Neuroprotective Panel of Olive Polyphenols

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Neurological diseases such as stroke and multiple sclerosis are associated with high morbidity and mortality, long-term disability, and social and economic burden. Therefore, they represent a major challenge for medical treatment. Numerous evidences support the beneficial effects of polyphenols from olive trees, which can alleviate or even prevent demyelination, neurodegeneration, cerebrovascular diseases, and stroke. Polyphenols from olive oils, especially extra virgin olive oil, olive leaves, olive leaf extract, and from other olive tree derivatives, alleviate inflammation and oxidative stress, two major factors in demyelination. In addition, they reduce the risk of stroke due to their multiple anti-stroke effects, such as anti-atherosclerotic, antihypertensive, antioxidant, anti-inflammatory, hypocholesterolemic, hypoglycemic, and anti-thrombotic. In addition, olive polyphenols have beneficial effects on the plasma lipid profiles and insulin sensitivity in obese individuals.

cerebrovascular diseases demyelination extra virgin olive oil multiple sclerosis neuroprotection olive leaves olive leaf extract olive oil olive polyphenols stroke

1. Introduction

The olive tree (*Olea europaea* L.) is a valuable source of polyphenols, including all olive derivatives. Of all olive oil products, extra virgin olive oil (EVOO) contains the highest amount of total phenols (200–800 mg/kg) [1]. Olive leaves and olive leaf extract have even higher concentrations of total phenols than olive fruit and olive oil [2][3][4]. Moreover, it is known that the olive leaf is a traditional raw material used in phytotherapy [5]. Polyphenols from virgin olive oil or EVOO, olive leaves, and leaf extract, and other polyphenols derived from the olive tree, have been widely identified in experimental, clinical, and epidemiological research as compounds that can exert many different beneficial effects in the body, especially with long-term consumption [6]. The most studied polyphenols include oleuropein, oleocanthal, oleacein, hydroxytyrosol, and tyrosol.

Polyphenols are organic compounds with different chemical structures and biological activities. Based on their chemical structure, we can distinguish about 8000 polyphenols. They have an aromatic ring and at least one hydroxyl group as a key structure [7]. Three groups of polyphenols are most often held responsible for biological effects: secoiridoid derivatives, phenolic alcohols, and phenolic acids [8]. All of these major phenolic subclasses are present in olive derivatives, as are flavonoids and lignans [9]. Quantitatively, secoiridoids are the most abundant [10]. The main secoiridoids are oleuropein and oleocanthal, while the main phenolic alcohols are hydroxytyrosol and tyrosol [11].

The beneficial effects of polyphenols on human health depend on their absorption, metabolism, and bioavailability [12]. After ingestion, they are hydrolyzed in the upper part of the intestine and only a small portion is absorbed [13]. The rest is processed in the large intestine by the intestinal microbiota into low molecular weight fatty acids [14]. Hydroxytyrosol is formed by the hydrolysis of oleuropein during the maturation of olive oil [15]. Since it is a polar compound, it is absorbed by passive transport in the intestine [16], with an absorption rate above 40% [15]. Studies have shown that hydroxytyrosol is more effective when administered as EVOO than in aqueous solution since the antioxidants contained in EVOO protect hydroxytyrosol from degradation in the gastrointestinal tract [17][18]. In addition, it has recently been demonstrated that female animals can metabolize and utilize hydroxytyrosol more efficiently [19]. For oleuropein, the most abundant phenolic compound in olive leaves, and the seeds, pulp, and peel of unripe olives [2], the study showed greater stability during digestion and higher bioavailability compared to hydroxytyrosol. Oleuropein reached the colon unchanged and therefore produced more diverse microbial metabolites. Considering the bioavailability results, it appears that oleuropein may be the most suitable hydroxytyrosol precursor for inclusion in food or nutraceutical formulations [20]. However, when phenols are consumed as a combination in a food or a crude extract, they may have a greater impact on health than a purified single compound [2].

Among the many beneficial functions of olive polyphenols, the neuroprotective function is one of the most important. A particularly important effect is the reduction of neuroinflammation as this is a component of many neurodegenerative and demyelinating diseases such as multiple sclerosis (MS) and pro-stroke disorders [21]. MS is the most common of the demyelinating diseases and is very challenging to treat. It is a chronic, autoimmune, inflammatory, demyelinating, and neurodegenerative disease of the central nervous system (CNS) that leads to disability due to permanent damage or deterioration of the nerves [22]. There is no cure, but the usual treatment helps to accelerate recovery from relapses and alleviate symptoms. By counteracting inflammation and oxidative stress that lead to the destruction of myelin and neurons, olive polyphenols could be a very helpful adjuvant therapy to slow the progression of demyelination and neurodegeneration. Here, the potential mechanisms of their anti-demyelination action are discussed. Each of the aforementioned olive polyphenols is believed to have some degree of anti-inflammatory or antioxidant activity [6] (**Figure 1**).

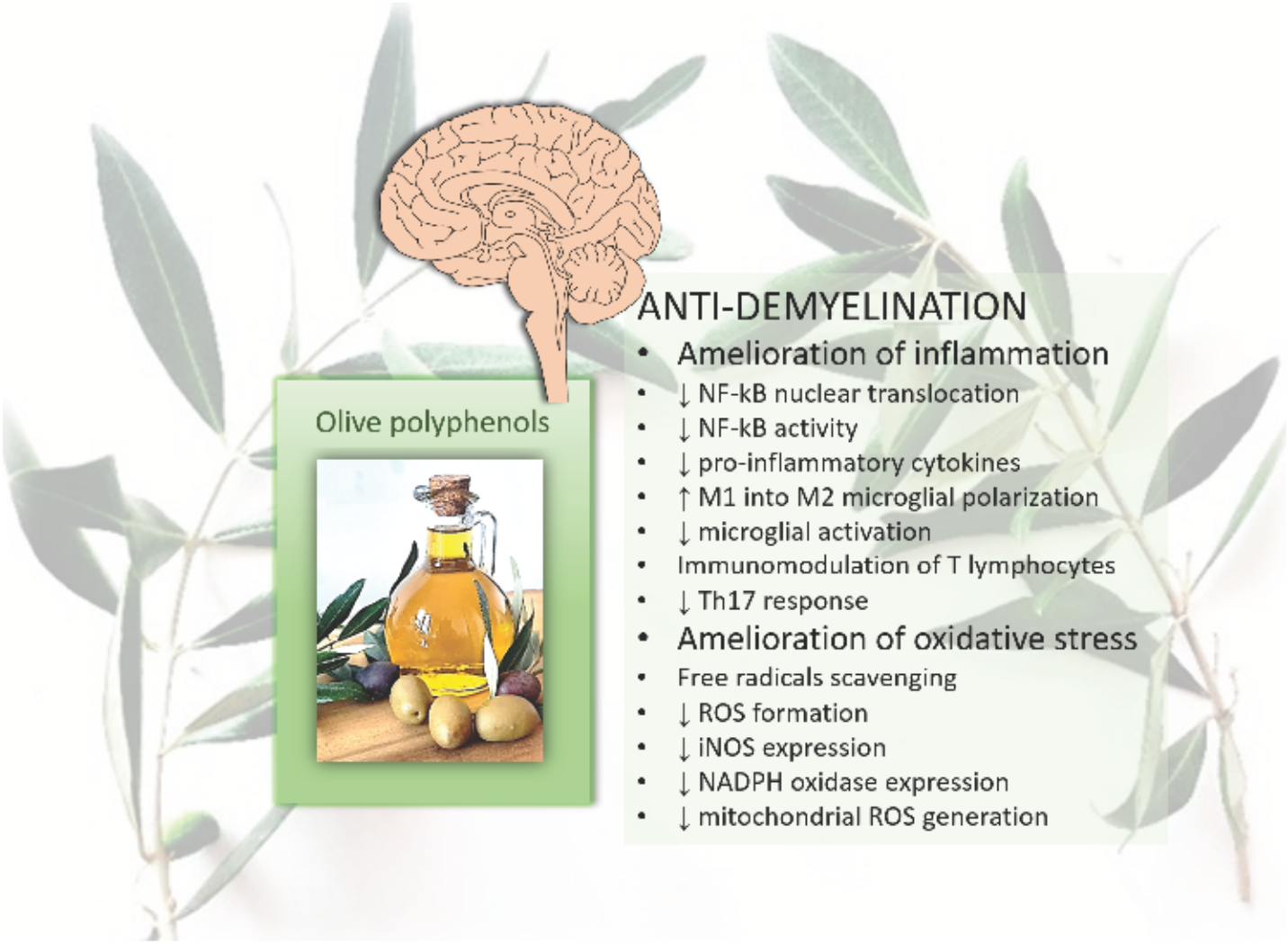

Figure 1. Main anti-demyelination effects of olive polyphenols. ↑, increases; ↓, decreases; NF-kB, nuclear factor kappa B; M1, microglia type 1; M2, microglia type 2; Th17, T helper 17 cells; ROS, reactive oxygen species; iNOS, inducible nitric oxide synthase; NADPH, nicotinamide adenine dinucleotide phosphate.

Stroke is another neurological disease with challenging treatment options. It is the second leading cause of disability and death in adults aged 65 years and older worldwide [23]. A number of pro-stroke mechanisms or risk factors are involved in the pathogenesis of stroke, including hypertension, atherosclerotic processes, and pro-atherosclerotic conditions such as lipid profile disorders, hyperglycemia, endothelial dysfunction, oxidative stress and inflammation, insulin resistance, and platelet activation (**Figure 2**). Thus, to reduce the risk of stroke, action is needed on many fronts [24]. Data from a number of studies suggest that olive polyphenols reduce the risk of stroke due to their multiple anti-stroke effects, such as anti-atherosclerotic, antihypertensive, antioxidant, anti-inflammatory, hypocholesterolemic, hypoglycemic, and anti-thrombotic [25][26][27][28][29].

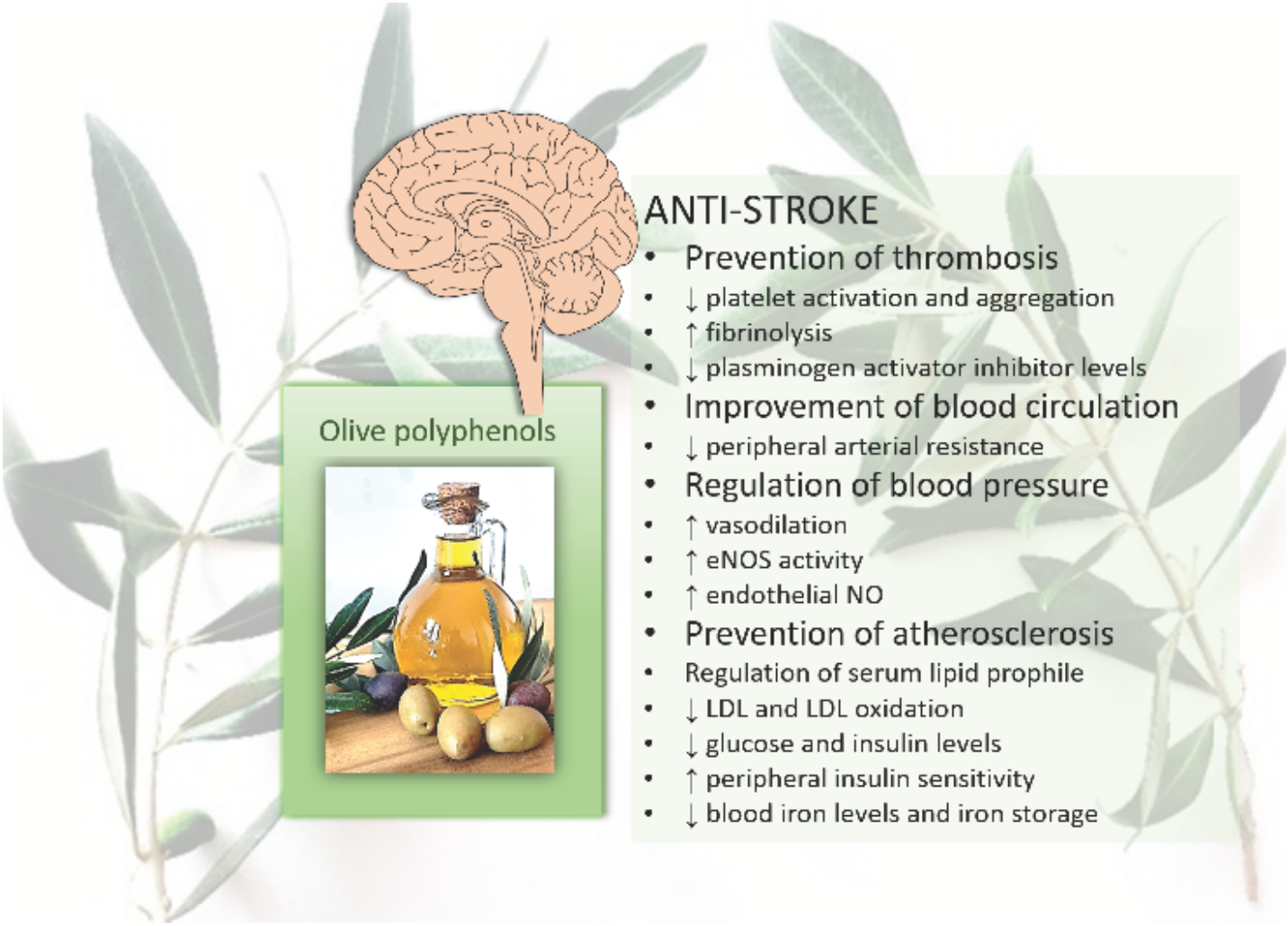

Figure 2. Main anti-stroke effects of olive polyphenols. ↑, increases; ↓, decreases; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; LDL, low-density lipoprotein.

2. Anti-Demyelination Action of Olive Polyphenols

Demyelinating diseases are characterized by the destruction of myelin leading to axon degeneration and neuronal loss, resulting in various neurological impairments [30]. The main representative of primary demyelination, caused by acute inflammatory damage to oligodendrocytes and myelin, is MS [31]. The disease usually affects younger people (between 20 and 40 years of age), and it is a major cause of disability in young adults and therefore a significant socioeconomic problem [32]. Neuroinflammation is an underlying mechanism of many neurodegenerative diseases, especially demyelinating diseases such as MS. It affects the CNS and indicates the presence of specific CNS autoantigens that trigger an immune response and cause tissue damage. Changes in the tissue promote the immune response and activation of microglia, which secrete cytokines and free radicals, leading to a local increase in oxidative stress and additional tissue damage [33]. MS is considered a T cell-mediated autoimmune disease. Myelin-reactive T cells migrate from the periphery across the blood–brain barrier (BBB) into the CNS, causing inflammation, demyelination, and neurodegeneration [34].

In addition to immunomodulation therapy used in patients with MS, natural compounds that can slow disease progression have been sought. Among others, EVOO and olive-derived polyphenols have been identified as compounds with anti-inflammatory activity. For a long time, it was assumed that the anti-inflammatory effects of EVOO were due to monounsaturated fatty acids, but recent studies have shown that polyphenols also play an important role [35]. What is known today is that polyphenols reduce morbidity and slow down the progression of neurodegenerative diseases [36]. They reduce oxidative stress and inflammation and modulate the immune system by affecting cytokine production and white blood cells' activity [35].

Hydroxytyrosol and oleuropein seem to have the best neuroprotective properties [12]. To achieve their neuroprotective effect, polyphenolic compounds must pass through the BBB and reach an appropriate concentration in the brain [37]. The selective nature of the BBB determines the availability of polyphenols in the CNS. In general, it is known that the aglycones of polyphenols can be better absorbed because they can cross membranes by a passive diffusion [9].

There are several mechanisms that have been proposed for the anti-inflammatory and neuroprotective effects of polyphenols: the prevention of nuclear translocation and reduction of nuclear factor kappa B (NF-κB) transcription factor activity; the reduction of production of pro-inflammatory factors such as interleukin-1-β (IL-1β) and tumor necrosis factor-α (TNF-α); the downregulation of inducible nitric oxide synthase (iNOS) involved in the immune response that produces NO as an immune defense mechanism, i.e., a free radical with an unpaired electron; the downregulation of cyclooxygenase-2 (COX-2) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase expression; the induction of sirtulin-1/AMP-activated protein kinase (SIRT1/AMPK) activation that reduces microglial activation; the suppression of the suppressor of cytokine signaling proteins (SOCS) and the Janus kinase (JAK) signal transducer and activator of the transcription (STAT) signaling pathway of cytokine signaling; and the increase in the mRNA and protein levels of anti-inflammatory cytokine IL-10 [12][38].

3. Anti-Stroke Action of Olive Polyphenols

Of all neurological disorders, cerebrovascular diseases are responsible for more than half of the burden and 85% of the deaths related to neurological diseases worldwide. Stroke was the second leading cause of death, for about 143 million people, worldwide in 2019, with numbers expected to increase by 2030 [23].

3.1. Olive Polyphenols and Hypertension

Hypertension is one of the most common disorders and, more importantly, is the main risk factor for cerebral insult. Due to high intraluminal pressure, the endothelium and smooth muscle in intracerebral arteries are exposed to increased stress leading to structural changes within the vessel wall. This leads not only to local thrombus formation, stenosis, occlusion, and ischemic lesions but also to the arteriosclerotic process. In other words, it leads to degenerative changes in smooth muscle cells and the endothelium, resulting in increased arterial stiffness associated with an increased risk of stroke [39][40]. Furthermore, all these changes lead to endothelial dysfunction and inadequate compensatory mechanisms unable to protect microvessels from increased pressure [41]. This also

accelerates ischemic attacks and cerebral infarcts or predisposes the subject to plasma extravasation and focal cerebral edema, lacunar infarcts, and intracerebral hemorrhage [42][43].

The vascular endothelium plays an important role in regulating vascular tone through the synthesis of NO, prostaglandins, and other relaxing factors and provides protection against oxidative, inflammatory, thrombotic, and atherosclerotic processes, thus serving as a controller of normal blood pressure [44][45]. The essential homeostatic processes regulated by the endothelium are modulated by crosstalk between endothelial cells and other vascular cell types, including smooth muscle cells, monocytes, and macrophages, which contribute to normal vascular function. However, impaired communication between endothelial cells and these vascular cell types has been associated with vascular dysfunction and pathological remodeling in hypertension, atherosclerosis, atherothrombosis, and other cardiovascular diseases [46].

Endothelial dysfunction may also precede the development of hypertension by contributing to increased peripheral resistance, i.e., through activation of the renin–angiotensin system, endothelin-1, catecholamines, and growth factors' production [41][47]. In addition, the induction of inflammatory processes and the production of ROS in the vessel wall may be associated with endothelial dysfunction. ROS are key signaling molecules through which vasoactive agents such as angiotensin II, endothelin-1, and others modify cell function through highly-regulated, redox-sensitive signal transduction. ROS stimulate multiple signaling pathways involved in inflammation and vascular remodeling (NF-κB, MAPK, JAK-2, STAT, etc.) and thus are involved in the development of hypertension [44].

There are many studied antihypertensive mechanisms of olive polyphenols, and yet this is only the beginning of a larger picture. Sustained consumption of phenolic-enriched virgin olive oil with different polyphenols causes improvements in endothelial function in humans [48]. The antihypertensive effects of olive oil and olive leaves are mainly attributed to the main phenolic compounds that reduce blood pressure through a number of specific mechanisms. Oleuropein is the most commonly described polyphenolic compound. A large number of studies in humans and laboratory rats have demonstrated its antihypertensive activity [49][50]. Olive leaf polyphenols have been shown to lower diastolic and systolic blood pressure in prehypertensive and hypertensive groups of patients [51][52][53][54][55][56].

The beneficial effects that olive oil and leaf phenolic compounds may have on endothelial function include the inhibition of monocyte adhesion and platelet activation, improvement in vasodilation [25] through the modulation of potent vasodilator and vasoconstrictor agents such as NO and endothelin-1 (ET-1) [57], and, furthermore, through the expression of their antioxidant and anti-inflammatory activity [56][58]. As stated earlier, all of these mechanisms of action are involved in the development of hypertension if not prevented or treated beforehand. The best known anti-inflammatory effects of olive polyphenols that can prevent endothelial dysfunction and progressive vasoconstriction include the inhibition of transcription factors NF-kB and AP-1, and the reduction in vascular TLR4 expression by the inhibition of mitogen-activated protein kinase (MAPK) signaling with the subsequent reduction in pro-inflammatory cytokines (IL-6, IL-10, TNF-α, IL-1β, etc.) and inflammatory markers (COX-2, PGE2, etc.) [6][59][60][61]. The novel anti-inflammatory effects of olive polyphenols hydroxytyrosol and oleuropein are thought to result

from the suppression of phosphorylation and release of platelet heat shock protein 27, an extracellular pro-inflammatory agent [62]. As mentioned earlier, the antioxidant effects of olive polyphenols include upregulation of the expression of antioxidant enzymes (glutathione peroxidase (GPx), glutathione disulfide reductase (GSR), SOD-1, etc.), the elimination of elevated superoxide levels, the reduction in increased NADPH oxidase activity, and the activation of antioxidant cell proteins such as SIRT1 and peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) [25][63][64][65]. Moreover, olive leaf polyphenolic compounds oleuropein and hydroxytyrosol are efficient cytoprotective agents against H_2O_2-induced oxidative stress and toxicity in human umbilical vein endothelial cells [66].

In a study by Choi et al. [67], treatment with oleuropein significantly increased an angiotensin II-induced decrease in the levels of peroxiredoxin (Prdx)-1 and -2 in vascular progenitor cells, which have an important antioxidant and protective function in cells. By regulating the expression of Prdx-1 and Prdx-2 and by activating the ERK1/2 phosphorylation cascade, oleuropein decreases cellular ROS levels and reduces oxidative stress. Hydroxytyrosol and tyrosol from olive mill wastewater, a by-product of olive oil processing, also showed potent antioxidant capabilities to counteract H_2O_2-induced oxidative stress and cell death in cell viability experiments that included endothelial cells and vascular smooth muscle cells [68].

In animal models of simultaneous renal hypertension and type 2 diabetes associated with the impaired release of NO, oleuropein showed sympathoplegic activities with subsequent lowering of systolic blood pressure. In addition to lowering systolic blood pressure, it also decreased the maximal response to phenylephrine and increased the maximal response to acetylcholine [69].

The antihypertensive effects of oleuropein can be seen by its negative chronotropic and inotropic effects on the heart [70]. This effect could be of great importance in isolated systolic hypertension. Moreover, virgin olive oil has been shown to have an inhibitory effect on angiotensin-converting enzyme (ACE) and thus to have a vasodilatory effect in spontaneously hypertensive rats [71][72]. Overall, olive polyphenols have a beneficial effect on cardiovascular parameters, including sequels of hypertensive disorder such as heart failure, myocardial infarction, and renal hypertension [25][26][27].

Many studies have confirmed the endothelium-dependent vasorelaxant effect of olive polyphenols. As previously mentioned, NO is an important protective molecule in the vascular system, and endothelial NO synthase (eNOS) is responsible for most of the vasodilatory NO production [73]. Olive phenolic compounds perform a particular task to increase NO bioavailability and the expression of eNOS [74]. an imbalance between NO and ET-1 leads to endothelial dysfunction, and it is possible that hyperglycemia and hyperlipidemia may decrease endothelial NO synthase phosphorylation and, consequently, intracellular NO levels and increase ET-1 synthesis. Hydroxytyrosol and extra virgin olive oil polyphenol extract partially reverse these abnormalities [57]. In addition, it was observed that hyperglycemia and free fatty acids decreased NO and increased acetylcholine-induced ET-1 levels by modulating intracellular calcium concentrations and endothelial NO synthase phosphorylation, events that were also reversed by hydroxytyrosol and the polyphenol extract [57]. Moreover, simple phenols from extra virgin olive oil,

tyrosol, and hydroxytyrosol can modulate the NO balance by decreasing its degradation (through decreased superoxide formation) and increasing its production through the Akt1/eNOS pathway [75].

Another possible mechanism by which oleuropein exerts the antihypertensive effect is by affecting renal water reabsorption in renal cells, i.e., by preventing vasopressin-induced aquaporin-2 translocation to the plasma membrane of renal cells [76]. In addition to diuresis, it also has a stimulating effect on natriuresis [77].

3.2. Olive Polyphenols and Vascular Dysfunction

Vascular dysfunction includes large artery dysfunction due to arterial stiffness, microvascular dysfunction (dysfunction of the microcirculation), and endothelial dysfunction (dysfunction of the endothelium) [78]. Arterial wall stiffening is determined by the reduced elastin–collagen ratio caused by the production of ROS and by inflammation, aging, hypertension, hyperglycemia, and dyslipidemia; all mechanisms that olive polyphenols reduce and counteract. In addition, arterial stiffness due to decreased compliance of the large peripheral arteries leads to increased pulsatile pressure and blood flow stress, which damage the cerebral microcirculation. Cerebral capillaries are particularly vulnerable to this damage due to low impedance, which can lead to a reactive increase in vascular resistance and subsequent impaired vasoreactivity and microvascular ischemia [79]. Olive polyphenol ingestion may help prevent these cerebral disorders, and thus cerebral stroke, by reducing blood pressure and associated endothelial dysfunction, and the occurrence of arterial stiffness. Arterial stiffness and endothelial dysfunction are distinct aspects of vascular disease, but there is certainly a crosstalk between these two pathophysiological processes [80]. As mentioned earlier, endothelial dysfunction is characterized by an imbalance between vasoconstrictor and vasodilator factors, by increased levels of ROS and pro-inflammatory factors, and by decreased NO secretion. All these lead to increased vasoconstriction, leukocyte adhesion, smooth muscle cell proliferation, extracellular matrix deposition, cell adhesion, platelet activation, prooxidation, thrombosis, impaired coagulation, vascular inflammation, and atherosclerosis [45][81].

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