Effects of Hydroxytyrosol in Endothelial Functioning

Subjects: Pharmacology & Pharmacy

Contributor: Ubashini Vijakumaran , Janushaa Shanmugam , Jun Heng , Siti Azman , MUHAMMAD DAIN YAZID , Nur Atiqah Haizum Abdullah , Nadiah Sulaiman

Pharmacologists have been emphasizing and applying plant and herbal-based treatments in vascular diseases. Olives, for example, are a traditional symbol of the Mediterranean diet. Hydroxytyrosol is an olive-derived compound known for its antioxidant and cardioprotective effects. Acknowledging the merit of antioxidants in maintaining endothelial function warrants the application of hydroxytyrosol in endothelial dysfunction salvage and recovery. Endothelial dysfunction (ED) is an impairment of endothelial cells that adversely affects vascular homeostasis. Disturbance in endothelial functioning is a known precursor for atherosclerosis and, subsequently, coronary and peripheral artery disease.

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1. Hydroxytyrosol in Oxidative Stress-Induced Endothelial Dysfunction

Oxidative stress plays a vital role in endothelial dysfunction. Nitric oxide (NO), also known as endothelium-derived relaxing factor [1], is derived from the oxidation of L-arginine amino acid by nitric oxide synthase [2]. It facilitates vascular homeostasis by maintaining vascular integrity and inhibiting platelet aggregation and neutrophil adhesion [3][4]. Nitric oxide also prevents the proliferation of artery smooth muscle cells in defense against atherosclerosis and neointima hyperplasia formation [5][6]. In addition, an increase in oxidative stress causes superoxide anion to degrade NO and form peroxynitrite ONOO− [7] which decreases the bioavailability of NO while triggering endothelial impairment [1]. On the other hand, reactive oxygen species (ROS) is a fundamental aspect of oxidative stress in endothelial cells (ECs). Hydrogen peroxide, superoxide anions, and hydroxyl radicals are the sources of the intracellular ROS production [8]. Zheng et al. [9] systematically reviewed the sources of endothelial ROS production and their underlying mechanism on ECs death. Moreover, ROS also increases intracellular calcium concentration and activates proto-oncogenes and pro-inflammatory genes [10]. Ironically, antioxidants promote cellular health by scavenging ROS. Silva et al. [11] elaborate in detail that decreased NO availability leads to endothelial dysfunction and disrupts vascular tone regulation. Oxidative stress in ED is observed in the clinical setting with renovascular hypertension and Gilbert syndrome patients, which suggest ED-related oxidative stress could be a therapeutic target for atherosclerosis [12]. Hydroxytyrosol has been proven to reduce oxidative markers such as ROS and malondialdehyde (MDA) and upregulate NO generation in vitro and in vivo [13][14][15][16]. The ortodiphenolic structure of HT is responsible for scavenging free radicals [17]. Serreli et al. [18] reported conjugated

metabolites of hydroxytyrosol and tyrosol-enhanced endothelial nitric oxide synthase (eNOS) expression and decreased superoxide production by activating AKT serine/threonine kinase 1 (AKT 1). However, two studies reported contradictory outcomes when HT failed to increase NO production [10][11] significantly. Interestingly, both studies utilized the exact same dosage of 30 μM HT. In contrast, studies that utilize higher HT concentrations between 50 to 100 μM, reported a significant NO generation. Therefore, a higher HT dose between 50 to 100 μM could efficiently promote NO production in vitro. Another key player in oxidative stress is sirtuin 1 (SIRT1), a part of the seven-protein family that regulates cellular activity [19]. SIRT1 regulate vascular NO generation and vascular aging. Impaired SIRT1 causes oxidative stress and inflammation [11] which accelerates the vascular aging [20]. Hydroxytyrosol-nitric oxide (HT-NO) compound reduced ROS generation by activating sirtuin 1 (SIRT1) [21]. Bayram et al. [22] reported that olive oil enriched with HT supplementation had reduced oxidative biomarkers in senescence-accelerated mouse-prone 8 (SAMP8) mice, which were observed via upregulation of SIRT1 mRNA expression and the nuclear factor erythroid 2–related factor 2 (Nrf2)-dependent gene expression. Hydroxytyrosol was reported to upregulate SIRT1 to salvage TNF-α-induced vascular adventitial fibroblasts [23]. Thus, HT primarily targets the SIRT1 gene and protein activation to maintain endothelial functioning.

Nuclear factor-E2-related factor 2 (Nrf2) is a transcription factor that binds to antioxidant response elements that regulate numerous antioxidant genes [24]. Nrf2 is one of the most potent antioxidant pathways potentially preventing oxidative injuries in vascular endothelial cells [25][26]. Hydroxytyrosol at 50μM increases the nuclear accumulation of Nrf2 and heme-oxygenase 1 (HO-1) expression while mediating wound healing [27]. However, no difference in NO production was observed. A new derivative of hydroxytyrosol, peracetylated hydroxytyrosol (Per-HTy) showed anti-inflammatory activity by increasing Nrf2 and HO-1 in lipopolysaccharide-induced murine macrophages [28]. Apart from hydroxytyrosol, Parzonko et al. tested oleuropein and oleacein on endothelial progenitor cells, successfully preventing cell damage induced by angiotensin II by inducing Nrf2-HO-1 expression. HT and oleic acid were also shown to increase HO-1 expression in murine dermal fibroblast [29]. Consequently, HT protects against oxidative stress and potentially increases the re-endothelialisation ability of injured arterial walls and neovascularisation of the ischemic tissue [30]. HT also protected endothelial cells from H_2O_2 by increasing Nrf2 expression and activating Akt and ERK1/2 [31]. Furthermore, olive oil has also been shown to activate AKT phosphorylation and Nrf2 expression while mediating migration and proliferation in dermal fibroblast [32].

Sindona et al. [33] reported that 3,4-DHPEA-EDA, a dialdehyde oleanolic acid linked to hydroxytyrosol and 3,4-DHPEA-EA oleuropein aglycone, enriched NO generation, while HT alone does not offer the same results. In contrast, 50 μM HT upregulated NO production by activating eNOS protein expression in porcine artery-derived endothelial cells [16]; whereas 100 μM of HT and hydroxytyrosol acetate (HC) suppresses the production of oxidative stress markers, malondialdehyde (MDA) and ROS, thus increasing the production of superoxide dismutase (SOD) in TNF-induced HUVECs [34]. Hydroxytyrosol at 30 μM reduces phorbol myristate acetate (PMA)-induced mitochondrial superoxide production in human umbilical vein endothelial cells (HUVECs) [35]. Furthermore, HT has been a mitochondrial ROS scavenger in the PMA-inflamed HUVECs [36]. HT also reduces mitochondrial superoxide production by enhancing the superoxide dismutase SOD activity [35]. The inconsistencies and contrasting outcomes could be a limitation of hydroxytyrosol application in clinical trials.

The bioavailability and half-life of hydroxytyrosol are crucial in validating HT effects in general. Hydroxytyrosol undergoes phase-I and phase-II metabolism in the intestine and liver, leading to poor bioavailability [37]. Oleuropein, oleacein, and ole aglycone are hydrolyzed in the digestion system and generate HT as metabolites [38]. Thus, research on the activity of HT metabolites is equally significant. Hydroxytyrosol and its glucuronide metabolites (GC) decrease superoxide production in rat aortic ring experimental set-up [39]. Generally, 1 µM of HT is sufficient to provide minimal activation of antioxidant activity [40][41][42][43]. Besides, a range between 1 to 100 µM of HT [16][35][40][41][43][44] is typically utilized for in vitro studies. Vissers et al. [45] reviewed the metabolism, bioavailability, and excretion of olive oil phenols. They concluded that a range of 50 up to 100 µM is required to exhibit an antioxidant effect in vitro.

Concerning in vivo studies, 5 to 80 mg/kg of hydroxytyrosol was reported to exhibit positive health benefits [41][44][46]. Catalan et al. [41] reported a significant increase in HT phase-II metabolites such as HT sulphate and homovanillic acid sulfate in urine and feces, post 24 h of olive extract supplementation. Moreover, supplementation of 10 mg/kg olive extract to mice showed a significant decrease in E-selectin, MCP-1, and ICAM-1 expression in tunica intima, media, and adventitia region [41]. However, no significant differences were observed in lipid profile and atherosclerotic lesions. Interestingly, 50 mg/kg of hydroxytyrosol and its derivatives significantly reduced lipid peroxide and increased GSH [44]. HT also inhibited thromboxane synthesis, and weakly lowers prostacyclin production which demonstrates their anti-platelet aggregation effects [44]. However, the best dosage could not be determined due to high variability in the dose range, duration of treatment, frequency of treatments, and cell types utilized in all studies with HT.

2. Hydroxytyrosol Defence in Endothelial Dysfunction-Induced Atherosclerosis

Vascular inflammation is a precursor for endothelial dysfunction (ED). ED recruits platelets and immune cells, triggering the production of inflammatory cytokines and chemokines to subdue inflammation [47]. However, persistently elevated generation of these inflammatory molecules is detrimental to vascular cells. Dysfunctional ECs are activated; thus, expressing adhesion molecules such as vascular cell adhesion molecule (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1), which in turn start to recruit inflammatory cells contributing to the progression of the atherosclerosis [48]. Hydroxytyrosol suppresses the production of E-selectin, P-selectin, VCAM-1, and ICAM-1 in TNF α-induced porcine aortic ECs proving HT mechanism in managing inflammation [40]. HT at 1 to 30 µmol/L reduces PMA-induced TNF-α, IL- 1β, VCAM-1, and ICAM-1 production in HUVECs [35]. Interestingly, HT plasma metabolite, hydroxytyrosol-3-O-sulfate, reduces adhesion molecules, including monocyte chemoattractant protein-1(MCP-1), whereas HT on its own failed to exert the same effect [40]. 5 µM hydroxytyrosol-3-O-sulfate effectively reduces E-selectin and VCAM-1, even though HT as is failed to [40]. In another study, HT impedes cardiovascular biomarkers platelet aggregation, VCAM-1, and thromboxane B_2 [49].

Hydroxytyrosol acetate exerts an anti-inflammatory effect via the SIRT6-mediated PKM2 signaling pathway and inhibits TNF activity by TNF receptor superfamily member 1A (TNFRSF1A) signaling pathway [34]. Activation of SIRT6 improved endothelial function in haplo-insufficient mice by inhibiting NAD(P)H oxidase, which is responsible

for oxidative stress [50]. Hydroxytyrosol also countered systemic inflammation in mice by inhibiting the expression of inflammatory markers, cyclooxygenase-2 (COX2), IL-1b, IL-6, and TNF-α via mediating the SIRT6/PKM2 signaling pathway [14]. SIRT6 regulates autophagy in HUVECs and diabetic-induced mice as well [51]. Similarly, SIRT6 overexpression decreased atherosclerotic lesions and ECs dysfunction markers in both mice and humans [52]. Hence, HT can potentially manage ED indirectly by mediating the SIRT6 pathway in addition to regulating oxidative stress via inhibiting pro-inflammatory molecules.

Foam cell formation in atherosclerosis also decreased with hydroxytyrosol supplementation. Macrophages tend to penetrate damaged endothelial lining and subsequently transform into foam cells by engulfing the oxidized LDL [53]. Hydroxytyrosol reduces foam cell formation and flavin-containing monooxygenase 3 (FMO3), a cholesterol efflux modulator expression induced by acrolein [42]. Additionally, HT regulates the reverse cholesterol transport pathway by increasing ATP-binding cassette transporter (ABCA1) expression. ABCA1 is responsible for the efflux of cholesterol from lipid-laden macrophages. Enhanced ABCA1 protein levels potentially increased cholesterol efflux [54][55]. HT has also been shown to lower FMO3 and lipid recruitment while increasing ABCA1 expression in the acrolein-induced atherogenesis [42]. The aggregation of lipids in the endothelial space is a subsequent event of ED that leads to atherosclerosis. In the development of atherosclerosis, impaired cholesterol and low-density lipoprotein (LDL) transport enable LDL to infiltrate into subendothelial space, oxidized, and subsequently taken up by macrophages [56]. HT were found to activate the AMPK pathway and phosphorylation of p38 which subsequently regulates lipid metabolism in atherosclerotic mice [57].

3. Hydroxytyrosol Prevents Endothelial-to-Mesenchymal Transition

Endothelial-to-mesenchymal transition (EndMT) is a state of acquiring molecular and cellular changes into mesenchymal-like phenotype by endothelial cells [58][59]. EndMT leads to modification of cell proliferation, contraction, migration potential, and loss of cell polarity [60]. These pathological changes give rise to cardiovascular complications like neointima hyperplasia [61][62] and atherosclerosis [63][64][65]. Terzuoli et al. [66] demonstrates that hydroxytyrosol sulfate metabolite HT-3Os deplete IL-1β-induced EndMT markers like notch receptor 3 (NOTCH3), while matrix metalloproteinase-2 (MMP2) and matrix metalloproteinase-9 (MMP9) reversed the process by upregulating let-7 miRNA expression, CD31, and downregulating the transforming growth factor beta 1 (TGF-β) signaling pathway [66][67]. Similarly, olive extract prevented TGFβ1-induced airway epithelial-to-mesenchymal transition by reducing vimentin expression and reversing its native morphology [68]. Inflammation and altered shear-stress drives are among a few of the EndMT manifestations that enhance the atherosclerosis [59]. Evrard et al. [69] studied single-cell imaging of mesenchymal cells transitioned from endothelium-in-atherosclerotic aortas where 3 to 9% of the intimal plaque cells are found to be of ECs origin. EndMT-derived smooth muscle cells via uncontrolled TGFβ generation were also found to aggravate intimal thickening in newly grafted vessels [70].

4. Hydroxytyrosol Ameliorates Angiogenesis and Wound Healing

Tube formation and migration are essential in angiogenesis, wound healing, and tissue regeneration of injured tissues. In this context, by ingesting olive oil, hydroxytyrosol accelerates cell migration and angiogenesis at low doses of 1 to 5 μM [43]. HT also promotes wound healing and ECs capability by upregulating matrix metalloproteinase-2 MMP-2, Rho/Rho-associated coiled-coil containing protein kinase (Rho/ROCK), Phospo Src, Phospho Erk1/2, Erk1/2, RhoA, Rac1, and Ras protein expressions [43]. Furthermore, HT accelerates vascular formation with concurrent overexpression of vascular endothelial growth factor receptor VEGF-R2 and activation of the PI3K-Akt-eNOS signaling pathway. Hydroxytyrosol was also found to promote angiogenic through HIF-1 [71]. Co-treatment of hydroxytyrosol with pulsed electromagnetic fields (PEMFs) on HUVEC increases cell proliferation, migration, and protection against H_2O_2-induced apoptosis via upregulation of Akt, mTOR, and TGF-β expression [72]. Conversely, HT facilitates wound healing in porcine pulmonary artery-derived ECs via inducing HO-1 and Nrf2 mRNA expression and PI3K/Akt /ERK1/2 pathways [27].

5. Epigenetic Effect of Hydroxytyrosol in Endothelial Functioning

The epigenetic mechanism is defined as gene regulation that includes DNA methylation, microRNA (miRNA), and histone modification that alters phenotypic changes without changing the DNA sequence [73][74]. Polyphenol treatment that induces epigenetic mechanism is referred to as an “epigenetic diet [75].” DNA methylation is a part of the epigenetic mechanism where a methyl group is transferred onto the C5 position of the cytosine to form 5-methylcytosine to repress gene expression [76]. Hydroxytyrosol treatment reversed H_2O_2-induced miR-9 promoter’s hypomethylation during oxidative stress conditions [77]. Lopez et al. [78] analyzed transcriptomics of HT-supplemented mice and found two novel targets of HT fibroblast growth factor 21 (Fgf21) and a liver-secreted peptide hormone RORA (RAR Related Orphan Receptor A) in lipid metabolism. Recently, a systematic review was conducted on the nutrigenomic effects of phenolic compounds of extra virgin olive oil (EVOO) and olive oil involving in vitro, in vivo, and human studies [79]. They concluded EVOO and olive oil polyphenols are able to modulate epigenetic mechanisms. Hydroxytyrosol was found to regulate miRNAs in cardiovascular, cancer, and neurodegenerative diseases.

6. The Effects of Hydroxytyrosol and Its Derivatives on Hypertension

Hypertension is a commonly occurring chronic medical condition and is currently defined and characterized by the presence of a persistent elevation in systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) to values above 130 mmHg and 80 mmHg, respectively [80]. It also represents one of the most important modifiable cardiovascular risk factors, with approximately 54% and 47% of all global stroke and coronary artery disease cases due to hypertension [81]. Multiple studies have shown that supplementation with olive polyphenolic compounds such as HT and its derivatives reduce SBP and DBP [82][83]. Clinical trials conducted by Hermans et al., involving a total of 663 patients, recorded a mean SBP reduction of 13 ± 10 mmHg and DBP reduction of 7.1 ± 6.6 mmHg after 8 weeks of supplementation with 100 mg oleuropein (Ole) and 20 mg HT daily, with larger reductions seen in

patients with higher baseline blood pressures [83]. Lockyer et al. [84] observed a significant, albeit modest reduction in mean-patient daytime SBP/DBP values of −3.95 ± 11.48 /−3.00 ± 8.54 mmHg, 6 weeks post-treatment with 136 mg Ole, and 6 mg HT compared to their control group. Similarly, a randomized double-blind clinical trial conducted by Quirós-Fernández et al. [82] revealed that supplementation with hydroxytyrosol and punicalagin (PC), another phenolic compound derived from pomegranates, yield a significant −15.75 ± 9.9 mmHg reduction in the SBP of pre-hypertensive and hypertensive patients compared to their control group. The anti-hypertensive effects shown by HT are likely attributed to its reactive oxygen species (ROS)-scavenging capabilities and its modulation of redox-sensitive signaling pathways which affect a combination of factors, among them being enhanced endothelial nitric oxide synthase (eNOS) production [85]. Endothelial dysfunction is characteristic of hypertensive patients due to an increase in the production of the superoxide (O_2^-) anion that can readily and quickly bind to NO, producing peroxynitrite ($OONO^-$) which renders ECs inefficient [86]. Thus, deficiencies in eNOS and systemic nitrite levels are generally associated with hypertension and other pathophysiological cardiovascular modifications (i.e., atherosclerosis, coronary artery disease) in both animal models and humans given its importance in BP and flow regulation (e.g., vasodilation, inhibition of platelet aggregation, and inhibition of vascular smooth muscle cell growth) [87][88][89].

Supplementation with Ole, which can be enzymatically hydrolyzed into HT, generated a prophylactic effect that prevented the onset of hypertension in rats and mice in a dose-dependent fashion, attributing to the upregulation of nitric oxide synthase protein expression [90][91]. Storniolo et al. [92] investigated the effects of HT in combination with other polyphenolic extracts from extra virgin olive oil using an in vitro model deficient in intracellular NO due to impaired eNOS phosphorylation. HT treatment increased phosphorylated eNOS with the phosphorylation process mediated through the PI3K/Akt signaling pathway, resulting in increased intracellular NO levels. The treatment group also showed a reduction in levels of endothelin-1 (ET-1), a potent vasoconstrictor which acts in contrast to NO and is highly expressed in hypertensive patients [92]. A combination of these factors contributes to the antihypertensive effects of HT and its derivatives [92][93].

HT's effects on NO could result from NAD^+-dependent deacetylase and sirtuin 1 (SIRT1) activation, which is involved in the regulation of NO production and NO-mediated endothelium-dependent vascular relaxation through the deacetylation and activation of eNOS [94]. Molecular docking studies showed good compatibility between HT and SIRT1, allowing both to directly bind to each other to activate SIRT1-mediated downstream signaling pathways such as the SIRT1-FOXO1-SOD1 pathway which has been shown to exert anti-hypertensive effects [21][23][95]. Increased levels of phosphorylated eNOS were detected post-treatment with a hydroxytyrosol-nitric oxide composite (HT-NO), but eNOS levels were decreased when SIRT1 expression or function was inhibited [21][23]. A separate in vivo study observed increased levels of activated eNOS when SIRT1 expression was upregulated [96], suggesting that certain compounds can indeed regulate eNOS activity and NO production; HT being one of them.

HT and its derivatives possess calcium antagonistic properties which play a significant role in blood pressure control and, therefore, their anti-hypertensive effects [97]. Gilani et al. showed that the reduction in mean arterial BP seen in olive extract-treated rats was dose-dependent, which is a common characteristic for calcium channel blockers, and followed a similar trend to verapamil, signifying that the anti-hypertensive effect of the treatment is

likely calcium channel-mediated [97]. Scheffler et al. [98] obtained comparable results in their study and concluded that Ole suppresses L-type Ca^{2+} channels directly and reversibly in a dose-dependent fashion. These studies suggest that Ca^{2+} antagonism is one of the mechanisms of action for which HT and its derivatives carry out their antihypertensive effects. Hydroxytyrosol and its derivatives demonstrate a positive anti-hypertensive effect, mainly occurring through SIRT1-mediated upregulation of eNOS deacetylation and phosphorylation, resulting in higher systemic NO levels promoting vasodilation and other BP-lowering effects. Their calcium channel-blocking properties reduce vascular resistance and reactivity to vasoconstriction-promoting and BP-raising signals from the sympathetic nervous system and RAAS, among others.

7. Hydroxytyrosol and Vascular Aging-Induced Endothelial Dysfunction

Aging is a continuous process where the body's physiological function starts to decrease starting from early adulthood. It is an unavoidable risk factor leading to cardiovascular diseases (CVD), as the prevalence of CVD increases with age [99]. In addition, despite being in excellent cardiovascular health condition, one cannot reverse the effect of aging in the progressive decline of cardiovascular homeostasis and function. As people age, the blood vessels undergo physiological changes leading to reduced vascular function, deterioration of endothelial function, and arterial stiffness [100]. There are several mechanisms involved in the progression of age-related endothelial dysfunction. The increase in oxidative stress, vascular inflammation, and shifts in conserved molecular pathways all contribute to the aging process [101]. One hallmark of endothelial dysfunction is the reduction of nitric oxide (NO). NO is a critical vasodilating molecule important for anti-thrombotic, anti-inflammatory and antioxidant functions [102]. Several age-related factors have been shown to contribute to the imbalance in the production and degradation of NO that results in endothelial dysfunction. Studies show increased arginase activity in the elderly. This, in return, leads to a deficiency of L-arginine and a reduction of NO [103]. In addition, the scavenging of NOs by reactive oxygen species during age-induced oxidative stress can reduce NOs availability [101]. Aged-induced oxidative stress produces a high concentration of O^-_2 which lead to the inactivation of NO and upregulation of peroxynitrite ($ONOO^-$) and nicotinamide adenine dinucleotide phosphate (NADPH), which further induce oxidative stress, continuing this vicious cycle of NO depletion [104].

Inflammatory responses are also associated with vascular aging. Chronic low-grade inflammation is a characteristic of age-related diseases which has been demonstrated by an increase in pro-inflammatory molecules in aging animal models [101][105]. The inflammatory responses are initiated by the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1β). This resulted in an increased expression of cell adhesion molecules (CAMs) expressed by the endothelial cells resulting in the recruitment and adhesion of circulating leukocytes to the endothelial wall [106]. Thus, changes to the structure of the vessel wall leading to endothelial dysfunction resulted. Both oxidative stress and inflammation reduce NO bioavailability, which can impair endothelial function in the elderly. An animal study by Wang et. al. shows that mice treated with a high dose of HT produce more antioxidant enzymes and anti-inflammatory cytokines [107]. HT exerts its anti-inflammatory property by down-regulating the expression of iNOS; thus, inhibiting the activation of NF-κB [108].

Since HT has been shown to exhibit antioxidant and anti-inflammatory properties, more studies were performed to look at the effect of HT in preventing age-related diseases such as neurodegenerative disorders [109][110]. Many studies have been done to ascertain the effect of HT on neurodegenerative diseases. However, not many have ventured into the impact of HT on vascular aging. As the mechanisms leading to vascular aging are closely related to other age-related diseases with the hallmark of increased oxidative stress and increase systemic inflammation, it is intriguing to see the potential of HT in attenuating vascular aging.

References

1. Cyr, A.R.; Huckaby, L.V.; Shiva, S.S.; Zuckerbraun, B.S. Nitric Oxide and Endothelial Dysfunction. Crit. Care Clin. 2020, 36, 307–321.
2. Tousoulis, D.; Kampoli, A.M.; Tentolouris, C.; Papageorgiou, N.; Stefanadis, C. The role of nitric oxide on endothelial function. Curr. Vasc. Pharm. 2012, 10, 4–18.
3. Zang, Y.; Popat, K.C.; Reynolds, M.M. Nitric oxide-mediated fibrinogen deposition prevents platelet adhesion and activation. Biointerphases 2018, 13, 06e403.
4. Galkina, S.I.; Golenkina, E.A.; Viryasova, G.M.; Romanova, Y.M.; Sud'ina, G.F. Nitric Oxide in Life and Death of Neutrophils. Curr. Med. Chem. 2019, 26, 5764–5780.
5. Tabata, K.; Komori, K.; Otsuka, R.; Kajikuri, J.; Itoh, T. Enhancement of Nitric Oxide Production Is Responsible for Minimal Intimal Hyperplasia of Autogenous Rabbit Arterial Grafts. Circ. J. 2017, 81, 1222–1230.
6. Somarathna, M.; Hwang, P.T.; Millican, R.C.; Alexander, G.C.; Isayeva-Waldrop, T.; Sherwood, J.A.; Brott, B.C.; Falzon, I.; Northrup, H.; Shiu, Y.T.; et al. Nitric oxide releasing nanomatrix gel treatment inhibits venous intimal hyperplasia and improves vascular remodeling in a rodent arteriovenous fistula. Biomaterials 2022, 280, 121254.
7. Incalza, M.A.; D'Oria, R.; Natalicchio, A.; Perrini, S.; Laviola, L.; Giorgino, F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vasc. Pharm. 2018, 100, 1–19.
8. Mittler, R. ROS Are Good. Trends Plant Sci. 2017, 22, 11–19.
9. Zheng, D.; Liu, J.; Piao, H.; Zhu, Z.; Wei, R.; Liu, K. ROS-triggered endothelial cell death mechanisms: Focus on pyroptosis, parthanatos, and ferroptosis. Front. Immunol. 2022, 13, 1039241.
10. Senoner, T.; Dichtl, W. Oxidative Stress in Cardiovascular Diseases: Still a Therapeutic Target? Nutrients 2019, 11, 2090.

11. Silva, B.; Pernomian, L.; Bendhack, L. Contribution of oxidative stress to endothelial dysfunction in hypertension. Front. Physiol. 2012, 3, 441.
12. Higashi, Y.; Maruhashi, T.; Noma, K.; Kihara, Y. Oxidative stress and endothelial dysfunction: Clinical evidence and therapeutic implications. Trends Cardiovasc. Med. 2014, 24, 165–169.
13. Yao, F.; Jin, Z.; Lv, X.; Zheng, Z.; Gao, H.; Deng, Y.; Liu, Y.; Chen, L.; Wang, W.; He, J.; et al. Hydroxytyrosol Acetate Inhibits Vascular Endothelial Cell Pyroptosis via the HDAC11 Signaling Pathway in Atherosclerosis. Front. Pharm. 2021, 12, 656272.
14. Fuccelli, R.; Fabiani, R.; Rosignoli, P. Hydroxytyrosol Exerts Anti-Inflammatory and Anti-Oxidant Activities in a Mouse Model of Systemic Inflammation. Molecules 2018, 23, 3212.
15. Mosca, A.; Crudele, A.; Smeriglio, A.; Braghini, M.R.; Panera, N.; Comparcola, D.; Alterio, A.; Sartorelli, M.R.; Tozzi, G.; Raponi, M.; et al. Antioxidant activity of Hydroxytyrosol and Vitamin E reduces systemic inflammation in children with paediatric NAFLD. Dig. Liver Dis. 2021, 53, 1154–1158.
16. Zrelli, H.; Wu, C.W.; Zghonda, N.; Shimizu, H.; Miyazaki, H. Combined treatment of hydroxytyrosol with carbon monoxide-releasing molecule-2 prevents TNF α-induced vascular endothelial cell dysfunction through NO production with subsequent NFκB inactivation. Biomed. Res. Int. 2013, 2013, 912431.
17. Martínez-Zamora, L.; Peñalver, R.; Ros, G.; Nieto, G. Olive Tree Derivatives and Hydroxytyrosol: Their Potential Effects on Human Health and Its Use as Functional Ingredient in Meat. Foods 2021, 10, 2611.
18. Serreli, G.; Le Sayec, M.; Diotallevi, C.; Teissier, A.; Deiana, M.; Corona, G. Conjugated Metabolites of Hydroxytyrosol and Tyrosol Contribute to the Maintenance of Nitric Oxide Balance in Human Aortic Endothelial Cells at Physiologically Relevant Concentrations. Molecules 2021, 26, 7480.
19. Singh, V.; Ubaid, S. Role of Silent Information Regulator 1 (SIRT1) in Regulating Oxidative Stress and Inflammation. Inflammation 2020, 43, 1589–1598.
20. Kitada, M.; Ogura, Y.; Koya, D. The protective role of Sirt1 in vascular tissue: Its relationship to vascular aging and atherosclerosis. Aging (Albany NY) 2016, 8, 2290–2307.
21. Wang, W.; Shang, C.; Zhang, W.; Jin, Z.; Yao, F.; He, Y.; Wang, B.; Li, Y.; Zhang, J.; Lin, R. Hydroxytyrosol NO regulates oxidative stress and NO production through SIRT1 in diabetic mice and vascular endothelial cells. Phytomedicine 2019, 52, 206–215.
22. Bayram, B.; Ozcelik, B.; Grimm, S.; Roeder, T.; Schrader, C.; Ernst, I.M.; Wagner, A.E.; Grune, T.; Frank, J.; Rimbach, G. A diet rich in olive oil phenolics reduces oxidative stress in the heart of SAMP8 mice by induction of Nrf2-dependent gene expression. Rejuvenation Res. 2012, 15, 71–81.

23. Wang, W.; Jing, T.; Yang, X.; He, Y.; Wang, B.; Xiao, Y.; Shang, C.; Zhang, J.; Lin, R. Hydroxytyrosol regulates the autophagy of vascular adventitial fibroblasts through the SIRT1-mediated signaling pathway. Can. J. Physiol Pharm. 2018, 96, 88–96.
24. Tonelli, C.; Chio, I.I.C.; Tuveson, D.A. Transcriptional Regulation by Nrf2. Antioxid. Redox Signal. 2018, 29, 1727–1745.
25. Chen, B.; Lu, Y.; Chen, Y.; Cheng, J. The role of Nrf2 in oxidative stress-induced endothelial injuries. J. Endocrinol. 2015, 225, R83–R99.
26. Zhang, Q.; Liu, J.; Duan, H.; Li, R.; Peng, W.; Wu, C. Activation of Nrf2/HO-1 signaling: An important molecular mechanism of herbal medicine in the treatment of atherosclerosis via the protection of vascular endothelial cells from oxidative stress. J. Adv. Res. 2021, 34, 43–63.
27. Zrelli, H.; Kusunoki, M.; Miyazaki, H. Role of Hydroxytyrosol-dependent Regulation of HO-1 Expression in Promoting Wound Healing of Vascular Endothelial Cells via Nrf2 De Novo Synthesis and Stabilization. Phytother. Res. 2015, 29, 1011–1018.
28. Montoya, T.; Aparicio-Soto, M.; Castejón, M.L.; Rosillo, M.; Sánchez-Hidalgo, M.; Begines, P.; Fernández-Bolaños, J.G.; Alarcón-de-la-Lastra, C. Peracetylated hydroxytyrosol, a new hydroxytyrosol derivate, attenuates LPS-induced inflammatory response in murine peritoneal macrophages via regulation of non-canonical inflammasome, Nrf2/HO1 and JAK/STAT signaling pathways. J. Nutr. Biochem. 2018, 57, 110–120.
29. Romana-Souza, B.; Saguie, B.O.; Pereira de Almeida Nogueira, N.; Paes, M.; Dos Santos Valença, S.; Atella, G.C.; Monte-Alto-Costa, A. Oleic acid and hydroxytyrosol present in olive oil promote ROS and inflammatory response in normal cultures of murine dermal fibroblasts through the NF-κB and NRF2 pathways. Food Res. Int. 2020, 131, 108984.
30. Parzonko, A.; Czerwińska, M.E.; Kiss, A.K.; Naruszewicz, M. Oleuropein and oleacein may restore biological functions of endothelial progenitor cells impaired by angiotensin II via activation of Nrf2/heme oxygenase-1 pathway. Phytomedicine 2013, 20, 1088–1094.
31. Zrelli, H.; Matsuoka, M.; Kitazaki, S.; Araki, M.; Kusunoki, M.; Zarrouk, M.; Miyazaki, H. Hydroxytyrosol induces proliferation and cytoprotection against oxidative injury in vascular endothelial cells: Role of Nrf2 activation and HO-1 induction. J. Agric. Food Chem. 2011, 59, 4473–4482.
32. de S Ribeiro, B.C.; de C Faria, R.V.; de S Nogueira, J.; Valença, S.S.; Chen, L.; Romana-Souza, B. Olive oil promotes the survival and migration of dermal fibroblasts through Nrf2 pathway activation. Lipids 2022. online ahead of print.
33. Sindona, G.; Caruso, A.; Cozza, A.; Fiorentini, S.; Lorusso, B.; Marini, E.; Nardi, M.; Procopio, A.; Zicari, S. Anti-inflammatory effect of 3,4-DHPEA-EDA on primary human vascular endothelial cells. Curr. Med. Chem. 2012, 19, 4006–4013.

34. Yao, F.; Yang, G.; Xian, Y.; Wang, G.; Zheng, Z.; Jin, Z.; Xie, Y.; Wang, W.; Gu, J.; Lin, R. The protective effect of hydroxytyrosol acetate against inflammation of vascular endothelial cells partly through the SIRT6-mediated PKM2 signaling pathway. Food Funct. 2019, 10, 5789–5803.
35. Calabriso, N.; Gnoni, A.; Stanca, E.; Cavallo, A.; Damiano, F.; Siculella, L.; Carluccio, M.A. Hydroxytyrosol Ameliorates Endothelial Function under Inflammatory Conditions by Preventing Mitochondrial Dysfunction. Oxidative Med. Cell. Longev. 2018, 2018, 9086947.
36. Karković Marković, A.; Torić, J.; Barbarić, M.; Jakobušić Brala, C. Hydroxytyrosol, Tyrosol and Derivatives and Their Potential Effects on Human Health. Molecules 2019, 24, 2001.
37. Robles-Almazan, M.; Pulido-Moran, M.; Moreno-Fernandez, J.; Ramirez-Tortosa, C.; Rodriguez-Garcia, C.; Quiles, J.L.; Ramirez-Tortosa, M. Hydroxytyrosol: Bioavailability, toxicity, and clinical applications. Food Res. Int. 2018, 105, 654–667.
38. Domínguez-Perles, R.; Auñón, D.; Ferreres, F.; Gil-Izquierdo, A. Gender differences in plasma and urine metabolites from Sprague–Dawley rats after oral administration of normal and high doses of hydroxytyrosol, hydroxytyrosol acetate, and DOPAC. Eur. J. Nutr. 2017, 56, 215–224.
39. Peyrol, J.; Meyer, G.; Obert, P.; Dangles, O.; Pechère, L.; Amiot, M.-J.; Riva, C. Involvement of bilitranslocase and beta-glucuronidase in the vascular protection by hydroxytyrosol and its glucuronide metabolites in oxidative stress conditions. J. Nutr. Biochem. 2018, 51, 8–15.
40. Catalán, Ú.; López de Las Hazas, M.C.; Rubió, L.; Fernández-Castillejo, S.; Pedret, A.; de la Torre, R.; Motilva, M.J.; Solà, R. Protective effect of hydroxytyrosol and its predominant plasmatic human metabolites against endothelial dysfunction in human aortic endothelial cells. Mol. Nutr. Food Res. 2015, 59, 2523–2536.
41. Catalán, Ú.; López de las Hazas, M.-C.; Piñol, C.; Rubió, L.; Motilva, M.-J.; Fernandez-Castillejo, S.; Solà, R. Hydroxytyrosol and its main plasma circulating metabolites attenuate the initial steps of atherosclerosis through inhibition of the MAPK pathway. J. Funct. Foods 2018, 40, 280–291.
42. Wu, X.; Li, C.; Mariyam, Z.; Jiang, P.; Zhou, M.; Zeb, F.; Haq, I.U.; Chen, A.; Feng, Q. Acrolein-induced atherogenesis by stimulation of hepatic flavin containing monooxygenase 3 and a protection from hydroxytyrosol. J. Cell. Physiol. 2018, 234, 475–485.
43. Abate, M.; Pisanti, S.; Caputo, M.; Citro, M.; Vecchione, C.; Martinelli, R. 3-Hydroxytyrosol Promotes Angiogenesis In Vitro by Stimulating Endothelial Cell Migration. Int. J. Mol. Sci. 2020, 21, 3657.
44. Muñoz-Marín, J.; De la Cruz, J.P.; Reyes, J.J.; López-Villodres, J.A.; Guerrero, A.; López-Leiva, I.; Espartero, J.L.; Labajos, M.T.; González-Correa, J.A. Hydroxytyrosyl alkyl ether derivatives inhibit platelet activation after oral administration to rats. Food Chem. Toxicol. 2013, 58, 295–300.
45. Vissers, M.N.; Zock, P.L.; Katan, M.B. Bioavailability and antioxidant effects of olive oil phenols in humans: A review. Eur. J. Clin. Nutr. 2004, 58, 955–965.

46. Lopez, S.; Montserrat-de la Paz, S.; Lucas, R.; Bermudez, B.; Abia, R.; Morales, J.C.; Muriana, F.J.G. Effect of metabolites of hydroxytyrosol on protection against oxidative stress and inflammation in human endothelial cells. J. Funct. Foods 2017, 29, 238–247.
47. D'Angelo, C.; Goldeck, D.; Pawelec, G.; Gaspari, L.; Di Iorio, A.; Paganelli, R. Exploratory study on immune phenotypes in Alzheimer's disease and vascular dementia. Eur. J. Neurol. 2020, 27, 1887–1894.
48. Zhu, Y.; Xian, X.; Wang, Z.; Bi, Y.; Chen, Q.; Han, X.; Tang, D.; Chen, R. Research Progress on the Relationship between Atherosclerosis and Inflammation. Biomolecules 2018, 8, 80.
49. López-Villodres, J.A.; Abdel-Karim, M.; De La Cruz, J.P.; Rodríguez-Pérez, M.D.; Reyes, J.J.; Guzmán-Moscoso, R.; Rodriguez-Gutierrez, G.; Fernández-Bolaños, J.; González-Correa, J.A. Effects of hydroxytyrosol on cardiovascular biomarkers in experimental diabetes mellitus. J. Nutr. Biochem. 2016, 37, 94–100.
50. Greiten, L.E.; Zhang, B.; Roos, C.M.; Hagler, M.; Jahns, F.-P.; Miller, J.D. Sirtuin 6 Protects Against Oxidative Stress and Vascular Dysfunction in Mice. Front. Physiol. 2021, 12, 753501.
51. Tong, J.; Ji, B.; Gao, Y.-H.; Lin, H.; Ping, F.; Chen, F.; Liu, X.-B. Sirt6 regulates autophagy in AGE-treated endothelial cells via KLF4. Nutr. Metab. Cardiovasc. Dis. 2022, 32, 755–764.
52. Xu, S.; Yin, M.; Koroleva, M.; Mastrangelo, M.A.; Zhang, W.; Bai, P.; Little, P.J.; Jin, Z.G. SIRT6 protects against endothelial dysfunction and atherosclerosis in mice. Aging (Albany NY) 2016, 8, 1064–1082.
53. Wang, B.; Tang, X.; Yao, L.; Wang, Y.; Chen, Z.; Li, M.; Wu, N.; Wu, D.; Dai, X.; Jiang, H.; et al. Disruption of USP9X in macrophages promotes foam cell formation and atherosclerosis. J. Clin. Investig. 2022, 132, e154217.
54. Ren, K.; Li, H.; Zhou, H.F.; Liang, Y.; Tong, M.; Chen, L.; Zheng, X.L.; Zhao, G.J. Mangiferin promotes macrophage cholesterol efflux and protects against atherosclerosis by augmenting the expression of ABCA1 and ABCG1. Aging (Albany NY) 2019, 11, 10992–11009.
55. Ogura, M. HDL, cholesterol efflux, and ABCA1: Free from good and evil dualism. J. Pharm. Sci. 2022, 150, 81–89.
56. Summerhill, V.I.; Grechko, A.V.; Yet, S.-F.; Sobenin, I.A.; Orekhov, A.N. The Atherogenic Role of Circulating Modified Lipids in Atherosclerosis. Int. J. Mol. Sci. 2019, 20, 3561.
57. Zhang, X.; Qin, Y.; Wan, X.; Liu, H.; Iv, C.; Ruan, W.; Lu, L.; He, L.; Guo, X. Hydroxytyrosol Plays Antiatherosclerotic Effects through Regulating Lipid Metabolism via Inhibiting the p38 Signal Pathway. Biomed. Res. Int. 2020, 2020, 5036572.
58. Dejana, E.; Hirschi, K.K.; Simons, M. The molecular basis of endothelial cell plasticity. Nat. Commun 2017, 8, 14361.

59. Kovacic, J.C.; Dimmeler, S.; Harvey, R.P.; Finkel, T.; Aikawa, E.; Krenning, G.; Baker, A.H. Endothelial to Mesenchymal Transition in Cardiovascular Disease: JACC State-of-the-Art Review. J. Am. Coll. Cardiol. 2019, 73, 190–209.

60. Li, A.; Peng, W.; Xia, X.; Li, R.; Wang, Y.; Wei, D. Endothelial-to-Mesenchymal Transition: A Potential Mechanism for Atherosclerosis Plaque Progression and Destabilization. DNA Cell Biol. 2017, 36, 883–891.

61. Chen, D.; Zhang, C.; Chen, J.; Yang, M.; Afzal, T.A.; An, W.; Maguire, E.M.; He, S.; Luo, J.; Wang, X.; et al. miRNA-200c-3p promotes endothelial to mesenchymal transition and neointimal hyperplasia in artery bypass grafts. J. Pathol. 2021, 253, 209–224.

62. Zhong, C.M.; Li, S.; Wang, X.W.; Chen, D.; Jiang, Z.L.; Zhang, C.; He, X.J.; Huang, C.; Jiang, Y.J.; Wu, Q.C. MicroRNA-92a -mediated endothelial to mesenchymal transition controls vein graft neointimal lesion formation. Exp. Cell Res. 2021, 398, 112402.

63. Xu, S.; Ilyas, I.; Little, P.J.; Li, H.; Kamato, D.; Zheng, X.; Luo, S.; Li, Z.; Liu, P.; Han, J.; et al. Endothelial Dysfunction in Atherosclerotic Cardiovascular Diseases and Beyond: From Mechanism to Pharmacotherapies. Pharm. Rev. 2021, 73, 924–967.

64. Chen, P.Y.; Schwartz, M.A.; Simons, M. Endothelial-to-Mesenchymal Transition, Vascular Inflammation, and Atherosclerosis. Front. Cardiovasc. Med. 2020, 7, 53.

65. Chen, P.Y.; Qin, L.; Baeyens, N.; Li, G.; Afolabi, T.; Budatha, M.; Tellides, G.; Schwartz, M.A.; Simons, M. Endothelial-to-mesenchymal transition drives atherosclerosis progression. J. Clin. Investig. 2015, 125, 4514–4528.

66. Terzuoli, E.; Nannelli, G.; Giachetti, A.; Morbidelli, L.; Ziche, M.; Donnini, S. Targeting endothelial-to-mesenchymal transition: The protective role of hydroxytyrosol sulfate metabolite. Eur. J. Nutr. 2020, 59, 517–527.

67. Razali, R.A.; Lokanathan, Y.; Yazid, M.D.; Ansari, A.S.; Saim, A.B.; Hj Idrus, R.B. Modulation of Epithelial to Mesenchymal Transition Signaling Pathways by Olea Europaea and Its Active Compounds. Int. J. Mol. Sci. 2019, 20, 3492.

68. Razali, R.A.; Nik Ahmad Eid, N.A.H.; Jayaraman, T.; Amir Hassan, M.A.; Azlan, N.Q.; Ismail, N.F.; Sainik, N.Q.A.V.; Yazid, M.D.; Lokanathan, Y.; Saim, A.B.; et al. The potential of Olea europaea extracts to prevent TGFβ1-induced epithelial to mesenchymal transition in human nasal respiratory epithelial cells. BMC Complement. Altern. Med. 2018, 18, 197.

69. Evrard, S.M.; Lecce, L.; Michelis, K.C.; Nomura-Kitabayashi, A.; Pandey, G.; Purushothaman, K.R.; d'Escamard, V.; Li, J.R.; Hadri, L.; Fujitani, K.; et al. Endothelial to mesenchymal transition is common in atherosclerotic lesions and is associated with plaque instability. Nat. Commun. 2016, 7, 11853.

70. Bischoff, J. Endothelial-to-Mesenchymal Transition. Circ. Res. 2019, 124, 1163–1165.

71. Martínez-Lara, E.; Peña, A.; Calahorra, J.; Cañuelo, A.; Siles, E. Hydroxytyrosol decreases the oxidative and nitrosative stress levels and promotes angiogenesis through HIF-1 independent mechanisms in renal hypoxic cells. Food Funct. 2016, 7, 540–548.
72. Cheng, Y.; Qu, Z.; Fu, X.; Jiang, Q.; Fei, J. Hydroxytyrosol contributes to cell proliferation and inhibits apoptosis in pulsed electromagnetic fields treated human umbilical vein endothelial cells in vitro. Mol. Med. Rep. 2017, 16, 8826–8832.
73. Zhang, L.; Lu, Q.; Chang, C. Epigenetics in Health and Disease. Adv. Exp. Med. Biol. 2020, 1253, 3–55.
74. Leri, M.; Scuto, M.; Ontario, M.L.; Calabrese, V.; Calabrese, E.J.; Bucciantini, M.; Stefani, M. Healthy Effects of Plant Polyphenols: Molecular Mechanisms. Int. J. Mol. Sci. 2020, 21, 1250.
75. Peedicayil, J. Epigenetic therapy-a new development in pharmacology. Indian J. Med. Res. 2006, 123, 17.
76. Moore, L.D.; Le, T.; Fan, G. DNA methylation and its basic function. Neuropsychopharmacology 2013, 38, 23–38.
77. D'Adamo, S.; Cetrullo, S.; Borzì, R.M.; Flamigni, F. Effect of oxidative stress and 3-hydroxytyrosol on DNA methylation levels of miR-9 promoters. J. Cell Mol. Med. 2019, 23, 7885–7889.
78. López de Las Hazas, M.C.; Martin-Hernández, R.; Crespo, M.C.; Tomé-Carneiro, J.; Del Pozo-Acebo, L.; Ruiz-Roso, M.B.; Escola-Gil, J.C.; Osada, J.; Portillo, M.P.; Martinez, J.A.; et al. Identification and validation of common molecular targets of hydroxytyrosol. Food Funct. 2019, 10, 4897–4910.
79. Del Saz-Lara, A.; López de Las Hazas, M.C.; Visioli, F.; Dávalos, A. Nutri-Epigenetic Effects of Phenolic Compounds from Extra Virgin Olive Oil: A Systematic Review. Adv. Nutr. 2022, 13, 2039–2060.
80. Iqbal, A.M.; Jamal, S.F. Essential Hypertension. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2022.
81. Wu, C.Y.; Hu, H.Y.; Chou, Y.J.; Huang, N.; Chou, Y.C.; Li, C.P. High Blood Pressure and All-Cause and Cardiovascular Disease Mortalities in Community-Dwelling Older Adults. Medicine 2015, 94, e2160.
82. Quirós-Fernández, R.; López-Plaza, B.; Bermejo, L.M.; Palma-Milla, S.; Gómez-Candela, C. Supplementation with Hydroxytyrosol and Punicalagin Improves Early Atherosclerosis Markers Involved in the Asymptomatic Phase of Atherosclerosis in the Adult Population: A Randomized, Placebo-Controlled, Crossover Trial. Nutrients 2019, 11, 640.
83. Hermans, M.P.; Lempereur, P.; Salembier, J.-P.; Maes, N.; Albert, A.; Jansen, O.; Pincemail, J. Supplementation Effect of a Combination of Olive (Olea europea L.) Leaf and Fruit Extracts in the

Clinical Management of Hypertension and Metabolic Syndrome. Antioxidants 2020, 9, 872.

84. Lockyer, S.; Rowland, I.; Spencer, J.P.E.; Yaqoob, P.; Stonehouse, W. Impact of phenolic-rich olive leaf extract on blood pressure, plasma lipids and inflammatory markers: A randomised controlled trial. Eur. J. Nutr. 2017, 56, 1421–1432.
85. Menichini, D.; Alrais, M.; Liu, C.; Xia, Y.; Blackwell, S.C.; Facchinetti, F.; Sibai, B.M.; Longo, M. Maternal Supplementation of Inositols, Fucoxanthin, and Hydroxytyrosol in Pregnant Murine Models of Hypertension. Am. J. Hypertens. 2020, 33, 652–659.
86. Grylls, A.; Seidler, K.; Neil, J. Link between microbiota and hypertension: Focus on LPS/TLR4 pathway in endothelial dysfunction and vascular inflammation, and therapeutic implication of probiotics. Biomed. Pharm. 2021, 137, 111334.
87. Wu, Y.; Ding, Y.; Ramprasath, T.; Zou, M.H. Oxidative Stress, GTPCH1, and Endothelial Nitric Oxide Synthase Uncoupling in Hypertension. Antioxid. Redox Signal. 2021, 34, 750–764.
88. Li, Q.; Youn, J.-Y.; Cai, H. Mechanisms and consequences of endothelial nitric oxide synthase dysfunction in hypertension. J. Hypertens. 2015, 33, 1128–1136.
89. Ataei Ataabadi, E.; Golshiri, K.; Jüttner, A.; Krenning, G.; Danser, A.H.J.; Roks, A.J.M. Nitric Oxide-cGMP Signaling in Hypertension: Current and Future Options for Pharmacotherapy. Hypertension 2020, 76, 1055–1068.
90. Ivanov, M.; Vajic, U.J.; Mihailovic-Stanojevic, N.; Miloradovic, Z.; Jovovic, D.; Grujic-Milanovic, J.; Karanovic, D.; Dekanski, D. Highly potent antioxidant Olea europaea L. leaf extract affects carotid and renal haemodynamics in experimental hypertension: The role of oleuropein. Excli J 2018, 17, 29–44.
91. Ilic, S.; Stojiljkovic, N.; Stojanovic, N.; Stoiljkovic, M.; Mitic, K.; Salinger-Martinovic, S.; Randjelovic, P. Effects of oleuropein on rat's atria and thoracic aorta: A study of antihypertensive mechanisms. Can. J. Physiol. Pharm. 2021, 99, 110–114.
92. Storniolo, C.E.; Roselló-Catafau, J.; Pintó, X.; Mitjavila, M.T.; Moreno, J.J. Polyphenol fraction of extra virgin olive oil protects against endothelial dysfunction induced by high glucose and free fatty acids through modulation of nitric oxide and endothelin-1. Redox Biol. 2014, 2, 971–977.
93. Nicholson, S.K.; Tucker, G.A.; Brameld, J.M. Physiological concentrations of dietary polyphenols regulate vascular endothelial cell expression of genes important in cardiovascular health. Br. J. Nutr. 2010, 103, 1398–1403.
94. Lu, C.L.; Liao, M.T.; Hou, Y.C.; Fang, Y.W.; Zheng, C.M.; Liu, W.C.; Chao, C.T.; Lu, K.C.; Ng, Y.Y. Sirtuin-1 and Its Relevance in Vascular Calcification. Int. J. Mol. Sci. 2020, 21, 1593.
95. Ren, C.Z.; Wu, Z.T.; Wang, W.; Tan, X.; Yang, Y.H.; Wang, Y.K.; Li, M.L.; Wang, W.Z. SIRT1 exerts anti-hypertensive effect via FOXO1 activation in the rostral ventrolateral medulla. Free Radic.

Biol. Med. 2022, 188, 1–13.

96. Qian, L.; Ma, L.; Wu, G.; Yu, Q.; Lin, H.; Ying, Q.; Wen, D.; Gao, C. G004, a synthetic sulfonylurea compound, exerts anti-atherosclerosis effects by targeting SIRT1 in ApoE(-/-) mice. Vasc. Pharm. 2017, 89, 49–57.
97. Gilani, A.H.; Khan, A.U.; Shah, A.J.; Connor, J.; Jabeen, Q. Blood pressure lowering effect of olive is mediated through calcium channel blockade. Int. J. Food Sci. Nutr. 2005, 56, 613–620.
98. Scheffler, A.; Rauwald, H.W.; Kampa, B.; Mann, U.; Mohr, F.W.; Dhein, S. Olea europaea leaf extract exerts L-type Ca2+ channel antagonistic effects. J. Ethnopharmacol. 2008, 120, 233–240.
99. Liberale, L.; Kraler, S.; Camici, G.G.; Lüscher, T.F. Ageing and longevity genes in cardiovascular diseases. Basic Clin. Pharm. Toxicol. 2020, 127, 120–131.
100. Ungvari, Z.; Tarantini, S.; Donato, A.J.; Galvan, V.; Csiszar, A. Mechanisms of Vascular Aging. Circ. Res. 2018, 123, 849–867.
101. Jani, B.; Rajkumar, C. Ageing and vascular ageing. Postgrad. Med. J. 2006, 82, 357–362.
102. Zhao, Y.; Vanhoutte, P.M.; Leung, S.W.S. Vascular nitric oxide: Beyond eNOS. J. Pharmacol. Sci. 2015, 129, 83–94.
103. Laina, A.; Stellos, K.; Stamatelopoulos, K. Vascular ageing: Underlying mechanisms and clinical implications. Exp. Gerontol. 2018, 109, 16–30.
104. Liguori, I.; Russo, G.; Curcio, F.; Bulli, G.; Aran, L.; Della-Morte, D.; Gargiulo, G.; Testa, G.; Cacciatore, F.; Bonaduce, D.; et al. Oxidative stress, aging, and diseases. Clin. Interv. Aging 2018, 13, 757–772.
105. Gordon, C.J.; Rowsey, P.J.; Bishop, B.L.; Ward, W.O.; Macphail, R.C. Serum biomarkers of aging in the Brown Norway rat. Exp. Gerontol. 2011, 46, 953–957.
106. Bruunsgaard, H.; Ladelund, S.; Pedersen, A.N.; Schroll, M.; Jørgensen, T.; Pedersen, B.K. Predicting death from tumour necrosis factor-alpha and interleukin-6 in 80-year-old people. Clin. Exp. Immunol. 2003, 132, 24–31.
107. Wang, Q.; Wang, C.; Abdullah; Tian, W.; Qiu, Z.; Song, M.; Cao, Y.; Xiao, J. Hydroxytyrosol Alleviates Dextran Sulfate Sodium-Induced Colitis by Modulating Inflammatory Responses, Intestinal Barrier, and Microbiome. J. Agric. Food Chem. 2022, 70, 2241–2252.
108. Zhang, X.; Cao, J.; Jiang, L.; Zhong, L. Suppressive Effects of Hydroxytyrosol on Oxidative Stress and Nuclear Factor-kappaB Activation in THP-1 Cells. Biol. Pharm. Bull. 2009, 32, 578–582.
109. Brunetti, G.; Di Rosa, G.; Scuto, M.; Leri, M.; Stefani, M.; Schmitz-Linneweber, C.; Calabrese, V.; Saul, N. Healthspan Maintenance and Prevention of Parkinson's-like Phenotypes with Hydroxytyrosol and Oleuropein Aglycone in C. elegans. Int. J. Mol. Sci. 2020, 21, 2588.

110. Peng, Y.; Hou, C.; Yang, Z.; Li, C.; Jia, L.; Liu, J.; Tang, Y.; Shi, L.; Li, Y.; Long, J.; et al. Hydroxytyrosol mildly improve cognitive function independent of APP processing in APP/PS1 mice. Mol. Nutr. Food Res. 2016, 60, 2331–2342.

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