Natural antioxidants: A novel approach for counteracting cardiometabolic risk
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Bergamot (Citrus Bergamia) is an endemic plant of Calabrian region in Southern Italy. To date, 95% of worldwide bergamot production occurs in the Ionic area of Calabria, where soil characteristics and pH (6.5–7.5) are particularly suitable for its cultivation.

Bergamot essential oil (BEO) is made up of a volatile fraction and a non-volatile residue. Volatile components make up approximately 93–96% by weight of bergamot oil, while the non-volatile residue represents the remaining 4–7%. The non-volatile fraction is a mixture of monoterpenes and sesquiterpenes hydrocarbons (such as limonene, γ-terpinene, and δ-piene) and their oxygenated derivatives (linalool and linalyl acetate). The non-volatile (4–7% of total) fraction containing coumarins and psoralens [such as bergapten (5-methoxypsoralen) and bergamottine (5-geranyloxypsoralen)]. The non-volatile residue, which influences the olfactory properties of the oil, contains waxes and polymethoxylated flavones other than about 0.2% bergapten which is responsible for the phototoxicity of BEO. The bergapten-free extract of the essence (BEO-BF) together with a natural essence deprived of the hydrocarbon fraction and of bergapten (BEO-HF/BF) are prepared by extractive industries for perfumery and cosmetic uses [2,3].

Bergamot differs from other citrus fruits not only because of the composition of these flavonoids, but also because of their particularly high content. Some of the flavonoids such as naringin, present also in grapefruit, have already been shown to be active in animal models of atherosclerosis, while neoeiropitritin and rutin exhibited the strongest capacity to inhibit LDL oxidation. Importantly, bergamot juice is rich in 3-hydroxy-3-methylglutaryl neohesperidosides of hesperetin (brutieridine) and naringenin (melitidine) with ability to inhibit HMG-CoA reductase. These compounds most likely contribute to the important hypolipemic effects of bergamot juice and vasoprotective effects of bergamot oil derivatives in rats and in humans as demonstrated by recent clinical studies carried out in patients treated with bergamot-derived polyphenolic fraction (BPF) obtained concentrating bergamot juice in a form of powder, enriched in flavonoids.

Epidemiologic studies have demonstrated that a Mediterranean diet rich in olive oil is associated with decrease in risk for cardiovascular disease, obesity, and diabetes. Although some of the protection may be from the unsaturated fatty acid components of such a diet, additional small molecules found in olive oil and olive plants may confer protection, including the polyphenol oleuropein and hydroxytyrosol.

The two main sources of olive polyphenols are olive leaves and the waste from the olive oil industry. Olive leaves have the highest antioxidant and scavenging power among the different parts of the olive tree. There are five groups of phenolic compounds principally present in olive leaves: oleuropeiosides (oleuropein and verbascoside); flavones (luteolin-7-glucoside, apigenin-7-glucoside, diosmetin-7-glucoside, luteolin, and diosmetin); flavonols (rutin); flavan-3-ols (catechin), and substituted phenols (tyrosol, hydroxytyrosol, vanillin, vanillic acid, and caffeic acid). The most abundant compound in olive leaves is oleuropein, followed by hydroxytyrosol, a precursor of oleuropein, the flavone-7-glucosides of luteolin and apigenin, and verbascoside, a conjugated glucoside of hydroxytyrosol and caffeic acid.

Oleuropein prevents cardiac disease by protecting membrane from lipid oxidation, by affecting coronary blood vessel dilation, by exerting antiarrhythmic action, by improving lipid metabolism, by protecting enzymes, by preventing hypertensive cell death in cancer patients and by its antiviral properties.

In the current review, we want to highlight the potential beneficial effects of synergistic action of BPF and oleuropein.

There is evidence to suggest that the anti-hypertensive activity of the olive leaf extract lies probably in its content of oleuropein acting synergistically with other active substances to exert both ACE inhibitory and calcium channel blocking activities.

The anti-hypertensive and cholesterol-lowering actions hypothesized for oleuropein suggest its potential synergistically action with BPF, able to induce in patients both hypolipemic and hypoglycaemic effects other than an improvement of reactive vasodilatation. This latter action also underlines an improvement of endothelial function in patients at risk of atherosclerosis.

Since oxidative stress has been shown to reduce reactive NO-dependent vasodilation, it is likely that BPF may well attenuate overproduction of oxygen reactive species in the vascular wall thereby restoring the imbalanced endothelial function in hyperlipemic patients.

A modern approach in cardiometabolic risk — The role of oxidative stress and LOX-1 expression in endothelial dysfunction and cardiometabolic risk
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Background: Overproduction of oxidized-low density lipoproteins (oxyLDL) has been found to contribute in endothelial cell (EC) dysfunction thereby leading to atherosclerosis development and progression. In particular, oxyLDL lead to apoptotic cell death of EC via oxidative stress production, mostly subsequent to overexpression of the scavenger receptor LOX-1. Here, we hypothesize that LOX-1 expression in EC represents a crucial event which attenuates protective autophagic response, thereby enhancing programmed endothelial cell death.

Methods and results: Bovine aortic endothelial cells (BAEC) in culture were exposed to oxyLDL (1–100 μM). After 48 h incubation, oxyLDL produced apoptotic cell death of BAEC as detected by FACS analysis, an effect counteracted by antioxidant N-acetyl-cysteine (NAC) as well as by the NO-donor SNAP. OxyLDL-induced apoptotic cell death was also accompanied by reduced VEGF-dependent phosphorylation of constitutive NO synthase (cNOS) in BAEC and consistent attenuation of autophagic response as detected by expression of beclin-1 and LC3, two reliable biomarkers of autophagy. Moreover, silencing LOX-1 receptor significantly restored LC3 expression in oxyLDL-treated BAEC, thus suggesting a key role of LOX-1 overproduction in oxyLDL-induced endothelial dysfunction.
Conclusions: OxyLDL leads to impaired NO generation and apoptotic cell death in BAEC. This effect occurs via overexpression of LOX-1 and the subsequent attenuation of protective autophagic response thereby contributing in the pathophysiology of oxyLDL-induced endothelial dysfunction which characterizes early stages of atherosclerotic process.

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The cross talk between oxyLDL and inflammation in atherosclerosis
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Abstracts

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), one of the scavenger receptors for oxidized low density lipoprotein (ox-LDL), plays a crucial role in signaling pathways involved in the process of oxidative stress and inflammation. As evidence supporting the vital role of LOX-1 keeps accumulating, there is growing interest in LOX-1 as a potential therapeutic target. Here, we review the discovery and genetics of LOX-1, describe existing evidence supporting the role of LOX-1 in atherogenesis and its major complication- myocardial ischemia, and summarize its modulation by some naturally occurring compounds that could be of therapeutic use.

Ox-LDL/LOX-1 relationship appears to be an important player in the development of atherosclerosis and its sequelae, such as MI and cardiac remodeling. The scavenger receptor LOX-1 activates most, if not all, signaling from the beginning to culmination of major life-threatening events related to this malady. From genetic studies, it is quite evident that certain individuals have propensity to develop CAD-related events. Since the current therapies of coronary heart disease, mainly LDL-cholesterol lowering drugs, are ineffective in a large number of patients, there is need for new targets that focus on the underlying signals of the disease process. A host of strategies are being proposed that would either block oxidation of LDL-cholesterol and/or reduce the expression of LOX-1. While the development of these strategies is eagerly awaited, some naturally occurring compounds appear quite promising and deserve clinical trials.

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The role of oxidative stress in vascular pathobiology
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Abstracts

The endothelium regulates vascular homeostasis through local elaboration of mediators that modulate vascular tone, platelet adhesion, inflammation, fibrinolysis, and vascular growth. Impaired vascular function contributes to the pathogenesis of atherosclerosis and acute coronary syndromes. Impaired endothelial function is associated with atherothrombotic risk factors and atherothrombotic disease, is pathophysiologically linked to acute cardiovascular syndromes. A central feature of impaired endothelial function in the presence of cardiac risk factors and under pathological conditions is impairment in endothelium-derived bioactivity.

Nitric oxide is produced in endothelial cells from the conversion of l-arginine to l-citrulline through the activity of (endothelial) nitric oxide synthase. EDNO regulates vascular tone through a dilator action on vascular smooth muscle cells that depends on soluble guanylyl cyclase activation and consequent increase in guanosine monophosphate. Additional antioxidant functions of EDNO relate to inhibition of platelet activity, leucocyte adhesion, and vascular smooth muscle cell proliferation. Mechanisms underlying impaired endothelial function in various disease states such as hypertension, diabetes mellitus, hypercholesterolemia, and atherosclerosis are likely multifactorial. There is growing evidence that oxidative stress (defined as an imbalance between endogenous oxidants and antioxidants in favour of the former) contributes to mechanisms of vascular dysfunction. These observations fit well with the recognition that increased oxidative stress may be central to the atherogenic process.

Although the mechanism of oxidative modification of LDL remains unknown, the importance of oxidation can be seen by the presence of oxidized LDL in atherosclerotic lesions. Experimentally, the amount of oxidized LDL is reflective of the atherosclerotic burden. Oxidized LDL induces a series of atherogenic processes, including transcription of proatherogenic genes, production of matrix metalloproteinases and tissue factor, antagonism of endothelial cell production of NO, and promotion of vascular smooth muscle cell apoptosis. The augmented production of superoxide anion also rapidly reacts with NO to produce peroxynitrite, a potent oxidant.

However, large trials of antioxidant vitamins, including the Grupo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) Prevention Trial, the Heart Outcomes Prevention Evaluation Study (HOPE), and the Heart Protection Study (HPS), have not demonstrated any reduction in clinical events with antioxidant vitamin E therapy. The antioxidants used in these trials, however, have limitations that may have precluded an adequate test of the hypothesis. Conventional antiplatelet therapy has also antioxidant effects by virtue of its ability to limit production of ROS by activated platelets. The importance of oxidative stress in the pathogenesis of atherosclerosis makes clear that the limitations of current therapies should not conclude therapeutic interest in this area but foster investigation into new avenues of treatment.

There is considerable need for additional investigation into the basic mechanisms of atherosclerosis. It is important to clarify the differential role of HDL cholesterol metabolism and other lipid disturbances as well as the biomechanical and rheologic factors in development and progression of disease in the noncoronary circulations. Greater research is needed in understanding regional differences in plaque formation and clinical manifestations of disease. Genetic variability across individuals and populations merits additional exploration using genomics and proteomics. Pathophysiological responses to changes in metabolic demand such as exercise and factors that determine development of collateral vessels and angiogenesis need greater attention. In particular, the interaction between reduced oxygen and substrate delivery and skeletal muscle, neurological, and metabolic function needs additional study. There is a need for improved functional imaging and biomarkers of disease progression and unstable patterns of atherosclerosis to assist in understanding of regional disease pathophysiology.

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Hypertension: Should we ablate all hypertensives? Pro
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Abstracts

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The relationship between hypertension and atherosclerosis is well established, and there is a clear need for improved functional imaging and biomarkers of disease progression and unstable patterns of atherosclerosis to assist in understanding of regional disease pathophysiology.