Antioxidants and Beneficial Microvascular Effects
Is This the Remedy?
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Cardiovascular (CV) disease is the leading cause of death and disability worldwide. Usually, CV disease derives from atherosclerosis and its complications. In this context, the vascular endothelial dysfunction plays a pivotal role in atherogenesis and can be triggered and maintained by increased oxidant generation. This, in turn, causes a disruption in the balance between NO and reactive oxygen species (ROS), finally resulting in decreased NO bioavailability, accumulation of lipid peroxidation products, induction of inflammatory genes, activation of matrix metalloproteinases, and increased vascular smooth muscle cell growth.

In many forms of hypertension, the increased generation of ROS derives from NADPH oxidase and could also induce endothelial NO synthase (eNOS) uncoupling. Thereby, increased ROS generation may favor a complete derangement of the NO system, with decreased NO bioavailability and a paradoxical NO synthase–related oxidative, that is, nitrosative, stress. Because of the antiatherogenic antithrombotic properties of NO and the proatherogenic prothrombotic actions of endogenous oxidants, a decreased NO bioavailability with increased oxidative and nitrosative stresses will result not only in impaired, endothelium-dependent vasorelaxation but also in the acceleration of atherogenesis and onset of acute atherothrombotic events. According to this, inhibiting formation of ROS with antioxidants has been proposed to positively affect vascular function and structure. Diverse compounds have been reported to exhibit a wide range of biological activities that may explain their potential cardioprotective properties.

Of particular interest, mechanistic studies support the role of melatonin and Pycnogenol (a flavonoid-rich extract of French maritime pine bark) in protecting against the initiation and progression of atherosclerosis, as well as providing for putative antihypertensive effects. The bioactivity and CV effects of these specific compounds seem to be mediated by a variety of mechanisms, but particular attention has been paid to their direct and indirect antioxidant actions.

In this issue of Hypertension, Rezzani et al7 report that 6 weeks of treatment with Pycnogenol and melatonin may protect the vasculature in spontaneously hypertensive rats (SHRs). Endothelium-dependent relaxation was assessed in mesenteric small resistance arteries by measuring the vasodilator response to acetylcholine after precontraction with norepinephrine. Then, variations in oxidative stress and vascular structure (aortic content of total collagen, collagen subtypes, and apoptosis rate) were evaluated. Compared with untreated SHRs, the authors observed that systolic blood pressure, media:lumen ratio, and media cross-section and media thickness of mesenteric small arteries were significantly reduced by either melatonin or Pycnogenol administration. Concordantly, although the response to acetylcholine was not fully normalized, a significant improvement in endothelial function, paralleled by a decreased inducible NO synthase protein expression and oxidative stress, was observed in treated SHRs. Of particular interest, total aortic collagen content (corresponding with type I, ie, fibrotic collagen) was significantly higher in untreated SHRs compared with both Wistar-Kyoto control rats and melatonin- or Pycnogenol-treated SHRs, in which type III, that is, constitutive collagen, was prevalent.

The observed findings confirm the fascinating hypothesis that oxidative stress deeply affects several mechanisms operating simultaneously. CV risk factors favor the development of both macrovascular and microvascular complications, and usually only an aggressive treatment can reduce the progression of the atherosclerotic risk. This experimental evidence is the first step for future studies that should be addressed to definitively clarify the strict relationships (to be confirmed in animal models and then tested and verified in humans) among foods, antioxidant supplementation, microvascular and macrovascular remodeling, and CV protection.

In keeping to this, the reported findings are exactly of interest in terms of identifying potential antioxidant compounds for diet supplementation in preventing structural and functional vascular alterations, which are the hallmarks of hypertension, probably a consequence of their specific antioxidant, anti-inflammatory, and free radical scavenging effects (also by decreasing inducible NO synthase, resulting in a reduction in the generation of inflammatory NO radicals). This evidence is strongly supported by studies suggesting that melatonin improved NO production, and decreased oxidative load leading to the prevention of endothelial structural alterations (these effects were at least in part attributed to rebalancing the pro-oxidant/antioxidants system, lowering calcium content, and increasing NO and cGMP levels in vascular tissue of rabbit aortic rings). In addition, in rats on a high-fat diet, melatonin administration attenuated atheromatous changes in arteries along with the normalization of blood pressure, body weight, blood glucose, improvement of antioxidant capacity, and lipid profile. Similarly, it has been observed that exposure of human endothelial cells to the (−) epicatechin (a monomeric flavanol well represented in Pycnogenol) resulted in the elevation of cellular levels of NO and cGMP and in protection against oxidative stress elicited by proinflammatory agonists also by inhibiting NADPH oxidase activity. Concordant to this, NO protection against oxidants and in-
Increased NO bioavailability has been suggested to be the main responsible for the vascular health benefits deriving from flavonoid consumption, particularly in conditions that are known to be characterized by increased oxidant production, decreased antioxidant defense mechanisms, or both.\textsuperscript{10} Pycnogenol protects against oxidative stress in several cell systems by doubling the intracellular synthesis of antioxidative enzymes and by acting as a potent scavenger of free radicals. Other antioxidant effects involve a role in the regeneration and protection of vitamin C and vitamin E. Moreover, Pycnogenol has been described to antagonize the vasoconstriction caused by epinephrine and norepinephrine by increasing the activity of eNOS.\textsuperscript{6} Of note, flavonoids and Pycnogenol have been reported to inhibit angiotensin-converting enzyme, associated with a mild antihypertensive effect.\textsuperscript{6,10} Thus, angiotensin-converting enzyme inhibition likely contrasts direct and indirect negative effects of angiotensin II on blood pressure levels, arterial function, and remodeling.\textsuperscript{2–4} Indeed, this inhibitory effect favors NO production by preventing the induction of NADPH oxidase activity and the production of superoxide anion, which trigger NO oxidation to peroxynitrite,\textsuperscript{2–4,10} and by preserving bradykinin at adequate concentrations to maintain eNOS activity. However, how flavonoids and melatonin interact with the biological system to improve endothelial function and affect arterial structure is uncertain as yet. All of the considered mechanisms might be physiologically related and, thus, clinically relevant (Figure).

The increasing trend in morbidity and mortality associated with CV risk factors is likely to have a profound impact on families, communities, health care resources, and funding. Thus, new cost-effective interventions that effectively manage the disease need to be sought. In this regard, knowledge on nutraceuticals and functional foods is progressively assuming clinical interest.

The reported findings shed new light on future investigation on this interesting topic. This may extend the knowledge on pathogenetic mechanisms of CV diseases, provide additional explanation for variability, and potentially generate new impulses for the development of novel therapeutic approaches.

### Disclosures

None.

### References
