Selected Plant-Derived Polyphenols for Peripheral Artery Disease

Subjects: Peripheral Vascular Disease | Cardiac & Cardiovascular Systems

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The purpose herein is to take into account the mechanisms that lead to endothelium dysfunction, such as the glycoxidation process and the production of advanced glycation endproducts (AGEs) that result in protein misfolding, and to suggest plant-derived polyphenols that could be useful in peripheral artery disease, PAD. Thus, five polyphenols are considered, baicalein, curcumin, mangiferin, quercetin and resveratrol, reviewing the literature in PubMed. The key molecular mechanisms and preclinical and clinical studies of each selected compound are examined. Furthermore, the safety profiles of the polyphenols are outlined, together with the unwanted effects reported in humans, also by searching the WHO database (VigiBase).

baicalein curcumin mangiferin quercetin resveratrol diabetes mellitus endothelial dysfunction preclinical studies clinical studies natural compounds

1. Baicalein

1.1. Chemistry and Sources

Baicalein (5,6,7–trihydroxyflavone) is a naturally occurring polyphenol found in several medicinal plants, in particular in the roots of *Scutellaria baicalensis* G. and *Scutellaria lateriflora* L., and in the seeds, leaves, fruits and bark of *Oroxylum indicum* (L.) Kurz [1][2], all species that grow in several Asian countries. Baicalein is the aglycone of baicalin (baicalein 7-O-glucuronide), which is also found as such in plants and, moreover, is formed after the biotransformation of baicalein in vivo [1][3].

1.2. Activity: Preclinical Studies

Baicalein and baicalin, and extracts containing them, are proposed for various pharmacological effects, such as anti-inflammatory, antiviral, antibacterial, anticancer, antineurodegenerative and protective, against cardiovascular diseases [1][4][5]. The molecular mechanisms of action of baicalein, as well as those of other flavonoids, are mainly linked to the antioxidant activity, which occurs in different steps of the oxidative process; for example, it has demonstrated a role as scavengers of free radicals already formed in the medium (including lipid peroxyl radicals), as chelators of metal ions and by removing oxidatively altered biomolecules [6][7]. The role of the OH groups in polyphenols is dependent on the global geometry of the molecule and interactions among neighbor groups; a detailed conformational analysis and linked antioxidant mechanisms have been recognized for baicalein [6]. Recent

studies on the structure-activity relationship suggest that the baicalein moiety is relevant for bioactivities [8]; however, the molecular mechanisms of baicalein are multiple and follow many molecular pathways that require further evaluation. The data confirm the beneficial role of *Scutellaria baicalensis,* which is widely used in traditional Chinese medicine to treat hypertension, respiratory infections, inflammation and diarrhea [9][10]. A study using three structurally related polyphenols, such as baicalin, baicalein and wogonin, showed the inhibition of endothelial cell barrier disruption, suggesting their protective activity against vascular inflammatory diseases [11]. Recently, studies have suggested that baicalein exhibits potential antidiabetic activities in metabolic syndrome [12]; the effect is related to the inhibition of α–glucosidase activity [13][14].

The in vitro and in vivo data suggest that baicalein is able to reduce vascular inflammation induced by high glucose levels. In human umbilical vein endothelial cells (HUVECs), baicalein (5–10 μM) was able to protect the cells from membrane disruption caused by a 25 mM glucose concentration; the polyphenol (10 μM) reduced the expression of the chemokines MPC–1 and IL–8, as well as ROS formation [11]. Furthermore, the alteration of vascular permeability induced by high glucose administration in mice was counteracted by baicalein (4.5–8.9 μg/mouse, i.v.) [11]. The vascular protective effect of baicalein was also demonstrated in vitro and in vivo as mediated by the inhibition of the high-mobility group box 1 (HMGB1) signaling pathway [15]. The role of baicalein on vascular function was assessed further by an in vitro study on the hybridoma endothelial cell line EA.hy926 [16]. The results indicate that baicalein is able to exploit protective effects against the oxidative stress of the endothelium, which is linked to the risk of diabetic angiopathy.

Baicalein has hypotensive effects on hypertensive rats, improving blood pressure and endothelium function [17]. Zhang et al., using streptozotocin and a high-fat-diet-induced diabetic rats, demonstrated that a 4–week treatment with baicalein (150 mg/kg/day) can reduce the level of blood glucose and improve insulin resistance, dyslipidemia and inflammation [18]. The effects have been attributed to the modulation of the gut microbiota, leading to increased levels of short-chain fatty acids (including acetate, propionate and butyrate), which are capable of improving gut barrier activity by stimulating epithelial growth and innate reactivity to invading bacteria [18].

A computational study revealed that baicalein is among the most promising candidates for the development of useful flavonoid derivatives in the treatment of DM [19]. Bioactivity is believed to derive from the structure that allows free-radical scavenging properties, reduces oxidized compounds, chelates metals and inhibits enzymes [19]. The experimental data suggest that baicalein can reduce oxidative stress, the expressions of iNOS and TGF–β1, as well as counteracting NF–κB activation [20]. Through a molecular modeling approach, together with microscopic and spectroscopic analyses, baicalein has also been proven to contrast the formation of AGEs and amyloid fibrils, phenomena that contribute to the loss of protein function and are connected to tissue damage [21].

In LPS-stimulated HUVECs, baicalein inhibits the expression of inflammatory cytokines IL–1β, IL–6 and TNF–α, as well as monocyte chemoattractant protein 1 (MCP–1) [22]. The authors also demonstrated that the inhibitory activity of baicalein occurs through the TLR4/NF–κB signaling pathway. The toll-like receptor 4 (TLR4)/NF–κB cascade pathway has been considered as a pivotal mechanism that leads to endothelial inflammation, activated by

inflammatory signals, such as bacterial toxins; the fact that this pathway was modulated by baicalein provides an explanation for its potential as an anti-inflammatory agent.

1.3. Activity: Clinical Studies

The pharmacokinetic characteristics of baicalein administered orally were evaluated in a cohort of 36 healthy Chinese subjects [23]. The study was a Phase-I single-center, randomized, double-blind, placebo-controlled, multiple ascending dose trial in which baicalein was administered at doses of 200, 400 and 600 mg once daily on days 1 and 10, 3 times daily on days 4 to 9. The absorption of the drug was rapid, with peak plasma levels evident within 2 h after administration. Treatment was found to be safe and well-tolerated; adverse events were mild and spontaneously resolved. Another study, consisting of multiple phases, considered a multiple design involving a total of 110 subjects, including a randomized, double-blind, placebo-controlled, single ascending dose study with doses of baicalein ranging from 100 to 800 mg [24]. In addition to the pharmacokinetic evaluation, the effect of food on the disposition of the drug was considered. The published clinical studies, although limited in sample dimension, indicate the favorable bioavailability and a good safety profile of baicalein, when used at suggested doses. However, to date, no studies on clinical effectiveness in the cardiovascular field are available.

1.4. Safety Profile

Baicalein is considered safe and with a good tolerability profile in humans, as per se, it did not have adverse reports in VigiBase [25], the WHO global database of potential side effects of medicinal products. Mild side effects were reported in a placebo-controlled study in which 68 healthy subjects were treated with a single dose of baicalein orally, 100 to 800 mg [24]. The most common side effects were increased levels of the C-reactive protein and triglycerides, and proteinuria; these undesirable effects did not depend on the dose of baicalein administered [24]. In a clinical trial, multiple doses of baicalein (200, 400 or 800 mg twice daily) in healthy volunteers produced various adverse effects, such as abdominal pain, constipation, and increased alanine transaminase and aspartate aminotransferase levels [26].

In fact, some concerns arose from reports on the possible liver toxicity of the use of plant extracts rich in flavonoids. Recently, it was shown in vitro that baicalein can inhibit human UDP-glucuronosyltransferases1A1, the enzyme that is primarily responsible for glucuronidation and the elimination of bilirubin [27], which can cause jaundice and severe liver disease. In general, further clinical trials involving a higher number of enrolled subjects are needed to produce a clearer picture of the safety profile of baicalein in humans.

2. Curcumin

2.1. Chemistry and Sources

Curcumin, also known as diferuloylmethane [(1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione], is a diarylheptanoid that represents the main component of the turmeric rhizome (*Curcuma longa* L. and

other *Curcuma* spp.), and has caused extensive investigations from biological and chemical points of view [28]. Turmeric is a widely used medicinal plant in Asian countries, appreciated for its antioxidant and anti-inflammatory activities, as well as for other multiple properties [29].

2.2. Activity: Preclinical Studies

Curcumin inhibits proinflammatory cytokines, TNF–α, ICAM–1, NOX2 and cyclo–oxygenase–2 expressions, and reduces the leucocyte-endothelium interaction in diabetes-induced rat vascular inflammatory models [30][31]. Curcumin has been widely evaluated with respect to the modulation of endothelial function [32]. Curcumin also presents a neuroprotective potential in the pathogenesis of Alzheimer's disease [33][34][35]. The many described biological activities of curcumin have been linked to its chemical instability that leads to the rapid autoxidation responsible for its antioxidant behavior. The oxidation of curcumin produces intermediate metabolites that conduct to a final bicyclopentadione [36][37]. Moreover, it has been demonstrated that electrophilic metabolites can covalently adduct to cellular protein targets, in particular those of the NF–κB pathway, which explains the anti-inflammatory activity of the natural compound. The methoxy groups of the molecule have also been shown to possess a role in its anti-inflammatory biological activity [38].

Ischemia and reperfusion injury in skeletal muscles, obtained by clamping the femoral artery and vein, is an experimental model that can provide information on the damage occurring in ischemic events of the limbs. Rats subjected to 4 h femoral occlusion followed by 2 h reperfusion, which received curcumin (100 mg/kg i.p., 1 h before reperfusion), presented a preservation of superoxide dismutase and catalase activities, as well as of the glutathione content in muscle tissues, compared to injured but not treated animals [39]. In the same context, the muscle and plasma levels of malondialdehyde and protein oxidation were reduced, as well as the plasma levels of inflammatory cytokines (TNF–α and IL–1β). The data suggest that curcumin has protective activity against the ischemic damage of skeletal muscles [39].

2.3. Activity: Clinical Studies

From a strict, clinical point of view, the data on the effectiveness of curcumin in PAD are limited. A meta-analysis of 5 randomized clinical trials conducted on a total of 192 healthy subjects with doses of curcumin ranging from 25 to 200 mg, showed that curcumin supplementation is able to improve vascular function, determined as the flow-mediated dilation of the brachial artery [40]. Alidadi et al. reported 7 randomized clinical trials conducted on humans, ranging from healthy subjects to obese people and type 2 diabetic patients, with a sample size ranging from 21 to 88 subjects [41]. Curcumin doses ranged from 150 mg/day to 2 g/day, over periods of 8–16 weeks. In healthy subjects, curcumin appeared to improve endothelial function, determined by a non-invasive ultrasound-based technique that measured flow-mediated dilation. On the contrary, in pathological conditions, curcumin treatment did not show an appreciable improvement in endothelial function, also due to the limited number of patients evaluated [41].

Despite its interesting biological properties, curcumin has the limitation of being poorly absorbed by the gastrointestinal tract due to its high hydrophobicity [42]. Several formulations were investigated to enhance curcumin bioavailability [43][44], in particular micro- and nano-formulations. An optimized curcumin formulation was developed and investigated [45]. It consisted of poly (propylene sulfide) (PPS) microparticles used for curcumin encapsulation and the delivery of the active principle on demand at the site of oxidative stress. An oil-in-water emulsion was obtained, which permitted, in the presence of ROS, the transition of hydrophobic PPS into more hydrophilic sulfoxide and sulfone, thus releasing curcumin. Following an in vitro evaluation of the system, the authors tested the formulation in vivo (curcumin-loaded PPS microspheres: 5 mg/kg of curcumin with 10.3 mg/kg of PPS, administered i.m. in the gastrocnemius and adductor muscles) in a streptozotocin-induced mouse model of DM in which hindlimb ischemia was induced [45]. The results show that curcumin microspheres were able to selectively reduce ROS levels in the tissue of the ischemic limbs, significantly increasing blood perfusion and the length of the vasculature, providing evidence for a favorable action of curcumin in the treatment of diabetic PAD. Another more recent attempt to produce “on demand” treatment for PAD has been reported [46]. It consists of PVAX (vanillyl alcohol-incorporated copolyoxalate) nanoparticles loaded with curcumin that release the drug at a pathologically elevated level of H_2O_2, as occurs at an ischemic site. After optimizing in vitro the formulation of curcumin–PVAX nanoparticles and demonstrating their antioxidant, anti-inflammatory and angiogenic activities, the authors evaluated the activity of the product in a mouse model of unilateral hindlimb ischemia. The in vivo results, obtained with the i.m. injection of curcumin–PVAX nanoparticles into the ischemic area on days 0, 3 and 7, showed significant blood-flow recovery and neovascularization, with almost complete blood-flow restoration 12 days after ischemia. The histological examination demonstrated the suppression of tissue damage and inflammatory responses, with an extensive expression of angiogenic factor CD31 [46]. Several other formulations of curcumin, including nano-formulations or encapsulation, have appeared on the market to ensure the optimal intake of the active compound [47][48].

2.4. Safety Profile

Regarding curcumin toxicity, the compound is considered safe and has a good tolerability profile in humans [49][50][51]. The reported side effects mainly include gastrointestinal disturbances. However, in Italy, several cases of acute hepatitis have been reported to be associated with formulations that provide high bioavailability and high doses of curcumin [52]. In fact, the availability of many different formulations of curcumin with an enhanced bioavailability profile has focused on the question of safety. For instance, Fuloria et al. considered the curcumin toxicity profile that emerged during the most recent preclinical and clinical studies; excessive amounts of curcumin may lead to alterations in testosterone levels in men, influence blood clotting and contrast iron absorption [48].

In VigiBase curcumin has 71 potential side effects [25], such as gastrointestinal disorders (i.e., diarrhea and nausea), nervous system disorders (e.g., asthenia and others) and hepatobiliary disorders (e.g., acute liver failure, increase in alanine aminotransferase and aspartate aminotransferase, and others). More trials are needed to understand the safety of curcumin for pharmacological use, also reducing the number of additives, and considering customized microencapsulation [48].

3. Mangiferin

3.1. Chemistry and Sources

Mangiferin is a natural C-glucoside xanthone (2-β-d-glucopyranosyl-1,3,6,7-tetrahydroxy-9H-xanthen-9-one) contained in many plant species, but especially in the fruit, kernels and the leaves of the mango tree (*Mangifera indica* L.), a native plant of India [53][54]. The mango tree also contains similar phenolic components, isomangiferin and homomangiferin, which contribute to the beneficial effects of the plant extracts [55][56]. Mangiferin has four hydroxyl groups in the xanthone nucleus and, thus, can be considered among the occurring phenolic compounds present in higher plants providing antioxidant activity.

3.2. Activity: Preclinical Studies

Mangiferin has been reported to be an antidiabetic, anti-inflammatory, antimicrobial, immunomodulator, anticancer and hypocholesterolemic agent [56]. It has high antioxidant activities due to its hydroxyl groups and redox-active aromatic system of the catechol moiety [54][57]. In addition to the described scavenger activity on ROS, mangiferin can modulate the expression of several genes involved in inflammation and apoptosis, including the induction of the antioxidant Nrf2 pathway [58][59]. Furthermore, it can protect mitochondrial membranes against lipid peroxidation and prevent hydroxyl radical formation by inhibiting Fenton-type reactions [60]. Mangiferin exhibits a strong inhibition of oxidative stress associated with the endoplasmic reticulum by reducing ROS production and attenuating inositol-requiring enzyme 1 (IRE1) phosphorylation [61]. Mangiferin has also been shown to be an inhibitor of the NF–κB signaling pathway [54]. Furthermore, it has been evaluated as a possible pharmacophore structure for the development of new compounds with pharmacological activity in multiple pathological conditions [57], possibly related to inflammation and DM.

In HUVECs, mangiferin (20 µM) counteracts paraquat-induced endothelium damage, preserving the p120–catenin protein level [62]. Furthermore, it protects endothelial cells from oxidative injury induced by H_2O_2 or glycated protein–iron chelate, suggesting a protective role against pathologies linked to oxidative stress [63]. In an experimental model of high glucose/hypoxia-induced angiogenesis, mangiferin was effective in inhibiting angiogenesis by reducing hypoxia-inducible factor–1α, vascular endothelial growth factor and matrix metallopeptidase (MMP)–2 and MMP–9 [64]. Instead, Daud et al. observed that mango extract and mangiferin stimulated the migration of bovine endothelial aortic cells in a modified Boyden chamber assay, suggesting a role for the polyphenol in the promotion of the formation of new blood vessels [65].

The rationale of mangiferin use in DM is also related to its inhibition of AGE formation, hence counteracting the vascular damage typical of the disease. In a rat model of streptozotocin-induced diabetes, Hou et al. observed a sustained suppression of AGE production and a decrease in the protein expression of RAGE receptors; another relevant effect of mangiferin was the inhibition of NF–κB with a reduction in inflammatory cytokines [66]. Using an animal model of a mouse fed with a high-fat diet, Jiang et al. observed that mangiferin (5–20 mg/kg) could reduce plasma lipids and aorta wall thickening [67]. In oxidized-LDL-induced HUVEC injury, the compound was able to

alleviate cellular dysfunction, reducing ROS levels, increasing the release of $NO^{\bullet}$ and activating the PTEN/Akt/eNOS signaling pathway [67]. Recently, a meta-analysis considering 19 studies on diabetic animals, mainly rats and mice, showed that mangiferin intake up to 422 mg/kg reduced blood glucose levels in a dose-dependent manner [68].

An extract of *Mangifera indica* administered to LDL-receptor-deficient mice for 2 weeks produced a reduction in plasma and liver cholesterol levels, ROS production in spleen mononuclear cells and increased plasma total antioxidant capacity [69]. Mangiferin activity in PAD was also indirectly investigated using ethanolic extracts of mango seed (EEMI) in an acute hindlimb ischemia-reperfusion model [70]. Streptozotocin-treated diabetic rats underwent a femoral artery ligation and, then, received EEMI (0.2–0.4 g/kg) for 14 days. Blood flow was observed to be significantly higher in treated animals than in the controls. The plasma levels of malondialdehyde, IL–6, TNF–α and IL–1β were reduced, while glutathione and IL–10 levels were increased in EEMI-treated animals, suggesting anti-inflammatory modulation [70]. In general, given the above reported experimental data, mangiferin appears to offer promise in the prevention and treatment of vascular disease also linked to diabetes and dyslipidemia.

3.3. Activity: Clinical Studies

A 12-week, double-blind, placebo-controlled clinical study was conducted on 104 overweight patients with hyperlipidemia subdivided into 2 groups, administering a dose of 150 mg/day of mangiferin or placebo for 12 weeks. Treatment with mangiferin produced a significant decrease in the serum levels of triglycerides and free fatty acids, and the insulin-resistance index [71]. However, clinical trials conducted on the use of mangiferin in cardiovascular diseases and, moreover, in patients with PAD are lacking.

3.4. Safety Profile

Mangiferin in high concentrations may cause damage to the mitochondrial respiratory chain, since free radicals are also needed for normal cellular activity [54]. The oral administration of 0.9 g of mangiferin has been reported to be harmless to adults [54][72]. Mangiferin per se did not have any adverse reports in VigiBase [25]; otherwise, *Mangifera indica* has 62 reports of unwanted effects, entirely from the Americas [25]. The side effects were mainly gastrointestinal (nausea and diarrhea), nervous system (dizziness) and skin (pruritus and erythema) disorders [25]. Overall, at moderate doses, the compound has been reported to be safe for humans.

4. Quercetin

4.1. Chemistry and Sources

Quercetin is pentahydroxyflavone (3,3′,4′,5,7-pentahydroxyflavone) having five hydroxyl groups belonging to the group of flavonols found in many fruits (e.g., apples, grapes, berries and citrus fruits) and vegetables (e.g., onions, broccoli and Italian chicory) [73], and widely used as a food supplement in various commercial products (generally, 500 mg, twice daily) for circulation, immune system function and respiratory function [74]. Natural derivatives of

quercetin, such as isoquercetin and rutin, exist in natural sources, for instance, in onions and citrus foods [75]. However, the low solubility in water and limited bioavailability of quercetin have limited the medical use of the compound. Several enzymatically modified derivatives of quercetin have been obtained and investigated, mainly for their favorable bioactivity and bioavailability. Quercetin derivatives have also been obtained by using engineered *Escherichia coli* and other microorganisms [75]. The structure-activity relationships of quercetin and its derivatives have been recently investigated in detail [76], including the antioxidant, anti-inflammatory and antidiabetic properties.

4.2. Activity: Preclinical Studies

Quercetin shows prominent antioxidant potential and is considered an effective free-radical scavenger mainly based on several in vitro studies [77][78][79]. The antioxidant activity of quercetin is believed to be linked to the regulation of GSH levels [73]; moreover, the hydroxyl groups on the side phenyl ring of the molecule can bind to amino acid residues of key enzymes, such as acetylcholinesterase and butyrylcholinesterase, both linked to oxidative properties. Quercetin also increases the levels of endogenous antioxidant enzymes, e.g., catalase, GSH peroxidase and superoxide dismutase. More specifically, considering the vascular effects, quercetin induces the vasodilation of isolated rat arteries [80][81][82] and, in vivo, antihypertensive effects on rats fed with a high-fat, high-sucrose diet [81] and in spontaneously hypertensive animals, without effect in normotensive animals [83]. Generally, this flavonoid showed antiangiogenic activity in several experimental models [84][85][86].

The protective effect of quercetin against the activation of ER stress was attributed to the upregulation of markers, such as the 78 kDa glucose-regulated protein (GRP78), a molecular chaperone, and the C/EBP-homologous protein (CHOP) in unresolved diabetic and experimental ER-stress conditions [87]. Furthermore, quercetin pretreatment decreased the expression of tunicamycin-induced ER-stress markers in HUVECs [87]. In another study, mitochondrial-targeted quercetin activities were observed to be a mechanism of protection against neurodegenerative diseases [88]. Quercetin has been reported to protect against hydrogen peroxide-induced pheochromocytoma cell neurodegeneration [89].

In general, quercetin has shown anti-inflammatory action in several experimental models, mainly through mechanisms that inhibit NF–κB and cofactors in the chromatin of proinflammatory genes [90]. Quercetin also increases glucose uptake from the blood by inducing the glucose transporter GLUT4, and promotes glucose storage by the liver [79][91].

4.3. Activity: Clinical Studies

Few trials have examined the effect of quercetin supplementation on blood pressure, with discordant results; however, generally, a reduction in systolic blood pressure both in healthy subjects and hypertensive patients has been reported [92][93][94][95]. Recently, a meta-analysis showed significant decrease in both systolic and diastolic blood pressure with quercetin supplementation; the treatments ranged from 4 to 10 weeks, with doses ≥500 mg/day [96]. Another meta-analysis showed a significant reduction in blood pressure and, furthermore, for

participants receiving quercetin for at least 8 weeks, a decrease in triglycerides in trials with a parallel design [97]. A double-blinded, placebo-controlled cross-over study conducted on 93 overweight or obese subjects aged 25 to 65 years with metabolic syndrome traits showed that quercetin administered at 150 mg/day (6-week-treatment period) reduced systolic blood pressure and plasma oxidized-LDL levels in overweight subjects with a high-CVD-risk phenotype [94].

In the scientific literature, no clinical studies have been reported on the use of quercetin in the treatment of PAD.

4.4. Safety Profile

Egert et al. reported that daily supplementation with 150 mg of quercetin/day, administered orally to volunteer subjects with a high-CVD-risk phenotype for 6 weeks, was safe [94]. In general, the clinical studies reported that the orally administered quercetin use was well-tolerated [96][97].

Quercetin per se has few adverse effects reported in VigiBase [25]; a total of 45 unwanted effects are described, mainly in the Americas and Europe. Nervous system disorders (e.g., dizziness and headache), respiratory disorders (e.g., dyspnea), pruritus and drug interaction are the most recurrent effects [25]. Nevertheless, in general, moderate doses of quercetin are described as safe.

5. Resveratrol

5.1. Chemistry and Sources

Resveratrol is a stilbene derivative (3,5,4′–trihydroxystilbene) occurring both as *trans*- and *cis*-isomers that are present in a variable percentage in several natural sources, the *trans*- form being the most abundant and mainly responsible for the cardiovascular effects [98]. Resveratrol is a phytoalexin (a class of antimicrobials synthesized by plants under pathogen infection) found in many plant foods. Its presence is well-known in red grapes (skin) and red wine, but even in tea and berries and also in various medicinal plants (e.g., *Polygonum* spp. roots) used in popular medicine as treatments for allergic and inflammatory diseases [99].

5.2. Activity: Preclinical Studies

Resveratrol has antioxidant and free-radical scavenger activities that may be responsible for its several biological activities, such as anti-inflammatory, antiatherosclerosis and anticarcinogenic effects [100][101]. The structural determinants of the antioxidant activity of resveratrol have been linked to the presence of hydroxylic functions, in particular, but not only, the hydroxyl group at 4′ position, as demonstrated by an investigation on the derivatives [102].The dose-dependent biphasic hormetic effects of resveratrol have been reported: at low concentrations, it acts as an antioxidant that protects tissues from oxidative stress, while at high concentrations, it may be a pro-oxidant that increases oxidative stress [103]. Similarly, low and high concentrations can provide chemoprevention or cytotoxicity, respectively, against cancer cells [104]. However, resveratrol is especially known for its beneficial effects in cardiovascular diseases. Several authors have shown that it causes vasodilation in different types of isolated

arteries obtained from various animal species (e.g., guinea pigs, pigs, rats and sheep) [105][106][107][108]. Studies showed that the anti-inflammatory activity of resveratrol is mainly mediated by antiadrenergic and antiprostaglandin activation [99]. Resveratrol reduced the sensitivity of myofilaments to free calcium in vascular smooth muscles and enhanced acetylcholine-stimulated calcium increase in the endothelium, promoting $NO^{\bullet}$ production and thus vasorelaxation [105]. At nanomolar concentrations, it induces the endothelial production of $NO^{\bullet}$ by activating the estrogen receptor-α (ERα)–Cav–1–c–SRC interaction, resulting in $NO^{\bullet}$ production through a Gα–protein-coupled mechanism [109]. It down-regulates VEGF/fetal liver kinase-1 (Flk–1) (VEGF receptor-2) expression and, therefore, modulates hyperpermeability and junction disruption in glomerular endothelial cells. In addition, resveratrol ameliorates high-glucose-induced hyperpermeability mediated by overexpressed caveolin-1 in aortic endothelial cells [110]. A recent study using a palmitate-induced insulin-resistance model revealed that resveratrol suppresses IKKβ/NF–κB phosphorylation, TNF–α and IL–6 production, and restores the IRS–1/Akt/eNOS signaling pathway in endothelial cells [111]. Resveratrol has been reported to block the TNF–α-induced activation of NF–κB in coronary arterial endothelial cells and inhibit inflammatory mediators [112], exerting the effect through the action on the IKK cascade, attributing to this mechanism its antioxidant properties. The report by Kim et al. demonstrated that resveratrol, as well as hesperidin and naringenin, reduces high-glucose-induced ICAM–1 expression via the p38 MAPK signaling pathway, contributing to the inhibition of monocyte adhesion to endothelial cells [113]. Recently, resveratrol showed an inhibitory effect against NF–κB p65 and proinflammatory mediators, including TNF–α, ICAM–1 and MCP–1 in endothelial cell lines [114]. Resveratrol confers a protective effect against high-glucose-induced oxidative stress in endothelial cells and vascular protection in high-fat-diet mice, through the Nrf2 pathway [115].

In several experimental models, in vitro and in vivo, resveratrol improved glucose homeostasis and insulin sensitivity [116][117]. An in vivo study conducted on diabetic rats demonstrated that the compound elicits antidiabetic potential by stimulating intracellular glucose uptake and the modulation of sirtuin-1 activity [118]. Resveratrol also relieves the status of diabetic nephropathy, kidney and oxidative stress in diabetic rats [119]. Resveratrol inhibits ATP-dependent K^+ channels and voltage-dependent delayed-rectifier K^+ channels in β-cells, suggesting its beneficial role in delaying the onset of insulin resistance and improving insulin secretion [120].

5.3. Activity: Clinical Studies

Resveratrol is mainly known since it offers a possible explanation for the so-called “French paradox”, which is the low frequency of heart disease in the French population despite the relatively high-fat dietary use, believed to be linked to red wine consumption, as a source of resveratrol [121]. Several clinical trials considered resveratrol both in healthy volunteers and patients with various cardiovascular diseases, but they all considered a limited number of participants. Patients with coronary artery disease received 10 mg/day of resveratrol for 3 months, showing an increase in flow-mediated vasodilation and, in general, an improvement in cardiovascular parameters [122]. A clinical study using resveratrol revealed that oral, 100 mg consumption for 12 weeks may support the prevention of cardiovascular disease and atherosclerosis by stimulating endothelial function [123]. Furthermore, resveratrol also modulates $NO^{\bullet}$ metabolism and contributes to improved vascular function in hypertensive and dyslipidemic patients [124]. In addition, a cross-over, double-blind, placebo-controlled study in which 22 healthy adults received 250 and

500 mg of resveratrol revealed dose-dependent increases in cerebral blood flow [125]. Another study also showed that the acute administration of 75 mg of resveratrol increased neurovascular coupling and cognitive performance in 36 subjects affected by T2DM, improving cerebral perfusion [126]. A meta-analysis concerning 3 clinical trials for a total of 50 DM subjects treated with resveratrol at doses of 10, 150 and 1000 mg daily, for a period of 4 to 5 weeks, did not show any favorable effects on the glycosylated hemoglobin A1c level or on insulin resistance [127]. Recently, a double-blind and randomized clinical trial, entitled “Resveratrol to Improve Outcomes in Older People With PAD” (RESTORE), was conducted on 66 patients with PAD treated with 125 mg/day or 500 mg/day of resveratrol, or placebo for 6 months [128]. However, the trial did not show reliable confirmation that resveratrol improves walking performance detected by the 6 min walk test among patients with PAD [128]. Other clinical studies enrolling a higher number of patients affected by PAD are required to evaluate the efficacy of resveratrol on this disease.

5.4. Safety Profile

Resveratrol exhibited the systemic inhibition of P450 cytochromes when taken in high doses [129]. Furthermore, the ingestion of 25 mg/kg of resveratrol for 60 days in rats altered their thyroid function, causing a goitrogenic effect [130]. Other studies using oral doses of 200 mg/kg/day in rats and 600 mg/kg/day in dogs did not report adverse effects [131]. Few clinical trials have evaluated the safety and tolerability of resveratrol; Brown et al. reported gastrointestinal discomfort at doses of 2.5 and 5 g/day [132]. The administration of resveratrol with single doses of 0.5, 1, 2.5 or 5 g orally in 40 healthy volunteers caused minor adverse events that resolved spontaneously in a few days [133]. In general, 150 mg/day for adults is accepted to be safe [134].

Resveratrol per se has very few adverse reports in VigiBase [25]; a total of 20 unwanted effects have been described in the Americas, Europe and Oceania. Among these, the most common are general disorders (e.g., malaise and fatigue) and disorders of the gastrointestinal and nervous systems [25]. Therefore, low doses of resveratrol could be considered safe and potentially useful for vascular disorders.

6. Conclusions

Natural-drug compounds that provide significant biological activities in the specific vascular district have been suggested, and the task of a chemical approach could be directed to optimize their bioavailability. However, caution should be devoted to the fact, as already observed that, for example, with curcumin, an absolute increase in bioavailability does not necessarily mean an improved benefit/risk ratio when the product is introduced for clinical use. Moreover, derivatives or analogs obtained on the structural basis of natural products do not necessarily produce to compounds that are safe for human use. The occurrence in the molecule of phenolic hydroxyl groups also raises the question of biological stability as drugs. Therefore, a new concept of the wise use of available natural resources should be applied, also in the prospective development of drugs, keeping in mind the limits and advantages of medicinal plants and relative natural compounds.

As a general consideration, a diet rich in polyphenols reduces the risk of cardiovascular adverse events, including PAD. Polyphenols, together with adequate moderate aerobic exercise, can help prevent and reverse age-

associated arterial stiffness. In fact, exercise therapy is considered a class IA (highest level) recommendation for the treatment of patients with PAD. Unfortunately, the long-term participation in perspective clinical and population-based programs is scarce, and therefore this approach is still just outlined. The use of polyphenols, both as dietary intake and dietary supplements, could represent a favorable approach to maintaining the integrity of peripheral blood vessels and limiting the harmful effect of oxidants. The present evidence suggests the validity of further clinical trials to define the role of this class of compounds in the prevention and treatment of vascular artery disease.

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