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Review

Modulation of endothelial nitric oxide by plant-derived products

Christoph A. Schmitt [a,b,*], Verena M. Dirsch [a,*]

[a] University of Vienna, Department of Pharmacognosy, Vienna, Althanstrasse 14, 1090 Vienna, Austria
[b] University College London, Wolfson Institute for Biomedical Research, London, UK

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ABSTRACT

Nitric oxide (NO), produced by endothelial nitric oxide synthase (eNOS), is recognised as a central anti-inflammatory and anti-atherogenic principle in the vasculature. Decreased availability of NO in the vasculature promotes the progression of cardiovascular diseases. Epidemiological and clinical studies have demonstrated that a growing list of natural products, as components of the daily diet or phytomedical preparations, may improve vascular function by enhancing NO bioavailability. In this article we first outline common pathways modulating endothelial NO production or bioavailability to provide a basis for subsequent mechanistic discussions. Then we comprehensively review natural products and plant extracts known to positively influence eNOS activity and/or endothelial function *in vitro* or *in vivo*.

We will discuss red wine, highlighting polyphenols, oligomeric procyanidins (OPC) and resveratrol as modulators of endothelial NO production. Other dietary products and their active components known to activate eNOS include cocoa (OPC and its monomer (−)-epicatechin), pomegranates (polyphenols), black and green tea (flavanoids, especially epigallocatechin gallate), olive oil (oleic acid and polyphenols), soy (genistein), and quercetin, one of the most abundant flavonoids in plants. In addition, phytomedical preparations made from ginkgo, hawthorn and ginseng, as well as formulations used in traditional Chinese Medicine, have been shown to affect endothelial NO production. Recurring phytochemical patterns among active fractions and purified compounds are discussed.

In summary, there is increasing evidence that several single natural products and plant extracts influence endothelial NO production. Identification of such compounds and characterisation of their cellular actions may increase our knowledge of the regulation of endothelial NO production and could provide valuable clues for the prevention or treatment of cardiovascular diseases.

Cardiovascular diseases are the leading cause of death in the developed world and are emerging as a cause of death in developing countries. Endothelial dysfunction, characterised by a reduced capacity of endothelial cells to suppress processes of inflammation, thrombosis and oxidative stress, is a central pathophysiologic process during the initiation and progression of atherosclerotic lesions [1,2]. Endothelial dysfunction, usually assessed as decreased endothelium-dependent vasodilation, predates clinically obvious vascular pathologies and is a direct predictor of atherosclerotic disease progression [3]. An important feature of a healthy endothelium is an adequate output of nitric oxide (NO), which is produced by the enzyme endothelial nitric oxide synthase (eNOS). eNOS catalyses oxidation of the guanidino group of L-arginine in the presence of molecular oxygen and various cofactors, resulting in the stoichiometric production of NO and L-citrulline [4,5].

NO is a highly lipophilic and diffusible gas. It permeates biological membranes, reaching targets outside the cellular compartment in which it was generated. Today, NO is recognised as a major anti-atherogenic factor in the vasculature due to a number of vasoprotective actions. NO directly relaxes vascular smooth muscle cells via activation of soluble guanylate cyclase, playing a major role

* Corresponding authors. Address: Wolfson Institute for Biomedical Research, University College London, The Cruciform Building, Gower Street, London WC1E 6BT, UK (C.A. Schmitt). Fax: +44 20 7209 0470 (C.A. Schmitt), fax: +43 1 4277 55969 (V.M. Dirsch).
E-mail addresses: c.schmitt@ucl.ac.uk (C.A. Schmitt), verena.dirsch@univie.ac.at (V.M. Dirsch).

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in the regulation of vascular tone. NO inhibits nuclear factor-κB-dependent expression of various chemoattractant and adhesion molecules, which mediate recruitment of leukocytes to the endothelium as one of the initial events during atherosclerotic plaque development. Moreover, NO decreases oxidation of low-density lipoprotein (LDL) and antagonises platelet aggregation by inhibiting platelet activation and tissue-factor expression. NO also suppresses abnormal proliferation of vascular smooth muscle cells, a process contributing to lumen narrowing in an atherosclerotic vessel or during restenosis [2]. The number of protective roles of NO in the vasculature is indicative that decreased availability of NO in the vasculature may promote the progression of vascular diseases.

Strategies for the prevention of cardiovascular diseases are receiving much attention. In particular, dietary habits appear to have a big influence on the onset of such diseases [6]. Epidemiological and clinical studies have demonstrated that a growing list of natural products, as components of the daily diet or phytomedical preparations, may improve vascular function by enhancing NO bioavailability. The identification of such compounds and characterisation of their cellular actions may increase our understanding of the regulation of endothelial NO production and could provide valuable clues for prevention or treatment of cardiovascular diseases.

The aims of this review are (1) to outline briefly the common pathways modulating endothelial NO production as a basis for subsequent mechanistic discussions, and (2) to provide a comprehensive review of natural products known to influence positively eNOS activity and/or endothelial function (see Fig. 1).

Regulation of eNOS

Due to the short half-life of NO, tight temporal and spatial regulation of its production is essential. Several highly organised layers of regulation exist, controlling eNOS gene expression and (reversible) post-translational modification of the enzyme. Bioavailability of NO in the vasculature is greatly influenced by the presence of superoxide, which degrades NO.

eNOS gene expression

Although eNOS was initially characterised as a constitutively expressed enzyme, it has become clear that eNOS expression can be up- or downregulated by (patho-) physiological stimuli [7,8]. Epigenetic mechanisms, such as methylation of the eNOS promoter and deacetylation of associated histone proteins, have emerged as important determinants of eNOS expression, specifically for the repression of transcription in non-endothelial cells [9,10].

Since eNOS mRNA half-life is reported to be 10–35 h [11], eNOS protein synthesis will presumably persist long after gene transcription has been repressed. Therefore, modulating the half-life of eNOS mRNA transcripts may be a faster and more efficient way to change eNOS protein expression. Stabilisation of eNOS mRNA can be achieved via 3′polyadenylation [12,13] or via decreased binding of eNOS mRNA destabilising proteins [14,15].

Post-translational modifications

eNOS phosphorylation is a major post-translational regulatory mechanism of eNOS activity and involves a number of kinases and phosphatases. At least six eNOS phosphorylation sites have been identified so far; the amino acid numbers refer to the human eNOS sequence, unless otherwise stated.

Ser^{1177} appears to be the most important positive regulatory domain. It is phosphorylated in response to most stimuli promoting eNOS activation and seems to enhance eNOS activity by increasing electron flux within the enzyme. Phosphorylation is catalyzed by protein kinase B (Akt) and a number of other kinases [16,17].

Thr^{495} represents the major negative regulatory site of eNOS and is constitutively phosphorylated in most endothelial cells in culture. Phosphorylation at Thr^{495} attenuates eNOS activity by interfering with calmodulin binding. In response to certain eNOS agonists – especially those increasing intracellular calcium – Thr^{495} can be rapidly dephosphorylated [18,19].

Further phosphorylation sites include Ser^{633}, where phosphorylation is speculated to be important for the maintenance of NO synthesis after activation of eNOS at Ser^{1177}. The consequences of phosphorylation at Ser^{615} and Ser^{114} as well as at certain tyrosine residues remain controversial or incompletely understood [17,20].

According to Mattagajasingh et al., deacetylation at constitutively acetylated Lys^{496} and Lys^{506} (bovine sequence) by SIRT1 (the mammalian orthologue of yeast silent information regulator 2) can enhance eNOS activity [21]. *S*-nitrosylation of eNOS leads to catalytic inhibition and subcellular redistribution of eNOS [22].

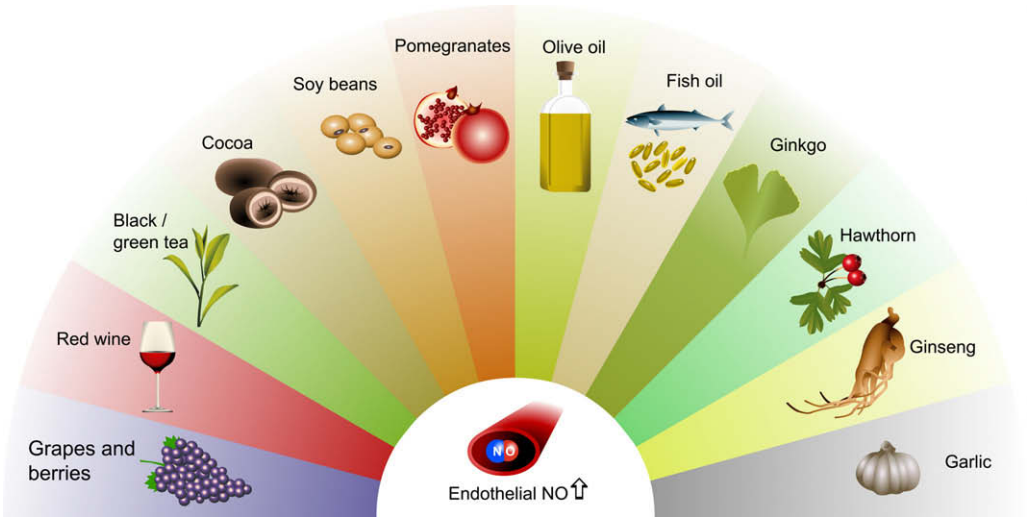

Fig. 1. Some prominent sources of natural products shown to enhance endothelial nitric oxide production and/or bioavailability.

Protein–protein interactions

Protein–protein interactions play an important role in the regulation of endothelial NO production. Calmodulin (CaM) was the first protein shown to interact with eNOS [23]. Bound CaM increases electron flow within the enzyme [24]. Many signalling pathways, especially those initiated by extracellular ligands of G-protein coupled receptors, such as acetylcholine, bradykinin, adenosine, thrombin or histamine, converge on rapidly increasing Ca_i^{2+} concentrations [20]. Therefore, CaM binding represents a fast and prevalent mechanism of eNOS activation. Heat shock protein 90 (Hsp90) increases the affinity of eNOS towards CaM [25] and provides a dynamic scaffold for eNOS activation by Akt and other regulatory proteins [26,27]. The caveolae scaffolding protein caveolin-1 (Cav-1) is an important negative regulator of eNOS in endothelial cells [28].

Among others, eNOS also co-localizes with proteins of the cytoskeleton [29] and the cationic amino acid transporter-1 (CAT-1), which is responsible for the uptake of the eNOS substrate L-arginine [30].

Substrate availability

The substrate L-arginine is an important limiting factor for NO production. Half-saturating arginine concentrations of eNOS were reported to be 3–30 μM [31,32]. Although intracellular L-arginine levels of up to 2 mM [33] are far in excess of the saturation point, intravenous L-arginine infusions have been shown to improve endothelial function acutely [34]. Several hypotheses have been put forward in order to explain this 'arginine paradox' [30,35,36].

Besides cellular uptake via CAT-1, L-arginine can also be recycled from L-citrulline via argininosuccinate synthase (AS) [37]. eNOS activity seems to be in part dependent on L-citrulline-recycling by AS, since inhibition of AS negatively affects NO production [38]. Furthermore, eNOS competes for its substrate with arginase, which converts L-arginine into L-ornithine and urea. Enhanced arginase activity may contribute to endothelial dysfunction [39].

Inactivation of NO by superoxide and eNOS uncoupling

Increased production of reactive oxygen species (ROS) in the vasculature is a hallmark of cardiovascular diseases [40,41]. Although sophisticated enzymatic systems for the detoxification of superoxide exist, the non-enzymatic reaction between superoxide and NO is kinetically preferred over enzymatic conversion of superoxide to hydrogen peroxide by superoxide dismutase [1]. The resulting inactivation of NO and formation of peroxynitrite play an important role in the pathogenesis of a variety of diseases [42]. Inhibition of vascular ROS production can enhance the availability of NO in the vasculature [43].

Under certain circumstance, however, eNOS itself can produce superoxide instead of NO. This phenomenon, known as eNOS uncoupling, is closely linked to availability of the crucial eNOS cofactor 5,6,7,8-tetrahydrobiopterin (BH_4) [44,45]. Peroxynitrite-mediated oxidation of BH_4 compromises eNOS function and leads to a vicious circle of BH_4 destruction, further eNOS uncoupling and increasing vascular ROS production [40,46]. Low endothelial levels of BH_4 are a hallmark of endothelial dysfunction.

Endothelial NO production can be restored or even increased above normal levels by enhancing availability of BH_4 in the vasculature. This can be achieved either by BH_4 supplementation [47], chemical stabilisation of BH_4 by ascorbate [48,49] or via upregulation of BH_4 biosynthesis in the endothelium. The latter has been demonstrated during shear stress as well as after treatment with some antihypertensive and cholesterol-lowering drugs [50–52].

Natural products and plant-derived preparations that influence endothelial nitric oxide bioavailability

The endothelium constitutes the predominant tissue to which any molecule is exposed after absorption into the blood stream and thus represents a potential site of action for compounds taken up with the daily diet. Since eNOS became recognised as a central anti-inflammatory and anti-atherogenic principle in the vasculature, research on natural products as potential modulators of endothelial NO production has increased significantly. In most cases, studies are based on epidemiological data linking nutritional habits with vascular diseases or on the traditional use of phytochemical preparations for their treatment or prevention. In this article we provide a comprehensive overview of natural products and plant-derived preparations for which positive effects on endothelial NO production have been described *in vitro* or *in vivo*. Additional technical information on markers and measurement of endothelium function can be found elsewhere [3].

Grapes and red wine

Epidemiologic data clearly indicate a significant negative correlation of moderate wine consumption with the risk of cardiovascular events [53,54]. Pioneering studies in the early 1990s demonstrated the potential of red wine and grape juice to promote endothelium-dependent dilation of isolated vessels [55]. These beneficial effects are now mainly attributed to the red wine polyphenol (RWP) fraction [56]. Long-term treatment of cultured endothelial cells with red wine or RWP induces eNOS expression and causes a sustained increase in endothelial NO production [57–59]. Upregulation of eNOS is probably based on synergistic mechanisms between the different polyphenolic components [60]. RWP has been shown to improve endothelial function in various animal models of hypertension [61–67]. Furthermore, 240 ml of red wine per day effectively counteracted endothelial dysfunction induced by a high-fat diet in otherwise healthy individuals [68]. However, long-term consumption of red wine failed to improve vascular function in type 2 diabetics and postmenopausal women [69,70]. In another study, four weeks of red wine consumption (375 ml per day) did not alter endothelium-dependent vasodilation and even increased blood pressure in healthy men [71].

Long-term effects of red wine and RWP, such as upregulation of eNOS protein expression, cannot explain the rapid NO-dependent dilation of isolated vessels observed in numerous studies using organ baths [55,72–78]. Mechanistic investigations revealed a partial dependence on calcium influx into the endothelium, triggering NO production presumably via binding of calmodulin to eNOS [79–82]. Similar findings were obtained in endothelial cells in culture: RWP increased Ca_i^{2+} concentrations and promoted phosphorylation of eNOS at Ser^{1177} via the phosphatidylinositol-3-kinase (PI_3K)/Akt-pathway, resulting in the convergence of two independent pathways of rapid eNOS activation [82–84]. During this process oxygen radicals, such as superoxide and hydrogen peroxide, appear to be generated and act as signalling molecules. Therefore, on a cellular level, the actions of RWP may even be considered pro-oxidant, as opposed to their reported function as antioxidants [83]. Such an idea fits with the concept of 'hormesis', suggesting that in response to moderate doses of 'stress' cells may activate compensatory mechanisms conferring protection against repeated exposure to this 'stress' in the future [85].

In humans, a single dose of red wine increased vascular NO production [86] and counteracted smoking-induced increases in blood pressure [87]. Endothelium-dependent vasodilation also acutely improved after intake of red wine in healthy individuals [88,89]. In two studies, the effect appeared to be stronger when alcohol

was removed from wine [90,91]. Dealcoholated red wine also enhanced endothelium-dependent vasodilation in rats and hypercholesterolaemic rabbits [66,92]. Karatzi et al. found that endothelium-dependent dilation in patients suffering from coronary artery disease (CAD) was enhanced by dealcoholated red wine but decreased by regular red wine [93]. In the study of Whelan et al., a meal combined with red or white wine improved endothelial function of CAD patients in both cases, suggesting that wine consumption as part of a meal may be beneficial. It seems, however, odd that the authors found no difference in plasma polyphenol levels between the red and white wine group, which one would expect to be lower after white wine consumption [94].

Rapid activation of eNOS and endothelium-dependent vasodilation has also been demonstrated for grape juice (*in vitro* and *in vivo*) [95,96], red grape polyphenol extract (*in vivo*) [97] and a grape skin extract (*in vitro* and *in vivo*) [55,98]. Grape seed extracts are especially rich in oligomeric procyanidins (OPC) and are able to promote endothelium-dependent dilation of aortic rings *ex vivo* [99–102]. Interestingly, the grade of vasodilation correlated with the degree of OPC oligomerisation, with the bigger molecules being more effective [103,104]. This finding is in agreement with Corder et al., who suggested that OPC may be responsible for the beneficial cardiovascular effects of red wine. Their study showed that the OPC content of several hundred red wines from all over the world correlated with the ability of the wines to inhibit the endothelial release of the vasoconstrictor endothelin-1 *in vitro*. Interestingly, the regions producing wines with the highest amount of OPC (southwest France and Sardinia) showed increased longevity of their population [105].

There is a broad base of experimental evidence for red wine polyphenols as activators of endothelial NO production *in vitro* and *in vivo*, especially derived from animal models of vascular diseases in which NO production is compromised. Alcohol is probably not relevant for activating the eNOS system, but may independently offer cardiovascular protection [106]. Mechanistically, one can discriminate between a long-term effect based on upregulation of eNOS gene expression, and acute actions on the endothelium due to rapid eNOS activation via increases in intracellular calcium and/or activation of the PI3K/Akt-pathway. All these data support the well-established cardiovascular benefit associated with moderate red wine consumption.

Resveratrol

Resveratrol (RV) is a stilbene derivative found in grape skin, red wine, berries and peanuts. In recent years, RV has attracted considerable attention due to its ability to counteract diseases associated with aging or an unhealthy lifestyle and to enhance the life span of a range of laboratory animals [107]. Resveratrol's molecular mechanism of action is not entirely clear. In endothelial cells, RV has been proposed to act via membrane-bound structures, e.g. oestrogen receptors [108], as well as intracellular targets, such as AMP-activated protein kinase, SIRT1 and PGC-1α (peroxisome proliferator-activated receptor-γ coactivator-1α) [107]. The latter play key roles in the metabolic adaptations to caloric restriction. Interestingly, caloric restriction also promotes (and partly depends on) upregulation of eNOS in several tissues [109].

Various studies have demonstrated improved endothelial function upon RV treatment in different animal models for metabolic diseases [110–114]. In most cases this was associated with decreased vascular production of superoxide, but not necessarily with altered eNOS expression [113]. RV also improved vascular function in healthy rats in one study [115], but failed to do so in another [113].

Two groups found that gene expression patterns of healthy mice treated with RV closely mimicked those induced by caloric restriction. In both situations, RV-treated mice showed less signs of aging, including increased aortic elasticity and cardiac function. Pearson et al. reported upregulation of eNOS and downregulation of NAD(P)H oxidase expression in mouse aorta, suggesting that RV may improve vascular function in these animals by both increasing NO and decreasing superoxide production. However, RV-treated mice on a standard diet did not live longer than untreated counterparts [116]. In contrast to existing literature, the delay of aging parameters observed in the study of Barger et al. appeared to be independent of SIRT1 upregulation [117].

A number of studies have demonstrated relaxation of isolated vessels in response to RV [118–127]. However, in most cases NO-dependent vasodilation only accounted for part of the observed effect. The contribution of various endothelium-independent actions seems to vary, depending on type and size of blood vessels [119,121,126] and may be more pronounced at higher RV concentrations [118].

RV increased eNOS expression in various types of endothelial cells in culture [57,58,60,66,128,129]. In one study in bovine aortic endothelial cells (BAEC), RV-mediated eNOS expression and NO production were dependent on oestrogen receptor alpha [130]. Apart from long-term effects on eNOS gene expression, nanomolar concentrations of RV acutely stimulated eNOS activity within 20 min in three different types of endothelial cells in culture. This rapid action was abolished by oestrogen receptor blockers and mimicked by oestradiol or selective agonists for oestrogen receptors alpha and beta, suggesting that both oestrogen receptor subtypes could mediate this effect [108]. Furthermore, RV restored NO production in human umbilical vein endothelial cells (HUVEC) exposed to oxidised LDL [131]. Mattagajasingh et al. discovered a novel mechanism of eNOS activation via deacetylation of lysine residues located in the calmodulin binding region. Interestingly, deacetylation was induced by RV and mediated by SIRT1. However, protein expression of eNOS or SIRT1 remained unaltered after treatment of rat aortic endothelial cells with RV for 16 h [21].

In addition to fully differentiated endothelial cells, RV has also been tested on endothelial progenitor cells (EPC), which are supposed to play an important role in the re-endothelialisation of injured blood vessels. Gu et al. found that RV promoted EPC proliferation and eNOS expression *in vitro* at a low concentration (1 μM), but had the opposite effect if applied at a high concentration (60 μM). Similarly, when rat aortas were artificially injured, eNOS expression was increased in damaged aortas of rats treated with a low RV dose, whereas no such effect was found in rats receiving a high RV dose [132]. RV may also exert beneficial NO-dependent effects in the heart, as observed in ischemia/reperfusion models [106].

Taken together, a number of *in vivo* and *in vitro* studies have shown improved vascular function in response to RV, which appeared to be at least partly due to increased NO availability. However, no such actions have been demonstrated in humans so far. In addition, to what extent RV or its metabolites accumulate *in vivo* is still a matter of debate. Since most red wines contain merely a few milligrams RV per litre and RV in the plasma is known to be metabolised rapidly it seems unlikely that bioactive levels can be achieved by red wine consumption alone [106,133]. The molecular mechanism of action of RV currently remains elusive, suggesting that it may act on different cellular targets, depending on its concentration, the type of target tissue and whether this is healthy or diseased.

Black and green tea

Tea is considered to be the second most frequently consumed beverage worldwide after water. Made from the leaves of *Camellia sinensis*, tea is a rich source of flavanoids. The type and amount of

flavonoids vary depending on preparation and fermentation procedures.

Consumption of black tea has been shown to improve endothelial function in patients with coronary artery disease [134]. In a double-blind, placebo-controlled study with a similar group of patients, one of the main components of green tea, epigallocatechin gallate (EGCG), acutely improved flow-mediated dilation. The changes in vascular reactivity coincided with increased EGCG plasma concentrations [135]. In healthy human subjects, however, a single dose of pure EGCG did not seem to alter vascular NO production [136]. In BAEC, EGCG was shown to activate eNOS rapidly via the PI_3K/Akt pathway [137]. Another study demonstrated that both black and green tea, as well as pure (−)-epicatechin and EGCG, increased NO production in HUVEC after incubation for 24 h [138].

Although catechin concentrations are much higher in green than in black tea, both teas increased eNOS activity in BAEC to the same extent, induced comparable endothelium-dependent vasodilation of rat aortic rings and improved endothelium-dependent vasodilation in healthy women [139]. In smokers, green tea ameliorated endothelial dysfunction within 2 h after consumption [140].

Cocoa

Cocoa drinks made from cocoa (*Theobroma cacao*) powder are further flavanol-rich beverages, which have received considerable attention in recent years [141]. In a double-blind study, Fisher et al. demonstrated that a cocoa drink induced vasodilation via increased endothelial NO production after five days of regular consumption in healthy humans [142]. Follow-up investigations revealed this effect to be mediated in part by (−)-epicatechin [136,143]. Similarly, daily consumption of a flavanol-rich, but not of a flavanol-poor, cocoa drink for two weeks improved insulin-mediated vasodilation in hypertensive patients [144]. In a randomised, placebo-controlled study in healthy men pure (−)-epicatechin acutely elevated plasma and urinary nitrite levels, suggesting activation of the eNOS system [136].

Solid dark chocolate may also exert positive effects on the endothelium. Consumption of flavonoid-rich dark chocolate bars over a period of two weeks improved endothelium-dependent vasodilation, whereas low-flavonoid chocolate bars had no effect. Only in the high-flavonoid group was a significant increase in plasma epicatechin detected [145]. Similarly, 100 g per day of flavanol-rich dark chocolate, but not flavanol-free white chocolate, improved endothelial function and lowered blood pressure in healthy patients [146]. Even a lower dose of 30 g dark chocolate per day over a period of 18 weeks was effective in lowering blood pressure and increasing vascular NO production in healthy men [147]. In the study of Hermann et al., a single dose of 40 g dark chocolate efficiently improved endothelial function over a period of several hours. In contrast, white chocolate was ineffective [148]. A randomised, placebo-controlled trial corroborated that both fluid cocoa and solid dark chocolate improved endothelium-dependent vasodilation. It seems, however, that sugar contained in many cocoa preparations (such as milk chocolate bars) may attenuate these effects [149]. The vascular actions of cocoa flavanols may be more pronounced among older people, whose endothelium function is more disturbed as a result of vascular aging processes [150].

Karim et al. studied the effect of isolated cocoa procyanidins using rabbit aortic rings. Interestingly they found that only oligomeric procyanidins (tetramers or bigger) elicited endothelium-dependent vasodilation and increased eNOS activity [151]. This finding is in agreement with similar observations regarding vascular reactivity of OPC found in red wine, grape seeds and hawthorn [104,105,152].

Soy isoflavones

Epidemiological data from Eastern countries suggest that regular dietary uptake of soy products may decrease cardiovascular risk. This is mainly attributed to soy isoflavones, which exert well-described beneficial effects on plasma lipid and lipoprotein levels [153]. It appears likely that such alterations create a favourable environment which indirectly enhances eNOS activity. In some studies, however, improved endothelial function was observed independently of changes in lipid metabolism. How, and under which circumstances, soy isoflavones are able to modulate endothelial NO production directly are questions that are currently under investigation.

One possible mode of action stems from their weak ability to mimic hormonal effects of oestrogens, which are known activators of eNOS [154,155]. In postmenopausal women, endogenous oestrogen synthesis capacity is compromised. Consequently, the vascular effects of soy isoflavones are often studied in model systems in which circulating oestrogen levels and eNOS activity is decreased, such as ovariectomised animals.

A diet high in soy isoflavones improved endothelium-dependent vasodilation in ovariectomised rats [156] and enhanced the vascular response to acetylcholine in atherosclerotic female (but not in male) rhesus monkeys [157]. Mahn et al. explored the long-term effects of a diet enriched in soy protein and isoflavones in rats. They found that after ten months, soy-consuming animals expressed increased amounts of eNOS in aortas and showed improved endothelium-dependent vasodilation. Interestingly, eNOS expression and vascular reactivity of animals on a standard diet could be improved to a similar extent within six (but not two) months after switching to a soy-enriched diet [158]. By contrast, Lund et al., found no benefit on the eNOS system by soy isoflavone supplementation in cerebral arteries of hypercholesterolaemic rabbits. However, in their study, oestrogen replacement proved to be ineffective as well, shedding doubt on the functionality of the model system applied [159].

The *in vivo* data obtained in humans are not as favourable as might be predicted from the results obtained in laboratory animals. Van der Schouwe et al. found that regular high intake of isoflavones correlated with improved vascular function in Western postmenopausal women [160]. In addition, a meal enriched in soy isoflavones acutely improved endothelium-dependent vasodilation in postmenopausal women [161]. However, several placebo-controlled studies on postmenopausal women conducted over periods of 2–12 weeks found no positive effect of soy isoflavone supplementation on endothelial function, which, in one case, was even slightly decreased in a male control group [162–164]. This suggests that in humans, improvement of vascular NO production upon soy isoflavone consumption is not as robust as are the well-documented beneficial alterations of plasma lipids.

Another possibility is that additional soy components besides isoflavones contribute to the beneficial effects of a soy-rich diet. Isolated soy – but not milk – protein improved endothelial function in hypercholesterolaemic postmenopausal women [165]. Comparing purified soy protein and soy protein plus isoflavones, Steinberg et al. found that soy protein containing isoflavones was slightly more effective in improving vascular function in healthy postmenopausal women. However, the plasma nitrate levels remained unaltered in both groups, suggesting that endothelial NO production was not affected by this treatment [166].

Studies using individual, purified soy isoflavones rather than crude extracts yielded more positive results. The predominant soy isoflavone genistein enhanced eNOS activity and endothelium-dependent vasodilation in postmenopausal women [167] as well as in spontaneously hypertensive rats [168,169]. In the study of Walker et al., it rapidly induced endothelium-dependent vasodi-

lation in postmenopausal women and even in healthy men. Genistein proved as effective as equimolar concentrations of 17beta-estradiol [170]. In isolated small human arteries, however, genistein induced vasodilation was insensitive to eNOS inhibition [121]. After treatment periods of several days, genistein induced eNOS activity in endothelial cells in culture [169,171]. However, the study of Liu et al. showed that genistein also acutely activated eNOS *in vitro* via activation of protein kinase A and phosphorylation at eNOS–Ser^{1177} [172]. A similar mechanism has also been described for equol, an isoflavone derived from the metabolism of daidzein by intestinal flora. Submicromolar concentrations of equol rapidly enhanced NO production in endothelial cells in culture by increasing intracellular calcium and subsequent phosphorylation of eNOS–Ser^{1177} [173].

Pomegranate

Pomegranate juice, made from the fruits of *Punica granatum*, contains high levels of polyphenols, especially of the hydrolysable tannin punicalagin. Pomegranate juice has been shown to increase eNOS expression in human coronary artery endothelial cells (HCAEC) and to decrease atherosclerosis development in hypercholesterolaemic mice [174,175]. In another study, using bovine pulmonary artery endothelial cells, however, eNOS expression and catalytic activity remained unaltered by pomegranate juice. Instead, it seemed that NO was protected from oxidative degradation via the scavenging of superoxide [176]. A pomegranate fruit extract displayed a similar range of effects, increasing eNOS expression and NO release in cultured human coronary aortic endothelial cells, as well as *in vivo* in the vasculature of diabetic rats [177,178].

Taken together, it appears that pomegranate polyphenols exert positive effects on the endothelium, mainly by increasing eNOS expression and by protecting NO from degradation via the scavenging of superoxide.

Olive and fish oil

Olive (*Olea europea*) oil is a cornerstone within the Mediterranean diet. The intake of olive oil, which contains high amounts of the monounsaturated fatty acid (MUFA) oleic acid (OA), is associated with decreased cardiovascular risk [179]. Consumption of a diet rich in MUFA for four weeks improved endothelial function in healthy men [180]. The role of OA as an active ingredient was investigated by Herrera et al. They administered to hypertensive rats olive and sunflower seed oil, which contained similar amounts of OA. However, only olive oil improved endothelium-dependent vasodilation. This suggests that other factors besides OA contribute to the vascular effects of olive oil [181].

Apart from fatty acids, olive oil also contains a range of polyphenolic compounds, which give the oil its individual taste. These are present in particularly high amounts in extra-virgin olive oil. Ruano et al. investigated the vascular effects of a low- and high-polyphenol variant of the same olive oil in hypercholesterolaemic patients. Two hours after consumption, endothelial function and plasma nitrate levels were increased in the group assigned to the polyphenol-rich olive oil [182]. One olive oil polyphenol of particular interest due to its potent antioxidant activity is hydroxytyrosol. Although hydroxytyrosol is considered to be a mediator of the benefical health effects associated with extra-virgin olive oil, it does not appear to modulate eNOS expression or activity directly, at least in endothelial cells in culture [183]. A range of triterpenic compounds can be found in pomace ('orujo') olive oil, a sub-product generated during olive oil making. Pomace olive oil improved endothelial function in hypertensive rats, a feature, which may be related to its content of the pentacyclic triterpene oleanolic acid [184,185].

Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are n-3 (omega-3) polyunsaturated fatty acids originally found in fish oil. They are widely agreed to confer a range of cardioprotective actions, including beneficial alterations of eicosanoid and lipid metabolism, as well as other direct effects on vascular smooth muscle cells [186]. Both DHA and EPA induced NO-dependent vasodilation in pigs and isolated rat aortas [187,188].

In patients with coronary heart disease and in a rat model of diabetes, however, fish oil or DHA supplementation was unable to improve endothelium-dependent vasodilation [189,190]. Although DHA, but not EPA, enhanced the vasodilator capacity in mildly hyperlipidaemic men, endothelium-independent effects appeared to be mainly responsible for this phenomenon [191]. In bovine coronary arteries, EPA, but not DHA, improved NO-dependent vasorelaxation. Further investigations by the same group using cultured BAEC revealed that EPA activated eNOS by promoting its disassociation from caveolin-1, a negative regulator of eNOS, followed by intracellular relocation of the enzyme to the cytosol [192]. Li et al. demonstrated that DHA may also be able to activate eNOS in HUVEC via a similar molecular mechanism [193]. Long-term incubation of HCAEC with DHA increased NO production presumably by enhancing Hsp90 expression [194]. In another study, however, incubation of HUVEC-derived EA.hy926 cells with EPA and DHA for 24 h did not change basal endothelial NO production, and even blunted the response to the eNOS agonist histamine [195].

In summary, the monounsaturated fatty acid OA seems to be an important determinant of beneficial vascular effects of olive oil. In addition, the triterpene olanolic acid and possibly polyphenols may positively modulate eNOS. The polyunsaturated omega-3 fatty acids EPA and DHA appear to directly affect endothelial NO production, possibly by altering the lipid composition of the plasma membrane, leading to displacement of eNOS from its negative regulator caveolin-1 [193]. *In vivo*, however, other eNOS-independent vasodilator mechanisms of n-3 fatty acids may play more important roles.

Garlic

Garlic (*Allium sativum*) is used worldwide as a remedy for various diseases. In the cardiovascular system garlic has been described to exert beneficial effects on blood lipid and cholesterol levels, which may help indirectly to maintain a healthy endothelium [196]. Crushing of garlic cloves leads to the formation of allicin, the predominant of various organosulphur compounds in garlic.

Early studies by Das et al. reported activation of NOS by an alcoholic garlic extract in cell free placenta and platelet homogenates [197]. This did not appear to be related to the high concentrations of L-arginine present in the extract [198]. Pulverized dried garlic applied to rats over a period of four weeks increased urinary excretion of NO metabolites [199]. An aqueous garlic extract was shown to ameliorate endothelial dysfunction in a rat model of diabetes after eight weeks of consumption [200]. In another study, 3-week treatment of rats with raw garlic improved the coronary endothelial response to acetylcholine in a rat model of pulmonary hypertension. Allicin-free boiled or aged garlic, however, had no effect [201]. Further studies by the same authors showed that an aqueous garlic extract induced acute vasodilation in isolated rat pulmonary arteries, which was reduced 70–80% by removal of the endothelium or NOS inhibition, suggesting a major, but not exclusive, contribution of eNOS-derived NO. Again, when allicin formation was blocked by boiling or ethanol extraction, vasodilation was completely abolished [202–204]. On the contrary, Kaye et al., found that dose-dependent vasodilation by allicin in the rat pulmonary vascular bed was insensitive to inhibitors of NOS, cyclooxygenase

or ATP-sensitive potassium (K_{ATP}) channels on vascular smooth muscle cells. In their study, diallyl disulfide did not alter rat pulmonary perfusion either [205]. In rat aortic arteries NOS inhibition was ineffective, whereas blockage of K_{ATP} channels prevented vasodilation by aqueous garlic extract, indicating a direct relaxant action on the vascular smooth muscle [206]. Although aqueous garlic extract and the purified compound *S*-allyl cysteine both increased cGMP production in HUVEC, the authors of this study found no changes in eNOS activity or protein levels, suggesting a protection of NO from degradation [207].

Aged garlic extract is obtained by storage of garlic cloves in (diluted) ethanol for several months resulting in the conversion of allicin and other odorous substances into more stable compounds. Aged garlic extract was described to improve flow-mediated vasodilation after 2–6 weeks of consumption in patients with coronary artery disease [208] as well as in healthy individuals with experimentally induced hyperhomocysteinaemia [209]. Another group reported acute stimulation of endothelial NO release by aged garlic extract in rats [210]. These studies suggest that factors other than allicin or its degradation products may improve endothelial function as well.

An important mechanistic finding was contributed by the study of Benavides et al., who linked relaxation of rat aortic rings by aqueous garlic extract to the generation of hydrogen sulfide (H_2S) from organosuphur compounds [211]. H_2S is known to induce vasorelaxation by acting as an opener of K_{ATP} channels on the vascular smooth muscle [212]. The authors also noted that unphysiologically high oxygen concentrations, at which vasorelaxant studies are usually carried out, would accelerate H_2S oxidation and therefore result in overestimation of the contribution of NO signaling to garlic-induced vasodilation. However, H_2S may also trigger release of NO from cellular *S*-nitrosothiols [211].

The study of Bautista et al. [213] attributed the *ex vivo* vasodilatory effect of allicin, diallyl disulfide and aqueous garlic extract in rat mesenteric arteries to the activation of TRPA1 calcium channels of vascular sensory neurons. In this regard, garlic compounds seem to resemble the mode of action of other irritant natural compounds, such as capsaicin or isothiocyanate [213]. Recent work in rat cerebral arteries found that TRPA1 is also expressed on endothelial cells. Thus TRPA1 agonists may also cause NO-independent vasodilation by promoting the release of endothelium-derived hyperpolarisation factor(s) [214,215].

Taken together, there are data suggesting beneficial impact of garlic on endothelial-dependent vasodilation. However, so far evidence regarding a direct action on eNOS remains sparse and a well-defined mechanism of action, especially regarding the characteristic organosulphur compounds, is lacking.

Caffeine and coffee

Caffeine is probably the most widely used pharmacological substance in the world. Umemura et al. showed that, while temporarily increasing blood pressure, caffeine improved endothelial function 1 h after intake [216]. NO-dependent vasodilation in response to caffeine was also demonstrated in rat aortic rings, presumably due to increases in endothelial Ca_i^{2+} concentrations [217]. In contrast, another group has shown that consumption of caffeinated coffee, but not decaffeinated coffee, decreased endothelial function for approximately 1 h in healthy adults [218]. Furthermore, several other studies have reported increased blood pressure and arterial stiffness after caffeine intake, which may indicate impaired endothelial function [219]. Investigating individual coffee components, Suzuki et al. demonstrated that 5-caffeoylguinic acid improved endothelial function in hypertensive rats [220].

Quercetin

Quercetin is considered one of the most abundant polyphenols in plants and in the diet [221] Quercetin has been shown to exert endothelium-dependent vasodilation of aortic rings in a wide range of studies [55,76,77,118,222–225] with only few exceptions [80,226]. Beneficial effects on endothelial function have further been demonstrated in various animal model systems [92,227–230], as well as in humans [136].

In cell culture experiments, quercetin was shown to enhance eNOS activity in HUVEC rapidly via increases in Ca_i^{2+} concentration [231]. Several other *in vitro* studies, however, showed no or even a negative effect of quercetin on eNOS expression and/or endothelial NO production [57,60,232,233]. Notably, addition of quercetin (or other redox active compounds) to cell culture media can promote generation of hydrogen peroxide [234]. Since hydrogen peroxide can, depending on its concentration, either activate eNOS or damage endothelial cells [235], this may lead to *in vitro* artifacts that may possibly explain the high degree of variation observed in these studies.

Because quercetin is highly abundant in plants, its uptake may correlate with the amount of fruit and vegetables in the diet. It is tempting to speculate that quercetin and its potential to enhance endothelial NO production constitute one aspect of the range of healthy effects associated with a diet rich in fruit and vegetables.

Phytomedical preparations

An extract of *Ginkgo biloba* leaves, traditionally used in Europe for the treatment of central vascular diseases, increased eNOS expression, eNOS–Ser^{1177} phosphorylation and improved coronary artery circulation in patients with coronary artery disease [236,237]. Hawthorn (*Crataegus laevigata*) extract was demonstrated to elicit endothelium-dependent vasodilation [238,239]. The extract subfraction containing the highest amount of OPC enhanced NO release from human coronary artery cells in culture, probably by inducing a favourable eNOS phosphorylation pattern [152].

Ginseng (*Panax ginseng*) root aqueous extract rapidly activated eNOS via the PI3K/Akt-pathway in HUVEC [240]. This effect might be mediated by the triterpen saponin ginsenoside Rg1, which induced eNOS phosphorylation via Akt at nanomolar concentrations in HUVEC [241]. In a similar fashion, but at slightly higher concentrations, ginsenoside Rb1 acutely induced eNOS–Ser1177 phosphorylation and NO production in human aortic endothelial cells. Interestingly, this effect was blocked by an androgen receptor antagonist [242]. Ginsenoside Rb1 also protected endothelial NO production in HUVEC from the deleterious effects of oxidised LDL [243] and preserved endothelium-dependent relaxation in porcine coronary arteries after incubation with homocysteine [244]. These data go in line with the observation of Jeon et al., who found increased eNOS activity at unaltered eNOS protein levels in rat aortic homogenates after three days of treatment with a saponin fraction of Korean red ginseng roots [245]. In the study of Persson et al., however, an aqueous extract of *Panax ginseng* did not alter NO production in bovine mesenteric arteries or HUVEC [246].

Salvia miltiorrhiza water extract, known in traditional Chinese medicine as 'Danshen', increased eNOS expression and activity in hamsters [247]. The pentacyclic triterpene ursolic acid seems to be one of the active constituents of 'Danshen' as it was demonstrated to be a potent inducer of eNOS expression [248]. Betulinic acid, a triterpene with a very similar chemical structure, represents an active principle of another traditional Chinese medicine preparation obtained from *Zizyphi Spinosi* seeds. It appears to posses the interesting dual property of eNOS up- and NADPH oxidase down-regulation, which synergistically enhances endothelial NO release

[249]. Finally, extracts of other ethnopharmacologically used plants from Madagascar and Thailand may exert positive effects on the eNOS/NO-system [250,251].

Miscellaneous

Ascorbic acid (vitamin C) was shown to enhance eNOS activity via stabilisation of the crucial eNOS cofactor BH_4 [48,49]. The lignan sesamol, derived from sesame seeds, increased eNOS expression and activity in HUVEC in culture [252]. Furthermore, an aqueous extract of sesame leaves enhanced NO-dependent vasodilation in guinea-pig aortic rings [253]. An artichoke (*Cynara scolymus*) leaf extract increased eNOS mRNA and protein expression *in vitro* and enhanced endothelium-dependent vasodilation of rat aorta [254]. Other natural products found in the diet for which stimulatory effects on eNOS have been described in cell culture models include the citrus flavanone hesperidin [255], the passion flower flavone chrysin [256], the legume flavanoid dioclein [257], the tannin 1-alpha-*O*-galloylpunicalagin [258], and the oat polyphenol aventhramide [259]. Furthermore, the anthocyan pigments cyanidin and cyanidin-3-glucoside, found in berries, have been shown to activate eNOS rapidly and to induce eNOS expression after longer incubation times *in vitro* [60,260–262]. On the contrary, an elderberry extract rich in cyanidin-3-glucoside did not relax porcine coronary arteries, whereas choke- and bilberry extracts containing a different anthocyanin pattern induced NO-dependent vasodilation [263]. A 1:100 dilution of cranberry juice was also able to relax rat aortic rings [264]. Freeze-dried strawberry homogenate caused endothelium-dependent relaxation of rabbit aortic rings and promoted phosphorylation of Akt and eNOS in HUVEC [265]. Watermelon juice, which is rich in L-citrulline, improved endothelium-dependent vasodilation, increased vascular BH_4 levels and lowered glucose levels in diabetic rats [266]. In this context, conversion of L-citrulline into the eNOS substrate L-arginine may play a role (see chapter Substrate availability). Oregano extract, obtained by dimethyl sulphoxide-extraction of *Origanum vulgare*, increased eNOS activity in HUVEC within 1 h [267]. Norfuraneol, a pentose-breakdown product found in cooked food, is able to increase endothelial NO production and eNOS activity in human endothelial cells in culture, presumably due to specific dephosphorylation of eNOS–Thr^{495} by protein phosphatase 1 [268]. Interestingly, long-term exposure of HAEC to cocaine significantly decreased eNOS expression and NO production, probably due to increased release of endothelin-1, a negative regulator of eNOS [269].

Summary

Although the abovementioned studies may vary in terms of scientific rigour, it is apparent that a wide range of natural products and plant extracts can enhance endothelial NO production both *in vitro* and *in vivo* (see Tables 1 and 2). A closer look at the phytochemistry reveals several recurring patterns.

Some chemical classes were independently discovered as active principles in more than one plant species. An important example of this are the oligomeric procyanidins (OPC), which were identified as active principles in red wine, grape seeds, cocoa and hawthorn extract [104,105,151,152]. The size of the OPC molecule appears to be an important determinant of its NO-dependent vasoactive action: the bigger, higher polymerised molecules were found to be more effective. The fact that absorption of intact OPC was demonstrated *in vivo* [270], has even prompted speculation about a potential 'OPC-receptor' present on endothelial cells, which may mediate such actions [271].

By far the most studies to this date have focused on plant polyphenols. However, the term 'polyphenols' describes a structurally heterogenous group of compounds. Additionally, many studies lack proper phytochemical characterisation of applied polyphenol preparations, implying that such preparations vary greatly in composition. Despite these limitations, studies investigating the vascular effect of polyphenolic preparations have been largely positive, especially concerning polyphenols extracted from red wine and pomegranate (see chapters Grapes and red wine and Pomegranate). There are data suggesting that vascular effects of a polyphenol mixture are due to synergy between its components. In some cases, however, individual phytochemicals have already been identified as main active principles and modulators of endothelial NO production. One can expect to see this list growing in the future.

Quercetin, one of the most abundant polyphenols in the diet, has been intensively studied. This is reflected in a broad base of experimental evidence for an eNOS-activating action (see chapter Quereetin). Resveratrol seems to improve vascular NO production probably by upregulating eNOS expression while inhibiting generation of superoxide, although the molecular mode of action currently remains elusive and up to date no such action has been

Table 1
Selected plant-derived liquid preparations and solid plant extracts affecting endothelial NO production and/or bioavailability.

Plant/extract	Studies with *positive* effects on eNOS/NO			Studies with *no/negative* effects on eNOS/NO		
	Cell culture	Isolated vessel	*In vivo*	Cell culture	Isolated vessel	*In vivo*
Cocoa drinks/chocolate (dark)		[151]	[142,144–150]			
Garlic (raw or aqueous extract)	[207]	[202–204]	[199–201]		[206,211]	
Garlic ("aged")			[208,210]			[201]
Gingko leave extract	[236]	[236]	[236,237]			
Ginseng root extract (aqueous)	[240]		[245]			[246]
Grape juice/grape juice extract	[58]	[55,95]	[96,97]			
Grape seed extract/OPC	[102,105]	[77,99–104]				
Grape skin extract		[55,98]				
Hawthorn extract		[152,238,239]				
Olive oil (extra virgin)			[180–182]			
Olive oil (pomace)			[184,185]			
Pomegranate juice/pomegranate extract	[174–176,178]		[174,177,178]	[176]		
Red wine	[59,60]	[55,75,76,78]	[65,66,68,86–90,94]		[226]	[69–71,91,93]
Red wine (dealcoholated)			[66,90–93]			[89]
Red wine (polyphenol extract)	[57,58,82–84]	[72–74,79–82]	[61–64,67]			
Soy isoflavones (plus soy protein)			[156–158,160,161,166]			[159,162–164]
Tea (green)	[138,139]	[139]	[139,140]			
Tea (black)	[138,139]	[139]	[134,139]			

Table 2
Selected purified natural products with reported positive effects on endothelial NO production. Compounds with at least two positive reports are listed.

Pure compound	Studies with *positive* effects on eNOS/NO			Studies with *no/negative* effects on eNOS/NO		
	Cell culture	Isolated vessel	*In vivo*	Cell culture	Isolated vessel	*In vivo*
Cyanidin	[60,260]				[80]	
Cyanidin-3-glucoside	[261,262]					
Delphinidin	[84,260]	[73,80]		[57,60]		
Docosahexaenoic acid (DHA)	[193,194]		[187,188]	[192,195]	[192]	[189–191]
Eicosapentaenoic acid (EPA)	[192]	[192]	[187,188]	[195]		[189,191]
(−)-Epicatechin	[138]		[136,143]	[60,233]	[80]	
Epigallocatechin gallate (EGCG)	[137,138]		[135]			[136]
Genistein	[169,171,172]		[167–170]		[121]	
Ginsenoside Rb1	[242,243]		[244]			
Quercetin	[231]	[55,76,77,118,222–225]	[92,136,227–230]	[57,60,232,233]	[80,226]	
Resveratrol	[21,57,58,60,66,108,128–131]	[118–127]	[110–116]		[55,121]	[113]

demonstrated in humans (see chapter Resveratrol). Investigation of endothelium-dependent vasodilation caused by cocoa showed that (−)-epicatechin plays an important role [136,143]. It maintains its eNOS-activating properties when applied as a purified compound [136,138]. Interestingly, (−)-epicatechin is also a possible building block out of which oligomeric procyanidins are formed. Delphinidin, an anthocyanidin frequently found in red wine and grape juice, has positively affected endothelial NO production in several studies [73,80,84,260]. Cyanidin, which compared to delphinidin lacks one phenolic hydroxyl group, as well as cyanidin-3-glucoside, was shown to activate eNOS in endothelial cells in culture [60,260–262]. The soy isoflavone genistein improved endothelial NO production both acutely and via upregulation of eNOS expression after longer treatment periods [167–172]. Finally, a group of pentacyclic triterpens seems to increase endothelial NO production potently: betulinic, oleanolic and ursolic acid share a very similar chemical structure based on the same elemental formula. Betulinic and ursolic acid have been identified as possible active principles in Chinese medicinal preparations [248,249], whereas oleanolic acid was independently discovered as a potential eNOS activator in pomace olive oil [184,185].

It is important to keep in mind that studies on isolated vessels or cell cultures do not take into account absorption and metabolic conversion of the applied compounds. For example, plasma levels of polyphenols do rarely exceed low micromolar levels and may therefore be orders of magnitude lower than concentrations applied when investigating their actions on isolated vessels or cells in culture. In addition, most polyphenols are metabolised rapidly in the liver, which has profound consequences on their solubility and thus membrane permeability [221]. Addition of redox-sensitive compounds to cell culture medium may even result in artificial generation of hydrogen peroxide, leading to false positive results [234]. Studies *in vivo*, on the other hand, do usually not allow discrimination between direct activation of eNOS and indirect modulation of endothelial function, for example due to changes in lipid metabolism, as it has been implicated for soy isoflavones.

It is interesting to note that endothelial cells are not the only sources of NO in the vasculature. For example, inducible NOS is expressed in many tissues under inflammatory conditions and neurons have been suggested to release significant amounts of NO derived from neuronal NOS into vessels [272]. Alternatively, NO may be released from nitrosothiols or created by reduction of nitrite, especially under hypoxic conditions. Plasma nitrite levels in turn are influenced by the diet [273]. In addition, endothelial cells release a range of further substances besides NO that may promote vasodilation, including prostacyclin, epoxyeicosatrienoic acids and other substances commonly referred to as endothelial-derived hyperpolarizing factors. Thus, there are numerous other ways for natural products to promote vasodilation or confer vascular protection [215,274].

In summary, there is increasing evidence that several single natural products and plant extracts derived from foodstuffs, drinks and also herbal medicines influence endothelial NO production. Despite large efforts and progress in the field, there is still room for further research activities, especially in terms of phytochemical analysis of active extracts and regarding the mode of action of identified single natural products. The understanding of the latter may increase our knowledge about eNOS regulation and provide valuable strategies for the prevention of cardiovascular disease.

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