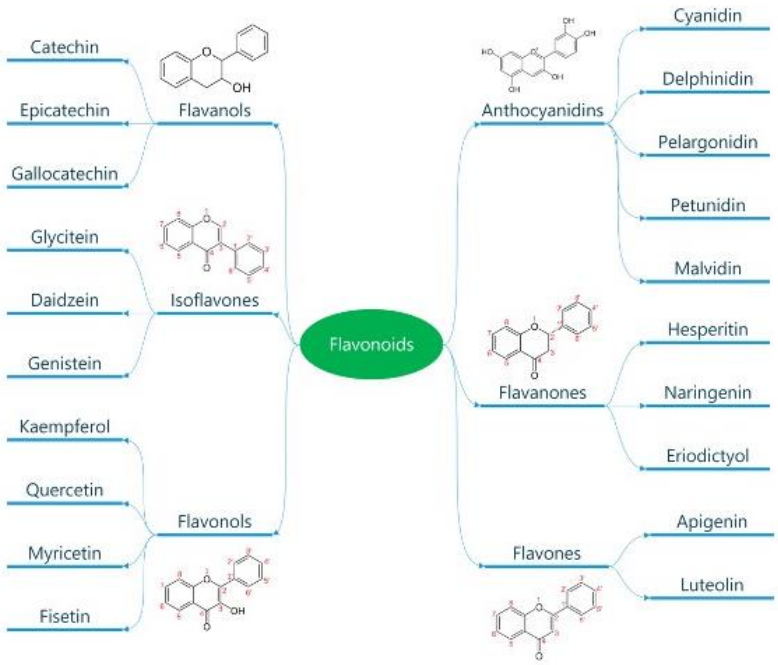

Figure 2. Classification of flavonoids. Flavonoids are a subclass of polyphenols and can be classified into flavonols, flavones, isoflavones, flavanones, antho-cyanidins and flavanols based on their ring structure as here illustrated. Flavonoids have diverse biological activities and potential health benefits, including antioxidant and anti-inflammatory effects. Reproduced with permission from Caiati et al. [7].

Absorption of Polyphenols

In the stomach, polyphenols are digested by pepsin, and peristaltic movements in the presence of a low pH into particles, even less than 500 microns in diameter [28]. The passage of polyphenols from the stomach to the small intestine occurs at a pH around 7, and then, pancreatic and biliary enzymes become activated[29]. Polyphenols under the form of aglycons enter the intestinal epithelium according to different modalities. For instance, polyphenols with low molecular weight, *i.e.*, phenolic acids, flavonoid aglycon, tea polyphenols, and cocoa polyphenols (epicatechin, procyanidin B2, and catechin) are absorbed by passive diffusion[30]. Another way of polyphenol absorption is the sodium-glucose transport through the sodium-glucose-linked transporter 1 (SGLT1)[31]. Accordingly, glycosides may be absorbed by SGTL1 in small amounts, and then, re-secreted into the digestive system, or they may be further digested by a cytosolic glucosidase[32]. Thus, polyphenols can undergo transepithelial transport through a monocarboxylic acid transporter, as in the case of caffeic acid, and ferulic acid (**Error! Reference source not found.**) [33]. Most polyphenols are absorbed in the large intestine, where they are digested by bacteria of the gut microbiota via glycosylation, hydroxylation, demethylation, deconjugation, ring cleavage, hydrolysis, epimerization, and chain shortening processes[34]. Polyphenols, once absorbed into the enterocytes of the small intestine, and before entering circulation, undergo the phase II of enzymatic detoxification with production of sulfates, glucuronides, and methylated derivatives [35]. Polyphenol bioavailability and accumulation in tissues depend on the multidrug resistance associated proteins, which are ATP-dependent efflux transporters, and referred to as phase III metabolism[36]. Then, polyphenols reach the blood stream mostly coupled to proteins, and the liver via the portal circulation, where they are conjugated to O-sulphate or O-glucuronide forms (a second phase metabolism), and finally are eliminated through kidneys[37]. (Table 1)

 doi:10.20944/preprints202505.1911.v1

Table 1. Antioxidant Activity of Polyphenols.

1.1 Scavenging activity depends on the donation of an electron or H atom from a hydroxyl group to afree radical [42]	
1.2 A catechol group in the structure of polyphenols is associated with antioxidant activity[39]	
1.3 The phenolic core of quercetin and catechin scavenges reactive oxygen species (ROS), acting as a buffer or collecting electrons[40]	
1.4 Polyphenols inhibit enzymes, such as xanthine oxidase and nicotinamide adenine dinucleotide phosphatase, thus, reducing the generation of ROS [41]	
1.5 Quercetin exhibits the best capacity to chelate metal ions[117]	

Antioxidant Properties of Polyphenols

Polyphenols behave as potent antioxidant agents thanks to catechol groups, and hydroxylation patterns, such as the 3-hydroxyl group in flavanols or electron shortage in anthocyanins[38]. Using the ferric reducing ability power, it has been demonstrated that the presence of a catechol ring in the structure of polyphenols is associated with their antioxidant activity[39]. Reactive oxygen species (ROS), *i.e.*,superoxide, hydrogen peroxide, and hypochlorous acid, are scavenged by quercetin, and catechin through the phenolic core, acting as buffer or collecting electrons [40]. Furthermore, polyphenols have been shown to inhibit enzymes that generate ROS, such as xanthine oxidase, and nicotinamide adenine dinucleotide phosphatase[41]. Among polyphenols, quercetin has the best capacity to chelate metal ions due to its low redox potential, thus preventing the production of ROS [27]. Scavenging activity of polyphenols is connected to their ability to donate an electron or H atom from an aromatic hydroxyl group to a free radical, thus abrogating its effect [42]. The antioxidant capacity of polyphenols *in vivo* is lower than *in vitro*, since it can be mimicked by other compounds[43]. For instance, *in vivo, the* polyphenol-mediated antioxidant activity exerted by apple consumption is mostly due to the metabolic effect of fructose on urate.

Effects of Polyphenols on the Vascular Endothelium

The major function of endothelial cells (ECS) is to regulate the vascular tone[44]. The endothelial (e) nitric oxide (NO) synthase (eNOS) generates NO from L- arginine, that, in turn, acts on the vascular smooth muscles, thus, triggering guanyl cyclase, with accumulation of cyclic guanosine monophosphate, which activates the protein kinase G, thus leading to vasorelaxation. Furthermore, the endothelium-derived hyperpolarizing factor causes vasorelaxation, targeting the K+ channels in the vasculature. Also, prostacyclin I2 (PGI2), generated during the cyclooxygenase (COX) pathway, leads to vasodilation. On the other hand, endothelial products, such as angiotensin II (ANG II), endothelin-1 (ET-1), and thromboxane (TXA) A2 play vasoconstrictive effects[45]. NO generation accounts for the main effects of polyphenols on the endothelium[46]. In this respect, red wine polyphenols are a potent inducer of serum NO in healthy subjects after 30 min from ingestion[47]. *In vitro* studies have demonstrated that healthy human peripheral blood monocytes are additional source of NO, thus contributing to the vasodilation after ingestion of red wine[16]. In this regard, short term oral treatment of normotensive rats with red wine polyphenols decreased blood pressure[48]. Such an effect depends on the induction of the gene responsible for inducible NO synthase, and COX-2 in the arteries, as well as on the calcium ion -dependent pathway[49]. In this

 doi:10.20944/preprints202505.1911.v1

last respect, RES and quercetin have been shown to induce increase in calcium concentration by opening the potassium channels or inhibiting Ca2+ ATP-ase within the endoplasmic reticulum of ECs [50]. Evidence has been provided that red wine polyphenols enhance endothelial NO production via the redox-responsive PI3/Akt channel, the increase in intracellular protein-Ca2+, and tyrosine phosphorylation with activation of eNOS[51,52]. Apart from NO generation, polyphenols exhibit other effects of the endothelium via increased release of PGI2 [53]. In fact, *in vitro* and *in vivo* studies, using cocoa extracts rich in procyanidins, demonstrated that the ratio leukotrienes to PGI2 was reduced. Moreover, polyphenols can increase endothelial NO by decreasing levels of phosphodiesterases (PDE)-2 and PDE-4[54]. (Table 2)

Table 2. Effects of Polyphenols on the Vascular Endothelium.

2.1	*Polyphenol-induced nitric oxide (NO) generation from endothelial cells and monocytes contributes to artery vasodilation[16,46,47]*
2.2	In rats, ingestion of red wine polyphenols generates hypotension through activation of inducible NO synthase, cyclooxygenase-2, and calcium ion-dependent pathway in the arteries[49,50]
2.3	Red wine polyphenols trigger endothelial NO production via the PI3/Akt pathway, the increase in intracellular protein-Ca2+, and tyrosine phosphorylation[51,52]
2.4	Cocoa extracts rich in procyanidins cause vasodilation via increased release of prostacyclin I2[53]
2.5	Polyphenols increase endothelial NO by decreasing phosphodiesterase (PDE)-2, and PDE-4[54]

Anti-Inflammatory Activity of Polyphenols

Inflammation is a response of the body to various stimuli, even including pathogens, mechanical insults, and damaged tissue. Pro-inflammatory cytokines,*e.g.*, interleukin (IL)-1 beta, IL-6, IL-8, and tumor necrosis factor (TNF)-alpha, as well as various enzymes, such as COX, lipooxigenase (LOX), and protein kinase are responsible for the inflammatory response . With special reference to the role of polyphenols, there is evidence that red wine polyphenols can *in vitro* reduce the production of pro-inflammatory cytokines, blocking the activation of the NF-kB pathway[55]. Moreover, red wine polyphenols can interfere with endotoxin binding to Toll-Like Receptor (TLR)-4, thus, abrogating the nuclear factor kappa-light chain enhancer of activated B cells (NF-kB) pathway with interruption of pro-inflammatory cytokine release[56]. Also, polyphenols contained in the fermented grape marc (FGM) induce activation of Foxp3+ T regulatory cells, with release of the anti-inflammatory cytokine, IL-10[57]. In addition, FGM reduces the respiratory burst of neutrophils and basophils in *in vitro* experiments, playing an antioxidant and anti- inflammatory activity[58]. Quercetin has been found to dampen the generation of prostaglandins, leukotrienes, and TAXs, abrogating production of COX and LOX[59,60]. In fact, both COX and LOX mediate the formation of arachidonic acid, which, in turn, fuels inflammation via release of IL-1 beta, and IL-8. The nucleotide-binding domain and leucine-rich repeat containing receptors (NLRs) belong to the family of pattern recognition receptors (PRR), triggering inflammatory responses upon danger and cell damage signals. Among them, NLRP3 inflammasome is a multiprotein complex, which activates the inflammatory caspase-1 [61]. Caspase-1 cleaves and maturates the pro-inflammatory cytokines, IL-1 beta and IL-18, as well as the

 doi:10.20944/preprints202505.1911.v1

protein gasodermin, contributing to the release of the above mediators, thus, initiating the cell death pyroptosis [62] . Activation of NLRP3 inflammasome is involved in CVD even including atherosclerosis, myocardial infarction, and cardiac remodeling[63]. In this framework, in the middle cerebral artery occlusion/reperfusion model, supplementation of various polyphenols decreased levels of NLRP3 [64]. This event is associated with the downregulation of IL-1 beta, and IL-18 in the serum or brain tissue[65]. In the myocardial ischemia (MI)/reperfusion model, certain polyphenols, *i.e.,* RES and flavone *in vivo* reduced levels of caspase-1 and IL-1 beta in the myocardial tissue[66,67]. In all these studies, the decrease in NLRP3 levels was associated with improvement of clinical markers[64]. Clinically, aged male subjects at high cardiovascular risk underwent acute administration of aged wine with decrease in *Tlr2, Nlrp3, and Il1receptor* genes[68]. (Table 3)

Table 3. Anti-Inflammatory Activity of Polyphenols.

3.1 Red wine polyphenols reduce the production of pro-inflammatory cytokines, inhibiting the NF-kB pathway, and/or activating T regulatory cells, with release of the anti-inflammatory cytokine, interleukin (IL)-10[16,57]

3.2 Fermented grape marc reduces the respiratory burst of human neutrophils, and basophils[58]

3.3 Quercetin decreases the release of IL-1 beta, and IL-8, abrogating the generation of cyclooxygenase and lipoxygenase[59,60]

3.4 Polyphenols dampen the activity of the inflammasome NLRP3, with downregulation of caspase1, IL-1 beta, and IL18[63-66]

3.5 Reduction of NLRP3 is associated with improvement of clinical markers, as seen in aged male subject at high cardiovascular risk following acute administration of red wine[64,68]

Anti-Atherogenic Effects of Polyphenols

Atherosclerosis represents a pathogenic common denominator of various diseases, including CAD, ischemic stroke, and peripheral artery disease [69]. This disease stems from the endothelial damage provoked by several offending factors that then drive augmentation of ROS in the blood. Those offending factors have been recently reported [7,70]: in brief, they are largely man-made like stress, pollutants of all sorts (especially those contained in the food like farming chemicals, fertilizers, pesticides and herbicides like glyphosate), drugs, processed food, tabacco smoking, air pollution, alcohol, cosmetic and cleaning products, heavy metal, chronic infections, electromagnetic radiation (cellular phone, cell-tower emitting radiation), ionizing radiation (in particular those medically derived like computed tomography scan and angiography), intravascular prosthesis like arterial stents. Diabetes per se induces tissue damage and it terribly enhances the damaging effects of the previously mentioned atherogenic factors so dramatically enhancing formation of ROS [7]. From a pathogenic point of view, increased levels of ROS further enhance endothelial damage, with the intervention of neutrophils, macrophages, and platelets [71]. In fact, prolonged contact of ECs with hydrogen peroxide, peroxynitrite, and oxidized low density lipoproteins (ox-LDL), leads to severe damage of the endothelium[7,69,72]. One of the initial consequence of coronary endothelial dysfunction is the reduction of NO production and the ensuing microvascular vasoconstriction at rest. This kind of derangement can be spotted with positron emission tomography (PET) since

 doi:10.20944/preprints202505.1911.v1

it causes myocardial dishomogeneous perfusion at rest [73] and is the mechanism that explains the angiographic slow coronary phenomenon as recently demonstrated [74].

Then such a strong oxidative drive involve LDL microparticles that get oxidated too. This causes the first step of atherosclerotic plaque formation, that is the generation of oxidized LDLs, which pass through the endothelial barrier, eliciting cytotoxic effects and the inflammatory response[75], since ox-LDL microparticles are modified substances that elicit strong immunologic reaction. Focusing on the molecular biology details, activated ECs express adhesins, *i.e.*, vascular cell adhesion-1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and E- selectins, which allow transmigration of monocytes and T cells into the arterial wall [76]. Particularly, monocytes engulf ox-LDL, becoming foam cells, which accumulate as fatty bands in the artery walls[77]. Then, a stabilized plaque is formed, which can break under prolonged inflammation [78]; this happens only in case of prolonged and unstopped exposure to those factors generating ROS with consequent escalating concentration of ox-LDL. Ruptured plaques cause thrombosis, which may lead to heart attacks, ischemic strokes, and peripheral ischemia [79]. There is evidence that polyphenols can exert beneficial effects on atherosclerosis. In cholesterol-fed rabbits, administration of red wine polyphenols decreased neointimal growth, lipid accumulation, and inflammation in the iliac arteries[80]. In hamsters, red wine supplementation reduced neointimal hyperplasia, inhibiting the entry of monocytes into the arterial wall [81]. Clinically, there is evidence that purple grape juice reduced the levels of plasmatic ox-LDL in patients with CAD[82]. Such an effect has been shown to depend on the production of NO by polyphenols, as also supported by others[83,84] (Table 4). However the main radical approach that can stop progression and start regression of atherosclerosis is the elimination of those damaging factors (mentioned before) that create ROS and cause chronic endothelium inflammation and ox-LDL [85].

Table 4. Anti-Atherogenic Effects of Polyphenols.

4.1	In cholesterol-fed rabbits and in hamsters administration of red wine polyphenols decreases neo-intimal growth, lipid accumulation, and entry of monocytes in the iliac arteries[80,81]
4.2	In patients with coronary artery disease, supplementation of purple grape juice reduces levels of oxidized lipoproteins through generation of nitric oxide[82-84]

Focus on the Cardiovascular Effects of Relevant Polyphenols

Flavan-3-Ols

Flavan-3 Ols (**Error! Reference source not found.**) represent the most abundant polyphenols in fruits, vegetables, red wine, green tea, and cocoa [86]. They encompass monomeric, oligomeric, and polymeric compounds. Monomeric forms include catechin, epicatechin, gallocatechin, epigallocatechin, epicatechin-3-O-gallate, and EGCG (**Error! Reference source not found.**). Oligomers or polymers are known as proanthocyanidins, while polymers composed of epicatechin or catechin are termed procyanidins. The antioxidant activity of flavan-3-ols is based on their ability to donate an electron or to chelate metal ions, thus, stopping, ROS production[87]. At the same time, flavan-3-ols maintain mitochondrial activity, while enhancing antioxidative enzymes involved in ROS scavenging [88,89]. The anti-inflammatory activity of flavan-3 -ols depends on the regulation of gene expression involved in cardiometabolic health. Particularly, they act on endothelial transcription factor GATA-2, the NF-kB p105 subunit, forkhead box C1, and peroxisome proliferator-activated receptor gamma[90]. In addition, flan-3-ols target different miRNA, regulating cellular pathways involved in cell adhesion, cellular signaling, and immune response[91]. Of note, cocoa flavan-3-ols metabolites enhance *ApOAI* expression, which represents the major component of high-density lipoproteins, thus exerting antiatherogenic properties[92]. The cardioprotective effects of

 doi:10.20944/preprints202505.1911.v1

flavan-3-ols have been attributed to two major microbial-derived metabolites, namely, the hydroxy-phenyl-gamma-valerolactones, and their derived hydroxy- phenyl valeric acids [93]. These metabolites have *in vivo* shown hypotensive activity in rats, and *in vitro* abrogation of monocyte adhesion to ECs treated with tumor necrosis factor (TNF)-alpha[94]. Another flavan-3-ol metabolite, the protocatechuic acid, diminished diabetic cardiomyopathy in rats, stimulating glucose metabolism, improving oxidative stress, and reducing inflammation[95]. Flavan-3-ols have been shown to act on gut dysbiosis, improving cardiac function. In fact, a metabolite from the gut microbiota, trimethylamine N-oxide (TMAO) has been associated with CVD pathogenesis in terms of increased cholesterol levels, and higher risk of atherosclerosis[96]. In this respect, the intake of cocoa and red berry flavan-3- ols reduces TMAO levels, improving cardiovascular markers in healthy aging adults[97]. Various clinical trials have been conducted, using cocoa flavan-3-ols in patients with CVD. In hypertensive individuals, consumption of dark chocolate led to a reduction of systolic blood pressure (SBP), and diastolic blood pressure (DBP) in comparison to baseline[98]. In another study, in essential hypertensive subjects, with impaired glucose tolerance, receiving 100g/day chocolate, a reduction of both SBP, and DBP, and an increase in flood- mediated dilation (FMD) were observed[99]. In patients with CAD receiving dietary high-flavan-3-ol intervention, an increase in brachial artery FMD, and a reduction in SBP were recorded[100]. In patients with congestive HF, intake of flavan-3-ol-rich chocolate improved FMD[101]. Other studies have been conducted with green tea catechins in both healthy, and unhealthy individuals. In healthy volunteers aged between 21 and 70 years, receiving two capsules of *Camelia sinensis* for 3 months, a reduction of SBP was observed[102]. In another group of healthy adult men aged 18-35 years, administration of 450 mg sour tea led to a reduction of SBP and DPB[103]. In healthy postmenopausal women, acute ingestion of catechin-rich green tea improved postprandial glucose status, while increasing serum thioredoxin levels, but no changes in cardiovascular risk factors were observed[104]. In overweight women aged 19-57 years, receiving low-calorie diet along with 3 capsules of green-tea or placebo capsules, a decrease in SBP, and DPB were observed in both groups[105]. Another trial conducted in healthy male volunteers, supplemented with an aqueous green tea extract, showed no alterations of cardiac risk factors[106]. Also, minor effects on cardiovascular risk markers were observed following tea catechin administration to active older people[107]. Taken together, the above data suggests that studies with polyphenols conducted in both healthy and unhealthy individuals has led to contrasting results.

Resveratrol

Stilbenes, and, particularly, RES (**Error! Reference source not found.**) despite a low bioavailability possess a strong antioxidant activity *in vitro.* RES protects cardiomyocytes, and ECS against ROS effects, inhibiting NADPH oxidases, while increasing the mitochondrial respiratory chain enzymes[108]. RES acts upregulating SIRT1, that, in turn, induces deacetylation of NF-kB, and enhancement of superoxide dismutase (SOD), catalase and glutathione peroxidase 1[109,110]. Furthermore, RES can reverse eNOS uncoupling, upregulating GCH1 expression in apolipoprotein E knockout mice[111]. Also, RES activates Nrf-2, which, in turn, increases cellular antioxidant content in placenta of sows and piglets[112]. As a potent anti-inflamamtory agent, RES can inhibit the expression of pro-inflammatory cytokines, downregulating TLR4 expression, and silencing NF-kB activity[113,114]. Moreover, RES can inhibit VCAM-1, ICAM-1, and E-selectin, suppressing the TNF-alpha-induced NF-kB activation[115]. RES inhibits COX-1 and COX-2 enzymes via SIRT1 activation, thus, decreasing PGE2 and TAX2, and consequently inflammation[116]. In patients with systolic HF, RES administration improved clinical conditions by inhibiting oxidative phosphorylation in leukocytes, gene expression encoding B cell receptors, and leukocyte extravasation signal[117]. ROS-mediated overexpression of (MAPKs) is involved in cardiac hypertrophy and remodeling[118]. RES can stimulate MKP-1 and downregulate mTOR, thus dampening mitogen-activated protein kinase (MAPK) activity, with reduction of cardiac and endothelial hypertrophy[119,120]. With special reference to cardiac fibrosis, it has been reported that RES can mitigate in rats cardia fibroblast

 doi:10.20944/preprints202505.1911.v1

activity, downregulating the transforming-growth factor-beta/Smad 2/3 signaling pathway via overexpression of the Smad 7 inhibitor protein and silencing miR-17 gene[121]. RES can modulate endothelial function, inhibiting overproduction of the vasoconstrictive agent, ET-1, enhancing eNOS phosphorylation, with increase in No production[122]. There is evidence that upregulation of ET-, and decrease in NO are involved in the pathogenesis of atherosclerosis[123]. The effects of RES on mitochondrial biogenesis have been documented. In fact, RES activates the AMPK/SIRT1/PGC1 alpha pathway, with enhancement of Nrf-1 and Nrf-2 transcription factors, thus, attenuating high-glucose oxidative stress, and cardiomyocyte apoptosis in diabetic mice[124]. As far as clinical trials are concerned, the effects of RES have been studied in patients with hypertension. In one study, long-term administration of RES could reduce hypertension along with standard medical therapy[125]. In a meta- analysis, in hypertensive subjects daily RES consumption reduced SBP, but not DBP[126]. Conversely, in other two studies the hypotensive effects of RES were not confirmed[117,127]. With special reference to vascular protection, RES long-term administration improved the FMD of the brachial artery in overweight and hypertensive individuals, stable CAD patients, and patients with metabolic syndrome, respectively[128-130]. In another study, acute RES administration to hypertensive patients improved FMD without changes of SBP[131]. A systematic review and meta-analysis have provided evidence that RES can modify lipid profile, diabetes and inflammation associated with atherosclerosis in metabolic syndrome patients[132-134]. A few clinical trials have been conducted in patients with HF. In post-MI patients, administration of 10 mg/day RES for 3 months improved the diastolic function[129]. In patients with angina pectoris, RES supplementation at 20 mg/day for 2 months reduced serum levels of the N-terminal prohormone brain natriuretic peptide (NT-proBNP) [135]. In patients with symptomatic systolic HF, 100 mg/day RES supplementation improved systolic and diastolic function, as well as serum biomarkers, such as NT-proBNP and IL-1 and Il-6 levels[117].

Curcumin

Curcumin (diferuloyl methane) is a natural polyphenol extracted from the rhizomes of the thurmeric plant *(Curcuma longa* L.) [136]. Structurally, curcumin possesses a constitutional double bond, thus behaving as an electron donor, which mitigates ROS effects[137]. Furthermore, curcumin exerts anti- inflammatory effects, as well as modulation of lipid metabolism, and of the immune system [138]. In cadmium-induced hypertensive rats, curcumin administration normalized vascular dysfunction and blood pressure[139]. Similar results were achieved in Sprague rats with lead acetate and cadmium chlorate-induced hypertension[140]. Furthermore, in spontaneous hypertensive rats, curcumin administration attenuated the coronary artery damage[141]. Also, in ANG-II-induced hypertensive rat model curcumin administration reduced the ANG-II type-I receptor-mediated vasoconstriction, thus preventing hypertension[142]. A few clinical trials have been conducted in hypertensive patients using curcumin. A group of 14 men and 24 women with an average blood pressure of 121-140/81-90 mm Hg received cavacurmin (500 mg), eicosapentaenoil acid, astaxanthin, and gamma linolenic acid for 4 weeks[143]. A significant decrease of SBP was observed only in women. In refractory or relapsing lupus nephritis patients, administration of curcumin (500 mg) for 3 months led to a significant decrease of SBP[144]. Moreover, a combination of curcumin and galactomannan (500 mg) was administered to obese subjects, with a declining trend in blood pressure, and aortic stiffness, and an increase in anti-inflammatory cytokines [145]. Conversely, in another study a 12-week treatment of healthy middle-aged and older adults with 200 mg curcumin did not modify blood pressure despite a reduction of oxidative stress and improvement of endothelial function[146]. Previously, evidence has been provided thar RES and curcumin in combination could lower oxidative stress, inflammation, and tumor growth[147]. Such a combination improved endothelial function, inhibiting the gene regulatory activity of TNF-alpha, and abrogating the NF-kB pathway.

Extra Virgin Olive Oil Polyphenols

 doi:10.20944/preprints202505.1911.v1

EVOO represents a food supply endowed with antioxidant and anti-inflammatory activities[148]. EVOO is mainly composed of monosaturated fatty acids, alpha- tocopherol, and polyphenols[149]. The phenylethanoid derivatives, hydroxytyrosol (HT), and thyrosol are the major polyphenols contained in EVOO[150]. HT is the most studied EVOO polyphenol in terms of anti-inflammatory activity and CVD prevention. In healthy male Wistar rats, HT administration inhibited collagen-induced platelet aggregation in whole blood[151]. This effect has been attributed to the inhibition of platelet synthesis of TxB2, production of vascular PGI2, and increase in vascular NO. Also, HT alkyl ether derivatives exerted similar effects, thus acting as anti-aggregating agents at the endothelial level [152]. In human clinical trials, HT has been studied for its capacity to attenuate the pathogenesis of atherosclerosis. In 30 hypercholesterolemic volunteers (aged 20-70 years), administration of HT derived from Coratina olives led to a normalization of SBP and lipid profile[153]. Similar results were achieved through supplementation of Body Lipid, containing HT, berberine, coenzyme Q10, and monacolin K to hypercholesteremic individuals[154]. In another study, administration of HT and punicalagin to adult population improved dyslipidemia, and decreased SBP and DBP in an adult population [155]. HT and punicalagin increased endothelial capacity and reduced ox-LDL. Furthermore, in 40 healthy volunteers administration of HT (15 mg/day for 3 weeks) increased in blood samples antioxidant activity, oxidation biomarkers (thiols) and SOD1, while malonedialdehyde (MDA) and NO metabolites were decreased[156]. Conversely, in another study administration of HT to human volunteers with mild hyperlipidemia did not influence CVD biomarkers, while levels of vitamin C increased[157]. In this framework, a very recent study based on the supplementation of 15 mg HT/day to patients 24 h after stroke for 45 consecutive days led to encouraging results[158]. In fact, a decrease in glycated hemoglobin and DBP and a modulation of the expression of gene encoding for apolipoproteins were recorded. A limitation of these studies is the possible co-presence of other compounds that can also contribute to the efficacy of the treatment. This is the case of trials conducted with dietary supplementation of EVOO, where the effects of polyphenols cannot be distinguished from that of other components, such as unsaturated fatty acids.

Cardiovascular Effects of Wheat Polyphenols

Wheat *(Triticum sp.)* is largely used all over the wor s evidence that 2-3 servings/ day of whole wheat grains reduce the risk of CVDs[160]. Among phenolic acids, ferulic acid is the major component of wheat, and the number of hydroxyl groups correlates with its antioxidant potential[161]. Experimentally, extracts enriched in ferulic, synaptic, and p-coumaric acids downregulated pro-inflammatory cytokines, and chemokine/interferon-gamma-inducible protein 10 kDa[162]. Furthermore, fermented wheat germ polyphenols could reduce lipid metabolism in hyperlipidemic rats, activating the AMPK pathway. Clinically, wheat aleurone improved redox status in overweight/obese individuals at higher risk of CVD [163]. Ferulic acid could lower total cholesterol, triglycerides,MAD, C-RP in hyperlipidemic individuals, thus preventing atherosclerosis outcome[164]. The role of quercetin, a flavonol, contained in whole wheat grain, has preclinically been investigated. Its athero-protective effects have been ascribed to the suppression of inflammation and apoptosis [165] . Quercetin derivatives can induce regression of atheromatous plaques, triggering autophagy, and inhibiting the breakdown of elastin, macrophage infiltration, and production of both matrix-metallo-proteinase 9, and adhesion molecules[166,167]. Also, quercetin could prevent cardiac/ischemia and/or reperfusion injury through regulation of the PI3K/Akt pathway[168]. (Table 5).

 doi:10.20944/preprints202505.1911.v1

Table 5. Cardiovascular Effects of Polyphenols.

5.1 ***Flavan-3-Ols***

5.1a-Flavan-3-ols metabolites, hydroxy-phenyl-gamma-valerolactones, hydroxy-phenyl valeric acid, and protocatechuic acid exhibit hypotensive activity in rats and decrease diabetic cardiomyopathy, with reduction of inflammatory biomarkers[93-95]

5.1b- Cocoa flavan-3-ols supplementation reduces trimethylamine-N oxide in healthy individuals, systolic blood pressure (SBP), and diastolic blood pressure (DBP) in hypertensive individuals, and in patients with coronary artery disease, while increasing flood-mediated dilation (FMD)[98,99,101]

5.1c- Administration of green tea catechins to healthy volunteers decreased SBP, and DBP, and improvedpostprandial glucose status, while lowering serum thioredoxin levels[102-104]

5.1d- No effects of green tea catechin supplementation were observed in healthy male volunteers, activeolder people, and overweight women[105-107]

5.2 Resveratrol (RES)

5.2a- In rodents, RES mitigates cardiac, endothelial hypertrophy, and cardiac fibrosis, dampening MAPK activity and transforming-growth factor-beta/Smad 2/3 signaling pathway[119-121]

5.2b- RES inhibits endothelin-1, with production of nitric oxide, and prevention of atherosclerosis [123]

5.2c- In diabetic mice, RES attenuated high-glucose oxidative stress, and cardiomyocyte apoptosis through enhancement of Nrf-1, and Nrf-2 transcription factors[124]

5.2d- In patients with hypertension, RES administration reduced hypertension[125,126], while in other two studies such an effect was not confirmed[117,127,142]

5.2e- In hypertensive patients, stable coronary artery disease patients, and patients with metabolic syndrome, long term RES administration improved the FMD of the brachial artery[128-131]

5.2f- RES administration can modify the lipid profile, diabetes, and inflammation in patients with atherosclerosis[132-134]

5.2g- In patients with heart failure, RES administration improved both systolic and diastolic function,reducing the serum levels of the N-terminal prohormone brain natriuretic peptide[117,129,135]

 doi:10.20944/preprints202505.1911.v1

5.3 Curcumin

5.3a- In hypertensive rat models, curcumin administration normalized vascular function, attenuating coronary artery damage[139-142]

5.3b- In hypertensive patients, refractory or relapsing lupus nephritis patients and obese subjects curcumin reduced blood pressure, with an increase in anti-inflammatory cytokines[143-145]

5.3c- In another study, curcumin did not modify blood pressure in healthy middle-aged and older adults[146]

5.4 Extra Virgin Olive Oil (EVOO)

5.4a- Hydroxytyrosol (HT) inhibited platelet aggregation in rats, decreasing thromboxane B2, and prostacyclin, while increasing nitric oxide [151,152]

5.4b- In hypercholesterolemic individuals, HT administration normalized the lipid profile, with reduction of SBP, and DBP study, HT [153-155]. In another administration did not modify lipid profile and cardiovascular biomarkers[157]

5.4c- In patients with stroke, administration of HT 24 h after stroke decreased glycated hemoglobin and DPB[158]

Adverse Efeects of Polyphenols

A few side effects attributed to polyphenol administration have been recorded. For instance, RES administration to humans may lead to emesis, mild hepatic dysfunction, and diarrhea[169,170]. In rats, high oral doses of RES (3g/Kg/day) provoked nephrotoxicity[171]. Also, flavonoids can cause mild gastrointestinal symptoms, insomnia, headache, palpitations and increase in serum transaminases[172,173]. Other side effects of polyphenol ingestion are represented by a reduced gastrointestinal transport of folic acid, thiamine, and iron[174].

Conclusions and Future Trends

There is a large body of evidence that polyphenols exert antioxidant, and anti-inflammatory activities, thus, regulating major pathways involved in cellular activation , and metabolism. In this respect, polyphenols exert beneficial effects on CVD, such as stroke, hypertension, and HF. For example, MD is a balanced diet, which promotes human health, even including prevention of CVD. However, dietary foods contain many compounds, *e.g.*, vitamins, minerals, polyphenols and unsaturated fatty acids, all endowed with protective effects in the host. Therefore, in this review emphasis has been placed on the cardioprotective effects of single polyphenols alone or a combination between them, to rule out potential effects of other dietary compounds. Undoubtedly, preclinical studies conducted with a variety of polyphenols suggest their beneficial effects on CVD. On the other hand, clinical trials are still a few and, sometimes, based on a low number of participants. Therefore, the actual effects of polyphenol intake on human healthy and unhealthy population need a more robust confirmation with more clinical trials.

Author Contributions: The authors confirm their contribution to the paper: study conception and design: E. J. author; data collection: E.J. author ; analysis and interpretation of results: E.J. author and C.C. author; draft

 doi:10.20944/preprints202505.1911.v1

manuscript: E.J. author and C.C. author. All authors reviewed the results and approved the final version of the manuscript.

Funding: This research received no external funding.

Abbreviations

ANG II	Angiotensin II
CAD	Coronary Artery Disease
COX	Cyclooxygenase
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
ECs	Endothelial Cells
EGCG	Epigallo-Catechin-Gallate
ENOS	Endothelial Nitric Oxide Synthase
ET-1	Endothelin-1
EVO	Extra Virgin Olive Oil
FGM	Fermented Grape Marc
FMD	Flood-Mediated Dilation
HF	Heart Failure
ICAM	Intercellular Adhesion Molecule-1
IL	Interleukin
LOX	Lipoxigenase
MAD	Malondialdehyde
MAPK	Mitogen-Activated Protein Kinase
MD	Mediterranean Diet
MI	Myocardial Ischemia
NF-kB	Nuclear Factor Kappa-Light Chain Enhancer of Activated B cells
NLRs	Nucleotide-Binding Domain and Leucine-Rich Repeat Containing Receptors
NO	Nitric Oxide
oxLDL	Oxidized Lipoproteins
Phosphodiesterase (PDE)	
PG	Prostaglandin
PGI2	Prostacyclin-I 2
PRR	Pattern Recognition Receptors
PVAs	Hydroxy-Phenyl-Valeric Acids
PVLs	Hydroxy-Phenyl-Gamma-Valerolactones
RES	Resveratrol
ROS	Reactive Oxygen Species
SBP	Systolic Blood Pressure
SGLT1	Sodium-Glucose-Linked Transporter 1
SOD	Superoxide Dismutase
TXA	Thromboxane
TMAO	Trimethyl-Amine-Oxide
TNF	Tumor Necrosis Factor-alpha
VCM	Vascular Cell Adhesion-1

REFERENCES

1. Laslett LJ, Alagona P, Jr., Clark BA, 3rd, Drozda JP, Jr., Saldivar F, Wilson SR, et al. The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. *J Am Coll Cardiol*. **2012**;60(25 Suppl):S1-49. Journal Article.
2. Force USPST, Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, et al. Risk Assessment for Cardiovascular Disease With Nontraditional Risk Factors: US Preventive Services Task Force Recommendation Statement. *JAMA*. **2018**;320(3):272-80. Journal Article.
3. Knowles JW, Ashley EA. Cardiovascular disease: The rise of the genetic risk score. *PLoS Med*. **2018**;15(3):e1002546. Journal Article.

 doi:10.20944/preprints202505.1911.v1

4. Chen J, Zhang X, Millican R, Sherwood J, Martin S, Jo H, et al. Recent advances in nanomaterials for therapy and diagnosis for atherosclerosis. *Adv Drug Deliv Rev*. **2021**;170:142-99. Journal Article.
5. Steven S, Frenis K, Oelze M, Kalinovic S, Kuntic M, Bayo Jimenez MT, et al. Vascular Inflammation and Oxidative Stress: Major Triggers for Cardiovascular Disease. *Oxid Med Cell Longev*. **2019**;2019:7092151. Journal Article.
6. Li J, Liao R, Zhang S, Weng H, Liu Y, Tao T, et al. Promising remedies for cardiovascular disease: Natural polyphenol ellagic acid and its metabolite urolithins. *Phytomedicine*. **2023**;116:154867. Journal Article.
7. Caiati C, Stanca A, Lepera ME. Free Radicals and Obesity-Related Chronic Inflammation Contrasted by Antioxidants: A New Perspective in Coronary Artery Disease. *Metabolites*. **2023**;13(6):712. Journal Article.
8. Iqbal I, Wilairatana P, Saqib F, Nasir B, Wahid M, Latif MF, et al. Plant Polyphenols and Their Potential Benefits on Cardiovascular Health: A Review. *Molecules*. **2023**;28(17). Journal Article.
9. Koelman L, Egea Rodrigues C, Aleksandrova K. Effects of Dietary Patterns on Biomarkers of Inflammation and Immune Responses: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Adv Nutr*. **2022**;13(1):101-15. Journal Article.
10. Lisco G, Giagulli VA, De Pergola G, Guastamacchia E, Jirillo E, Triggiani V. Pancreatic Macrophages and their Diabetogenic Effects: Highlight on Several Metabolic Scenarios and Dietary Approach. *Endocr Metab Immune Disord Drug Targets*. **2023**;23(3):304-15. Journal Article.
11. Soldati L, Di Renzo L, Jirillo E, Ascierto PA, Marincola FM, De Lorenzo A. The influence of diet on anti-cancer immune responsiveness. *J Transl Med*. **2018**;16(1):75. Journal Article.
12. Garcia-Arellano A, Ramallal R, Ruiz-Canela M, Salas-Salvado J, Corella D, Shivappa N, et al. Dietary Inflammatory Index and Incidence of Cardiovascular Disease in the PREDIMED Study. *Nutrients*. **2015**;7(6):4124-38. Journal Article.
13. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. *Ther Adv Cardiovasc Dis*. **2017**;11(8):215-25. Journal Article.
14. van den Brink W, van Bilsen J, Salic K, Hoevenaars FPM, Verschuren L, Kleemann R, et al. Current and Future Nutritional Strategies to Modulate Inflammatory Dynamics in Metabolic Disorders. *Front Nutr*. **2019**;6:129. Journal Article.
15. Quideau S, Deffieux D, Douat-Casassus C, Pouysegu L. Plant polyphenols: chemical properties, biological activities, and synthesis. *Angew Chem Int Ed Engl*. **2011**;50(3):586-621. Journal Article.
16. Magrone T, Magrone M, Russo MA, Jirillo E. Recent Advances on the Anti-Inflammatory and Antioxidant Properties of Red Grape Polyphenols: In Vitro and In Vivo Studies. *Antioxidants (Basel)*. **2019**;9(1). Journal Article.
17. Serreli G, Boronat A, De la Torre R, Rodriguez-Morato J, Deiana M. Cardiovascular and Metabolic Benefits of Extra Virgin Olive Oil Phenolic Compounds: Mechanistic Insights from In Vivo Studies. *Cells*. **2024**;13(18). Journal Article.
18. Briones-Valdivieso C, Briones F, Orellana-Urzua S, Chichiarelli S, Saso L, Rodrigo R. Novel Multi-Antioxidant Approach for Ischemic Stroke Therapy Targeting the Role of Oxidative Stress. *Biomedicines*. **2024**;12(3). Journal Article.
19. Godos J, Ferri R, Lanza G, Caraci F, Vistorte AOR, Yelamos Torres V, et al. Mediterranean Diet and Sleep Features: A Systematic Review of Current Evidence. *Nutrients*. **2024**;16(2). Journal Article.
20. Andriantsitohaina R, Auger C, Chataigneau T, Etienne-Selloum N, Li H, Martinez MC, et al. Molecular mechanisms of the cardiovascular protective effects of polyphenols. *Br J Nutr*. **2012**;108(9):1532-49. Journal Article.

 doi:10.20944/preprints202505.1911.v1

21. Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr*. **2005**;81(1 Suppl):230S-42S. Journal Article.
22. Clark JL, Zahradka P, Taylor CG. Efficacy of flavonoids in the management of high blood pressure. *Nutr Rev*. **2015**;73(12):799-822. Journal Article.
23. Crozier A, Del Rio D, Clifford MN. Bioavailability of dietary flavonoids and phenolic compounds. *Mol Aspects Med*. **2010**;31(6):446-67. Journal Article.
24. Dubrovina AS, Kiselev KV. Regulation of stilbene biosynthesis in plants. *Planta*. **2017**;246(4):597-623. Journal Article.
25. Oyagbemi AA, Omobowale TO, Ola-Davies OE, Asenuga ER, Ajibade TO, Adejumobi OA, et al. Quercetin attenuates hypertension induced by sodium fluoride via reduction in oxidative stress and modulation of HSP 70/ERK/PPARgamma signaling pathways. *Biofactors*. **2018**;44(5):465-79. Journal Article.
26. Mahmoud AM, Hernandez Bautista RJ, Sandhu MA, Hussein OE. Beneficial Effects of Citrus Flavonoids on Cardiovascular and Metabolic Health. *Oxid Med Cell Longev*. **2019**;2019:5484138. Journal Article.
27. Gal R, Halmosi R, Gallyas F, Jr., Tschida M, Mutirangura P, Toth K, et al. Resveratrol and beyond: The Effect of Natural Polyphenols on the Cardiovascular System: A Narrative Review. *Biomedicines*. **2023**;11(11). Journal Article.
28. Bohn T. Bioavailability of Non-Provitamin A Carotenoids. *Curr Nutr Food Sci* **2008**(4):240-58. Journal Article.
29. Day AJ, Canada FJ, Diaz JC, Kroon PA, McLauchlan R, Faulds CB, et al. Dietary flavonoid and isoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase. *FEBS Lett*. **2000**;468(2-3):166-70. Journal Article.
30. Kosinska A, Andlauer W. Cocoa polyphenols are absorbed in Caco-2 cell model of intestinal epithelium. *Food Chem*. **2012**;135(3):999-1005. Journal Article.
31. Henry-Vitrac C, Desmouliere A, Girard D, Merillon JM, Krisa S. Transport, deglycosylation, and metabolism of trans-piceid by small intestinal epithelial cells. *Eur J Nutr*. **2006**;45(7):376-82. Journal Article.
32. Rahman B, Schneider HP, Broer A, Deitmer JW, Broer S. Helix 8 and helix 10 are involved in substrate recognition in the rat monocarboxylate transporter MCT1. *Biochemistry*. **1999**;38(35):11577-84. Journal Article.
33. Konishi Y, Kobayashi S, Shimizu M. Transepithelial transport of p-coumaric acid and gallic acid in Caco-2 cell monolayers. *Biosci Biotechnol Biochem*. **2003**;67(11):2317-24. Journal Article.
34. Selma MV, Espin JC, Tomas-Barberan FA. Interaction between phenolics and gut microbiota: role in human health. *J Agric Food Chem*. **2009**;57(15):6485-501. Journal Article.
35. Leonarduzzi G, Testa G, Sottero B, Gamba P, Poli G. Design and development of nanovehicle-based delivery systems for preventive or therapeutic supplementation with flavonoids. *Curr Med Chem*. **2010**;17(1):74-95. Journal Article.
36. Lambert JD, Sang S, Yang CS. Biotransformation of green tea polyphenols and the biological activities of those metabolites. *Mol Pharm*. **2007**;4(6):819-25. Journal Article.
37. Bohn T, Blackwood M, Francis D, Tian Q, Schwartz SJ, Clinton SK. Bioavailability of phytochemical constituents from a novel soy fortified lycopene rich tomato juice developed for targeted cancer prevention trials. *Nutr Cancer*. **2013**;65(6):919-29. Journal Article.
38. Kahkonen MP, Heinonen M. Antioxidant activity of anthocyanins and their aglycons. *J Agric Food Chem*. **2003**;51(3):628-33. Journal Article.

 doi:10.20944/preprints202505.1911.v1

39. Sharma P, Jha AB, Dubey RS, Pessarakli M. Reactive Oxygen Species, Oxidative Damage, and Antioxidative Defense Mechanism in Plants under Stressful Conditions. *Journal of Botany*. **2012**;2012(1):217037. Journal Article.
40. Krinsky NI. Mechanism of action of biological antioxidants. *Proc Soc Exp Biol Med*. **1992**;200(2):248-54. Journal Article.
41. O'Reilly JD, Mallet AI, McAnlis GT, Young IS, Halliwell B, Sanders TA, et al. Consumption of flavonoids in onions and black tea: lack of effect on F2-isoprostanes and autoantibodies to oxidized LDL in healthy humans. *Am J Clin Nutr*. **2001**;73(6):1040-4. Journal Article.
42. Pollard SE, Kuhnle GG, Vauzour D, Vafeiadou K, Tzounis X, Whiteman M, et al. The reaction of flavonoid metabolites with peroxynitrite. *Biochem Biophys Res Commun*. **2006**;350(4):960-8. Journal Article.
43. Lotito SB, Frei B. The increase in human plasma antioxidant capacity after apple consumption is due to the metabolic effect of fructose on urate, not apple-derived antioxidant flavonoids. *Free Radic Biol Med*. **2004**;37(2):251-8. Journal Article.
44. Cines DB, Pollak ES, Buck CA, Loscalzo J, Zimmerman GA, McEver RP, et al. Endothelial cells in physiology and in the pathophysiology of vascular disorders. *Blood*. **1998**;91(10):3527-61. Journal Article.
45. Sanches-Silva A, Testai L, Nabavi SF, Battino M, Pandima Devi K, Tejada S, et al. Therapeutic potential of polyphenols in cardiovascular diseases: Regulation of mTOR signaling pathway. *Pharmacol Res*. **2020**;152:104626. Journal Article.
46. Duarte J, Andriambeloson E, Diebolt M, Andriantsitohaina R. Wine polyphenols stimulate superoxide anion production to promote calcium signaling and endothelial-dependent vasodilatation. *Physiol Res*. **2004**;53(6):595-602. Journal Article.
47. Matsuo S, Nakamura Y, Takahashi M, Ouchi Y, Hosoda K, Nozawa M, et al. Effect of red wine and ethanol on production of nitric oxide in healthy subjects. *The American journal of cardiology*. **2001**;87(8):1029-31: A6. Journal Article.
48. Li HF, Chen SA, Wu SN. Evidence for the stimulatory effect of resveratrol on Ca(2+)-activated K+ current in vascular endothelial cells. *Cardiovasc Res*. **2000**;45(4):1035-45. Journal Article.
49. Andriambeloson E, Stoclet JC, Andriantsitohaina R. Mechanism of endothelial nitric oxide-dependent vasorelaxation induced by wine polyphenols in rat thoracic aorta. *Journal of cardiovascular pharmacology*. **1999**;33(2):248-54. Journal Article.
50. 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):1579-87. Journal Article.
51. Schramm DD, Wang JF, Holt RR, Ensunsa JL, Gonsalves JL, Lazarus SA, et al. Chocolate procyanidins decrease the leukotriene-prostacyclin ratio in humans and human aortic endothelial cells. *Am J Clin Nutr*. **2001**;73(1):36-40. Journal Article.
52. Ndiaye M, Chataigneau M, Lobysheva I, Chataigneau T, Schini-Kerth VB. 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 journal : official publication of the Federation of American Societies for Experimental Biology*. **2005**;19(3):455-7. Journal Article.
53. Fu W, Conklin BS, Lin PH, Lumsden AB, Yao Q, Chen C. Red wine prevents homocysteine-induced endothelial dysfunction in porcine coronary arteries. *J Surg Res*. **2003**;115(1):82-91. Journal Article.
54. Lugnier C, Schini VB. Characterization of cyclic nucleotide phosphodiesterases from cultured bovine aortic endothelial cells. *Biochem Pharmacol*. **1990**;39(1):75-84. Journal Article.

 doi:10.20944/preprints202505.1911.v1

55. Magrone T, Jirillo E. Potential application of dietary polyphenols from red wine to attaining healthy ageing. *Curr Top Med Chem*. **2011**;11(14):1780-96. Journal Article.
56. Magrone T, Jirillo E. Polyphenols from red wine are potent modulators of innate and adaptive immune responsiveness. *Proc Nutr Soc*. **2010**;69(3):279-85. Journal Article.
57. Marzulli G, Magrone T, Kawaguchi K, Kumazawa Y, Jirillo E. Fermented grape marc (FGM): immunomodulating properties and its potential exploitation in the treatment of neurodegenerative diseases. *Curr Pharm Des*. **2012**;18(1):43-50. Journal Article.
58. Marzulli G, Magrone T, Vonghia L, Kaneko M, Takimoto H, Kumazawa Y, et al. Immunomodulating and anti-allergic effects of Negroamaro and Koshu Vitis vinifera fermented grape marc (FGM). *Curr Pharm Des*. **2014**;20(6):864-8. Journal Article.
59. Al-Khayri JM, Sahana GR, Nagella P, Joseph BV, Alessa FM, Al-Mssallem MQ. Flavonoids as Potential Anti-Inflammatory Molecules: A Review. *Molecules*. **2022**;27(9). Journal Article.
60. Krauth V, Bruno F, Pace S, Jordan PM, Temml V, Preziosa Romano M, et al. Highly potent and selective 5-lipoxygenase inhibition by new, simple heteroaryl-substituted catechols for treatment of inflammation. *Biochem Pharmacol*. **2023**;208:115385. Journal Article.
61. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol Cell*. **2002**;10(2):417-26. Journal Article.
62. Gaidt MM, Hornung V. Pore formation by GSDMD is the effector mechanism of pyroptosis. *EMBO J*. **2016**;35(20):2167-9. Journal Article.
63. Liu D, Zeng X, Li X, Mehta JL, Wang X. Role of NLRP3 inflammasome in the pathogenesis of cardiovascular diseases. *Basic Res Cardiol*. **2018**;113(1):5. Journal Article.
64. Villalva M, Martinez-Garcia JJ, Jaime L, Santoyo S, Pelegrin P, Perez-Jimenez J. Polyphenols as NLRP3 inflammasome modulators in cardiometabolic diseases: a review of in vivo studies. *Food Funct*. **2023**;14(21):9534-53. Journal Article.
65. Jiang J, Gu X, Wang H, Ding S. Resveratrol improves cardiac function and left ventricular fibrosis after myocardial infarction in rats by inhibiting NLRP3 inflammasome activity and the TGF-beta1/SMAD2 signaling pathway. *PeerJ*. **2021**;9:e11501. Journal Article.
66. Feng H, Mou SQ, Li WJ, Zhang N, Zhou ZY, Ding W, et al. Resveratrol Inhibits Ischemia-Induced Myocardial Senescence Signals and NLRP3 Inflammasome Activation. *Oxid Med Cell Longev*. **2020**;2020:2647807. Journal Article.
67. Lv D, Cheng X, Tang L, Jiang M. The cardioprotective effect of total flavonoids on myocardial ischemia/reperfusion in rats. *Biomed Pharmacother*. **2017**;88:277-84. Journal Article.
68. Zhang Y, RuXian G. Didymin, a natural flavonoid, relieves the progression of myocardial infarction via inhibiting the NLR family pyrin domain containing 3 inflammasome. *Pharm Biol*. **2022**;60(1):2319-27. Journal Article.
69. Falk E. Pathogenesis of atherosclerosis. *J Am Coll Cardiol*. **2006**;47(8 Suppl):C7-12. Journal Article.
70. Caiati C, Pollice P, Favale S, Lepera ME. The Herbicide Glyphosate and Its Apparently Controversial Effect on Human Health: An Updated Clinical Perspective. *Endocr Metab Immune Disord Drug Targets*. **2020**;20(4):489-505. Journal Article.
71. Hopkins PN. Molecular biology of atherosclerosis. *Physiol Rev*. **2013**;93(3):1317-542. Journal Article.
72. Caiati C. Contrast-Enhanced Ultrasound Reveals That Lipoprotein Apheresis Improves Myocardial But Not Skeletal Muscle Perfusion. *JACC Cardiovasc Imaging*. **2019**;12(8 Pt 1):1441-3. Journal Article.

 doi:10.20944/preprints202505.1911.v1

73. Gould KL, Ornish D, Scherwitz L, Brown S, Edens RP, Hess MJ, et al. Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. *JAMA : the journal of the American Medical Association*. **1995**;274(11):894-901. Journal Article.
74. Caiati C, Iacovelli F, Mancini G, Lepera ME. Hidden Coronary Atherosclerosis Assessment but Not Coronary Flow Reserve Helps to Explain the Slow Coronary Flow Phenomenon in Patients with Angiographically Normal Coronary Arteries. *Diagnostics (Basel)*. **2022**;12(9):2173. Journal Article.
75. Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. *Nat Rev Immunol*. **2006**;6(7):508-19. Journal Article.
76. Singh RB, Mengi SA, Xu YJ, Arneja AS, Dhalla NS. Pathogenesis of atherosclerosis: A multifactorial process. *Exp Clin Cardiol*. **2002**;7(1):40-53. Journal Article.
77. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res*. **2000**;87(10):840-4. Journal Article.
78. Jennings LK. Mechanisms of platelet activation: need for new strategies to protect against platelet-mediated atherothrombosis. *Thromb Haemost*. **2009**;102(2):248-57. Journal Article.
79. Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med*. **2008**;359(9):938-49. Journal Article.
80. Feng AN, Chen YL, Chen YT, Ding YZ, Lin SJ. Red wine inhibits monocyte chemotactic protein-1 expression and modestly reduces neointimal hyperplasia after balloon injury in cholesterol-Fed rabbits. *Circulation*. **1999**;100(22):2254-9. Journal Article.
81. Rolnik A, Żuchowski J, Stochmal A, Olas B. Quercetin and kaempferol derivatives isolated from aerial parts of Lens culinaris Medik as modulators of blood platelet functions. *Industrial Crops and Products*. **2020**;152:112536. Journal Article.
82. Stein JH, Keevil JG, Wiebe DA, Aeschlimann S, Folts JD. Purple grape juice improves endothelial function and reduces the susceptibility of LDL cholesterol to oxidation in patients with coronary artery disease. *Circulation*. **1999**;100(10):1050-5. Journal Article.
83. Fuhrman B, Lavy A, Aviram M. Consumption of red wine with meals reduces the susceptibility of human plasma and low-density lipoprotein to lipid peroxidation. *Am J Clin Nutr*. **1995**;61(3):549-54. Journal Article.
84. Ciumarnean L, Milaciu MV, Runcan O, Vesa SC, Rachisan AL, Negrean V, et al. The Effects of Flavonoids in Cardiovascular Diseases. *Molecules*. **2020**;25(18). Journal Article.
85. Ornish D, Brown SE, Scherwitz LW, Billings JH, Armstrong WT, Ports TA, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet*. **1990**;336(8708):129-33. Journal Article.
86. Pinto P, Santos CN. Worldwide (poly)phenol intake: assessment methods and identified gaps. *Eur J Nutr*. **2017**;56(4):1393-408. Journal Article.
87. Fan FY, Sang LX, Jiang M. Catechins and Their Therapeutic Benefits to Inflammatory Bowel Disease. *Molecules*. **2017**;22(3). Journal Article.
88. Rodriguez-Ramiro I, Martin MA, Ramos S, Bravo L, Goya L. Comparative effects of dietary flavanols on antioxidant defences and their response to oxidant-induced stress on Caco2 cells. *Eur J Nutr*. **2011**;50(5):313-22. Journal Article.
89. Khan SG, Katiyar SK, Agarwal R, Mukhtar H. Enhancement of antioxidant and phase II enzymes by oral feeding of green tea polyphenols in drinking water to SKH-1 hairless mice: possible role in cancer chemoprevention. *Cancer Res*. **1992**;52(14):4050-2. Journal Article.
90. Ruskovska T, Massaro M, Carluccio MA, Arola-Arnal A, Muguerza B, Vanden Berghe W, et al. Systematic bioinformatic analysis of nutrigenomic data of flavanols in cell models of cardiometabolic disease. *Food Funct*. **2020**;11(6):5040-64. Journal Article.

 doi:10.20944/preprints202505.1911.v1

91. Godos J, Vitale M, Micek A, Ray S, Martini D, Del Rio D, et al. Dietary Polyphenol Intake, Blood Pressure, and Hypertension: A Systematic Review and Meta-Analysis of Observational Studies. *Antioxidants (Basel)*. **2019**;8(6). Journal Article.
92. Oleaga C, Ciudad CJ, Izquierdo-Pulido M, Noe V. Cocoa flavanol metabolites activate HNF-3beta, Sp1, and NFY-mediated transcription of apolipoprotein AI in human cells. *Mol Nutr Food Res*. **2013**;57(6):986-95. Journal Article.
93. Mena P, Bresciani L, Brindani N, Ludwig IA, Pereira-Caro G, Angelino D, et al. Phenyl-gamma-valerolactones and phenylvaleric acids, the main colonic metabolites of flavan-3-ols: synthesis, analysis, bioavailability, and bioactivity. *Nat Prod Rep*. **2019**;36(5):714-52. Journal Article.
94. Lee CC, Kim JH, Kim JS, Oh YS, Han SM, Park JHY, et al. 5-(3',4'-Dihydroxyphenyl-gamma-valerolactone), a Major Microbial Metabolite of Proanthocyanidin, Attenuates THP-1 Monocyte-Endothelial Adhesion. *International journal of molecular sciences*. **2017**;18(7). Journal Article.
95. Bhattacharjee N, Dua TK, Khanra R, Joardar S, Nandy A, Saha A, et al. Protocatechuic Acid, a Phenolic from Sansevieria roxburghiana Leaves, Suppresses Diabetic Cardiomyopathy via Stimulating Glucose Metabolism, Ameliorating Oxidative Stress, and Inhibiting Inflammation. *Front Pharmacol*. **2017**;8:251. Journal Article.
96. Rahman MM, Islam F, Or-Rashid MH, Mamun AA, Rahaman MS, Islam MM, et al. The Gut Microbiota (Microbiome) in Cardiovascular Disease and Its Therapeutic Regulation. *Front Cell Infect Microbiol*. **2022**;12:903570. Journal Article.
97. Garcia-Cordero J, Mateos R, Gonzalez-Ramila S, Seguido MA, Sierra-Cinos JL, Sarria B, et al. Dietary Supplements Containing Oat Beta-Glucan and/or Green Coffee (Poly)phenols Showed Limited Effect in Modulating Cardiometabolic Risk Biomarkers in Overweight/Obese Patients without a Lifestyle Intervention. *Nutrients*. **2023**;15(9). Journal Article.
98. Grassi D, Necozione S, Lippi C, Croce G, Valeri L, Pasqualetti P, et al. Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. *Hypertension*. **2005**;46(2):398-405. Journal Article.
99. Grassi D, Desideri G, Necozione S, Lippi C, Casale R, Properzi G, et al. Blood pressure is reduced and insulin sensitivity increased in glucose-intolerant, hypertensive subjects after 15 days of consuming high-polyphenol dark chocolate. *J Nutr*. **2008**;138(9):1671-6. Journal Article.
100. Heiss C, Jahn S, Taylor M, Real WM, Angeli FS, Wong ML, et al. Improvement of endothelial function with dietary flavanols is associated with mobilization of circulating angiogenic cells in patients with coronary artery disease. *J Am Coll Cardiol*. **2010**;56(3):218-24. Journal Article.
101. Flammer AJ, Sudano I, Wolfrum M, Thomas R, Enseleit F, Periat D, et al. Cardiovascular effects of flavanol-rich chocolate in patients with heart failure. *Eur Heart J*. **2012**;33(17):2172-80. Journal Article.
102. Nantz MP, Rowe CA, Bukowski JF, Percival SS. Standardized capsule of Camellia sinensis lowers cardiovascular risk factors in a randomized, double-blind, placebo-controlled study. *Nutrition*. **2009**;25(2):147-54. Journal Article.
103. Kafeshani M, Entezari MH, Karimian J, Pourmasoumi M, Maracy MR, Amini MR, et al. A comparative study of the effect of green tea and sour tea on blood pressure and lipid profile in healthy adult men. *ARYA Atheroscler*. **2017**;13(3):109-16. Journal Article.
104. Takahashi M, Miyashita M, Suzuki K, Bae SR, Kim HK, Wakisaka T, et al. Acute ingestion of catechin-rich green tea improves postprandial glucose status and increases serum thioredoxin concentrations in postmenopausal women. *Br J Nutr*. **2014**;112(9):1542-50. Journal Article.

 doi:10.20944/preprints202505.1911.v1

105. Diepvens K, Kovacs EM, Nijs IM, Vogels N, Westerterp-Plantenga MS. Effect of green tea on resting energy expenditure and substrate oxidation during weight loss in overweight females. *Br J Nutr*. **2005**;94(6):1026-34. Journal Article.
106. Frank J, George TW, Lodge JK, Rodriguez-Mateos AM, Spencer JP, Minihane AM, et al. Daily consumption of an aqueous green tea extract supplement does not impair liver function or alter cardiovascular disease risk biomarkers in healthy men. *J Nutr*. **2009**;139(1):58-62. Journal Article.
107. Miyazaki R, Kotani K, Ayabe M, Tsuzaki K, Shimada J, Sakane N, et al. Minor effects of green tea catechin supplementation on cardiovascular risk markers in active older people: a randomized controlled trial. *Geriatr Gerontol Int*. **2013**;13(3):622-9. Journal Article.
108. Xia N, Daiber A, Forstermann U, Li H. Antioxidant effects of resveratrol in the cardiovascular system. *Br J Pharmacol*. **2017**;174(12):1633-46. Journal Article.
109. Bagul PK, Deepthi N, Sultana R, Banerjee SK. Resveratrol ameliorates cardiac oxidative stress in diabetes through deacetylation of NFkB-p65 and histone 3. *J Nutr Biochem*. **2015**;26(11):1298-307. Journal Article.
110. Spanier G, Xu H, Xia N, Tobias S, Deng S, Wojnowski L, et al. Resveratrol reduces endothelial oxidative stress by modulating the gene expression of superoxide dismutase 1 (SOD1), glutathione peroxidase 1 (GPx1) and NADPH oxidase subunit (Nox4). *J Physiol Pharmacol*. **2009**;60 Suppl 4:111-6. Journal Article.
111. Xia N, Daiber A, Habermeier A, Closs EI, Thum T, Spanier G, et al. Resveratrol reverses endothelial nitric-oxide synthase uncoupling in apolipoprotein E knockout mice. *J Pharmacol Exp Ther*. **2010**;335(1):149-54. Journal Article.
112. Meng Q, Guo T, Li G, Sun S, He S, Cheng B, et al. Dietary resveratrol improves antioxidant status of sows and piglets and regulates antioxidant gene expression in placenta by Keap1-Nrf2 pathway and Sirt1. *Journal of Animal Science and Biotechnology*. **2018**;9(1):34. Journal Article.
113. Yeung F, Hoberg JE, Ramsey CS, Keller MD, Jones DR, Frye RA, et al. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. *EMBO J*. **2004**;23(12):2369-80. Journal Article.
114. Yang Y, Li S, Yang Q, Shi Y, Zheng M, Liu Y, et al. Resveratrol reduces the proinflammatory effects and lipopolysaccharide- induced expression of HMGB1 and TLR4 in RAW264.7 cells. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology*. **2014**;33(5):1283-92. Journal Article.
115. Zhang Y, Liu H, Tang W, Qiu Q, Peng J. Resveratrol prevents TNF-alpha-induced VCAM-1 and ICAM-1 upregulation in endothelial progenitor cells via reduction of NF-kappaB activation. *J Int Med Res*. **2020**;48(9):300060520945131. Journal Article.
116. Meng T, Xiao D, Muhammed A, Deng J, Chen L, He J. Anti-Inflammatory Action and Mechanisms of Resveratrol. *Molecules*. **2021**;26(1). Journal Article.
117. Gal R, Deres L, Horvath O, Eros K, Sandor B, Urban P, et al. Resveratrol Improves Heart Function by Moderating Inflammatory Processes in Patients with Systolic Heart Failure. *Antioxidants (Basel)*. **2020**;9(11). Journal Article.
118. Muslin AJ. MAPK signalling in cardiovascular health and disease: molecular mechanisms and therapeutic targets. *Clin Sci (Lond)*. **2008**;115(7):203-18. Journal Article.
119. Kondoh K, Nishida E. Regulation of MAP kinases by MAP kinase phosphatases. *Biochim Biophys Acta*. **2007**;1773(8):1227-37. Journal Article.
120. Song J, Huang Y, Zheng W, Yan J, Cheng M, Zhao R, et al. Resveratrol reduces intracellular reactive oxygen species levels by inducing autophagy through the AMPK-mTOR pathway. *Front Med*. **2018**;12(6):697-706. Journal Article.

 doi:10.20944/preprints202505.1911.v1

121. Zhang Y, Lu Y, Ong'achwa MJ, Ge L, Qian Y, Chen L, et al. Resveratrol Inhibits the TGF-beta1-Induced Proliferation of Cardiac Fibroblasts and Collagen Secretion by Downregulating miR-17 in Rat. *Biomed Res Int*. **2018**;2018:8730593. Journal Article.
122. Parsamanesh N, Asghari A, Sardari S, Tasbandi A, Jamialahmadi T, Xu S, et al. Resveratrol and endothelial function: A literature review. *Pharmacol Res*. **2021**;170:105725. Journal Article.
123. Forstermann U, Xia N, Li H. Roles of Vascular Oxidative Stress and Nitric Oxide in the Pathogenesis of Atherosclerosis. *Circ Res*. **2017**;120(4):713-35. Journal Article.
124. Ma S, Feng J, Zhang R, Chen J, Han D, Li X, et al. SIRT1 Activation by Resveratrol Alleviates Cardiac Dysfunction via Mitochondrial Regulation in Diabetic Cardiomyopathy Mice. *Oxid Med Cell Longev*. **2017**;2017:4602715. Journal Article.
125. Theodotou M, Fokianos K, Mouzouridou A, Konstantinou C, Aristotelous A, Prodromou D, et al. The effect of resveratrol on hypertension: A clinical trial. *Exp Ther Med*. **2017**;13(1):295-301. Journal Article.
126. Liu Y, Ma W, Zhang P, He S, Huang D. Effect of resveratrol on blood pressure: a meta-analysis of randomized controlled trials. *Clin Nutr*. **2015**;34(1):27-34. Journal Article.
127. Walker JM, Eckardt P, Aleman JO, da Rosa JC, Liang Y, Iizumi T, et al. The effects of trans-resveratrol on insulin resistance, inflammation, and microbiota in men with the metabolic syndrome: A pilot randomized, placebo-controlled clinical trial. *J Clin Transl Res*. **2019**;4(2):122-35. Journal Article.
128. Wong RH, Howe PR, Buckley JD, Coates AM, Kunz I, Berry NM. Acute resveratrol supplementation improves flow-mediated dilatation in overweight/obese individuals with mildly elevated blood pressure. *Nutr Metab Cardiovasc Dis*. **2011**;21(11):851-6. Journal Article.
129. Magyar K, Halmosi R, Palfi A, Feher G, Czopf L, Fulop A, et al. Cardioprotection by resveratrol: A human clinical trial in patients with stable coronary artery disease. *Clin Hemorheol Microcirc*. **2012**;50(3):179-87. Journal Article.
130. Fujitaka K, Otani H, Jo F, Jo H, Nomura E, Iwasaki M, et al. Modified resveratrol Longevinex improves endothelial function in adults with metabolic syndrome receiving standard treatment. *Nutr Res*. **2011**;31(11):842-7. Journal Article.
131. Marques B, Trindade M, Aquino JCF, Cunha AR, Gismondi RO, Neves MF, et al. Beneficial effects of acute trans-resveratrol supplementation in treated hypertensive patients with endothelial dysfunction. *Clin Exp Hypertens*. **2018**;40(3):218-23. Journal Article.
132. Asgary S, Karimi R, Momtaz S, Naseri R, Farzaei MH. Effect of resveratrol on metabolic syndrome components: A systematic review and meta-analysis. *Rev Endocr Metab Disord*. **2019**;20(2):173-86. Journal Article.
133. Hoseini A, Namazi G, Farrokhian A, Reiner Z, Aghadavod E, Bahmani F, et al. The effects of resveratrol on metabolic status in patients with type 2 diabetes mellitus and coronary heart disease. *Food Funct*. **2019**;10(9):6042-51. Journal Article.
134. Simental-Mendia LE, Guerrero-Romero F. Effect of resveratrol supplementation on lipid profile in subjects with dyslipidemia: A randomized double-blind, placebo-controlled trial. *Nutrition*. **2019**;58:7-10. Journal Article.
135. Militaru C, Donoiu I, Craciun A, Scorei ID, Bulearca AM, Scorei RI. Oral resveratrol and calcium fructoborate supplementation in subjects with stable angina pectoris: effects on lipid profiles, inflammation markers, and quality of life. *Nutrition*. **2013**;29(1):178-83. Journal Article.
136. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. *Biochem Pharmacol*. **2008**;75(4):787-809. Journal Article.

 doi:10.20944/preprints202505.1911.v1

137. Mansuri ML, Parihar P, Solanki I, Parihar MS. Flavonoids in modulation of cell survival signalling pathways. *Genes Nutr*. **2014**;9(3):400. Journal Article.
138. Hewlings SJ, Kalman DS. Curcumin: A Review of Its Effects on Human Health. *Foods*. **2017**;6(10). Journal Article.
139. Kukongviriyapan U, Pannangpetch P, Kukongviriyapan V, Donpunha W, Sompamit K, Surawattanawan P. Curcumin protects against cadmium-induced vascular dysfunction, hypertension and tissue cadmium accumulation in mice. *Nutrients*. **2014**;6(3):1194-208. Journal Article.
140. Tubsakul A, Sangartit W, Pakdeechote P, Kukongviriyapan V, Apaijit K, Kukongviriyapan U. Curcumin Mitigates Hypertension, Endothelial Dysfunction and Oxidative Stress in Rats with Chronic Exposure to Lead and Cadmium. *Tohoku J Exp Med*. **2021**;253(1):69-76. Journal Article.
141. Hu J, Shen T, Xie J, Wang S, He Y, Zhu F. Curcumin modulates covalent histone modification and TIMP1 gene activation to protect against vascular injury in a hypertension rat model. *Exp Ther Med*. **2017**;14(6):5896-902. Journal Article.
142. Yao Y, Wang W, Li M, Ren H, Chen C, Wang J, et al. Curcumin Exerts its Anti-hypertensive Effect by Down-regulating the AT1 Receptor in Vascular Smooth Muscle Cells. *Sci Rep*. **2016**;6:25579. Journal Article.
143. Birudaraju D, Cherukuri L, Kinninger A, Chaganti BT, Shaikh K, Hamal S, et al. A combined effect of Cavacurcumin, Eicosapentaenoic acid (Omega-3s), Astaxanthin and Gamma -linoleic acid (Omega-6) (CEAG) in healthy volunteers- a randomized, double-blind, placebo-controlled study. *Clin Nutr ESPEN*. **2020**;35:174-9. Journal Article.
144. Khajehdehi P, Zanjaninejad B, Aflaki E, Nazarinia M, Azad F, Malekmakan L, et al. Oral supplementation of turmeric decreases proteinuria, hematuria, and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis: a randomized and placebo-controlled study. *J Ren Nutr*. **2012**;22(1):50-7. Journal Article.
145. Campbell MS, Fleenor BS. The emerging role of curcumin for improving vascular dysfunction: A review. *Crit Rev Food Sci Nutr*. **2018**;58(16):2790-9. Journal Article.
146. Santos-Parker JR, Strahler TR, Bassett CJ, Bispham NZ, Chonchol MB, Seals DR. Curcumin supplementation improves vascular endothelial function in healthy middle-aged and older adults by increasing nitric oxide bioavailability and reducing oxidative stress. *Aging (Albany NY)*. **2017**;9(1):187-208. Journal Article.
147. Zhang L, Wang X, Si H. Synergistic anti-inflammatory effects and mechanisms of the combination of resveratrol and curcumin in human vascular endothelial cells and rodent aorta. *J Nutr Biochem*. **2022**;108:109083. Journal Article.
148. Jimenez-Lopez C, Carpena M, Lourenco-Lopes C, Gallardo-Gomez M, Lorenzo JM, Barba FJ, et al. Bioactive Compounds and Quality of Extra Virgin Olive Oil. *Foods*. **2020**;9(8). Journal Article.
149. Cicerale S, Conlan XA, Sinclair AJ, Keast RS. Chemistry and health of olive oil phenolics. *Crit Rev Food Sci Nutr*. **2009**;49(3):218-36. Journal Article.
150. Finicelli M, Squillaro T, Galderisi U, Peluso G. Polyphenols, the Healthy Brand of Olive Oil: Insights and Perspectives. *Nutrients*. **2021**;13(11). Journal Article.
151. Gonzalez-Correa JA, Navas MD, Munoz-Marin J, Trujillo M, Fernandez-Bolanos J, de la Cruz JP. Effects of hydroxytyrosol and hydroxytyrosol acetate administration to rats on platelet function compared to acetylsalicylic acid. *J Agric Food Chem*. **2008**;56(17):7872-6. Journal Article.
152. Munoz-Marin J, De la Cruz JP, Reyes JJ, Lopez-Villodres JA, Guerrero A, Lopez-Leiva I, et al. Hydroxytyrosyl alkyl ether derivatives inhibit platelet activation after oral administration to rats. *Food Chem Toxicol*. **2013**;58:295-300. Journal Article.

 doi:10.20944/preprints202505.1911.v1

153. Cicero AFG, Fogacci F, Di Micoli A, Veronesi M, Grandi E, Borghi C. Hydroxytyrosol-Rich Olive Extract for Plasma Cholesterol Control. Applied Sciences [Internet]. 2022; 12(19).
154. D'Addato S, Scandiani L, Mombelli G, Focanti F, Pelacchi F, Salvatori E, et al. Effect of a food supplement containing berberine, monacolin K, hydroxytyrosol and coenzyme Q(10) on lipid levels: a randomized, double-blind, placebo controlled study. *Drug Des Devel Ther*. **2017**;11:1585-92. Journal Article.
155. Quiros-Fernandez R, Lopez-Plaza B, Bermejo LM, Palma Milla S, Zangara A, Candela CG. Oral Supplement Containing Hydroxytyrosol and Punicalagin Improves Dyslipidemia in an Adult Population without Co-Adjuvant Treatment: A Randomized, Double-Blind, Controlled and Crossover Trial. *Nutrients*. **2022**;14(9). Journal Article.
156. Colica C, Di Renzo L, Trombetta D, Smeriglio A, Bernardini S, Cioccoloni G, et al. Antioxidant Effects of a Hydroxytyrosol-Based Pharmaceutical Formulation on Body Composition, Metabolic State, and Gene Expression: A Randomized Double-Blinded, Placebo-Controlled Crossover Trial. *Oxid Med Cell Longev*. **2017**;2017:2473495. Journal Article.
157. Lopez-Huertas E, Fonolla J. Hydroxytyrosol supplementation increases vitamin C levels in vivo. A human volunteer trial. *Redox Biol*. **2017**;11:384-9. Journal Article.
158. Naranjo A, Alvarez-Soria MJ, Aranda-Villalobos P, Martinez-Rodriguez AM, Martinez-Lara E, Siles E. Hydroxytyrosol, a Promising Supplement in the Management of Human Stroke: An Exploratory Study. *International journal of molecular sciences*. **2024**;25(9). Journal Article.
159. Alam M, Baenziger PS, Frels K. Emerging Trends in Wheat (Triticum spp.) Breeding: Implications for the Future. *Front Biosci (Elite Ed)*. **2024**;16(1):2. Journal Article.
160. Laddomada B, Caretto S, Mita G. Wheat Bran Phenolic Acids: Bioavailability and Stability in Whole Wheat-Based Foods. *Molecules*. **2015**;20(9):15666-85. Journal Article.
161. Li W, Sun XY, Mariga AM, Yang Q, Fang Y, Hu QH, et al. Effects of ferulic acid on the polymerization behavior of gluten protein and its components. *Food Hydrocolloids*. **2024**;147. Journal Article.
162. Calabriso N, Massaro M, Scoditti E, Pasqualone A, Laddomada B, Carluccio MA. Phenolic extracts from whole wheat biofortified bread dampen overwhelming inflammatory response in human endothelial cells and monocytes: major role of VCAM-1 and CXCL-10. *Eur J Nutr*. **2020**;59(6):2603-15. Journal Article.
163. Costabile G, Vitale M, Della Pepa G, Cipriano P, Vetrani C, Testa R, et al. A wheat aleurone-rich diet improves oxidative stress but does not influence glucose metabolism in overweight/obese individuals: Results from a randomized controlled trial. *Nutr Metab Cardiovasc Dis*. **2022**;32(3):715-26. Journal Article.
164. Salazar-Lopez NJ, Astiazaran-Garcia H, Gonzalez-Aguilar GA, Loarca-Pina G, Ezquerra-Brauer JM, Dominguez Avila JA, et al. Ferulic Acid on Glucose Dysregulation, Dyslipidemia, and Inflammation in Diet-Induced Obese Rats: An Integrated Study. *Nutrients*. **2017**;9(7). Journal Article.
165. Lu XL, Zhao CH, Yao XL, Zhang H. Quercetin attenuates high fructose feeding-induced atherosclerosis by suppressing inflammation and apoptosis via ROS-regulated PI3K/AKT signaling pathway. *Biomed Pharmacother*. **2017**;85:658-71. Journal Article.
166. Cao H, Jia Q, Shen D, Yan L, Chen C, Xing S. Quercetin has a protective effect on atherosclerosis via enhancement of autophagy in ApoE(-/-) mice. *Exp Ther Med*. **2019**;18(4):2451-8. Journal Article.
167. Kondo M, Izawa-Ishizawa Y, Goda M, Hosooka M, Kagimoto Y, Saito N, et al. Preventive Effects of Quercetin against the Onset of Atherosclerosis-Related Acute Aortic Syndromes in Mice. *International journal of molecular sciences*. **2020**;21(19). Journal Article.
168. Ferenczyova K, Kalocayova B, Bartekova M. Potential Implications of Quercetin and its Derivatives in Cardioprotection. *International journal of molecular sciences*. **2020**;21(5). Journal Article.

 doi:10.20944/preprints202505.1911.v1

169. Brown VA, Patel KR, Viskaduraki M, Crowell JA, Perloff M, Booth TD, et al. Repeat dose study of the cancer chemopreventive agent resveratrol in healthy volunteers: safety, pharmacokinetics, and effect on the insulin-like growth factor axis. *Cancer Res*. **2010**;70(22):9003-11. Journal Article.
170. la Porte C, Voduc N, Zhang G, Seguin I, Tardiff D, Singhal N, et al. Steady-State pharmacokinetics and tolerability of trans-resveratrol 2000 mg twice daily with food, quercetin and alcohol (ethanol) in healthy human subjects. *Clin Pharmacokinet*. **2010**;49(7):449-54. Journal Article.
171. Crowell JA, Korytko PJ, Morrissey RL, Booth TD, Levine BS. Resveratrol-associated renal toxicity. *Toxicol Sci*. **2004**;82(2):614-9. Journal Article.
172. Hu J, Webster D, Cao J, Shao A. The safety of green tea and green tea extract consumption in adults - Results of a systematic review. *Regul Toxicol Pharmacol*. **2018**;95:412-33. Journal Article.
173. Cruz-Correa M, Shoskes DA, Sanchez P, Zhao R, Hylind LM, Wexner SD, et al. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. *Clin Gastroenterol Hepatol*. **2006**;4(8):1035-8. Journal Article.
174. Hurrell R, Egli I. Iron bioavailability and dietary reference values. *Am J Clin Nutr*. **2010**;91(5):1461S-7S. Journal Article.