

Mini Review

Antioxidative Components in Atherosclerosis- Animal Experiments

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Abstract

Atherosclerosis is a chronic vascular inflammatory disease characterized by oxidative stress and endothelial dysfunction. Oxidation of low-density lipoprotein (LDL), cholesterol is a key step in the development of atherosclerosis. Pathogenesis of atherosclerosis can begin with shear stress-induced endothelial dysfunction, which can lead to endothelial and platelet activation and adhesion of monocytes to the activated endothelium. These monocytes, upon differentiation into proinflammatory macrophages, can increase the uptake of oxidized LDL (oxLDL), and become foam cells, thereby exacerbating inflammatory signaling. Although the prolonged use of antioxidative components, such as polyphenols and supplemental vitamins C and E, has been proven effective in preventing atherosclerosis in animal models, this has not yet been demonstrated in human clinical trials. The use of multiple antioxidants with different mechanisms of action simultaneously has shown positive effects in the treatment of atherosclerosis. There is some indication that a diet rich in antioxidants may be beneficial in the prevention of cardiovascular events.

Keywords

- Antioxidant
- Atherosclerosis
- ox-LDL
- Polyphenols

ABBREVIATIONS

TBARS: 2-thiobarbituric Acid Reactive Substance; ROS: Reactive Oxygen Species; LDL: Low-density Lipoprotein; OxLDL: Oxidized Low-density Lipoprotein; LOX-1: Low-density Lipoprotein receptor-1; MMP-9: Matrix Metalloproteinase-9; PECAM-1: Platelet Endothelial Cell Adhesion Molecule

INTRODUCTION

Atherosclerosis-related ischemic heart disease and stroke have been major causes of worldwide morbidity and mortality for decades [1,2]. Atherosclerosis is considered a progressive inflammatory systemic disease primarily affecting the walls of large and medium arteries, such as the aorta and carotid and coronary arteries, at sites prone to shear stress, such as branches, curvatures, and bifurcations [3,4]. Cardiovascular (CV), risk factors such as hypercholesterolemia, hyperglycaemia, hyperglycemia, hypertension, smoking, and aging promote vascular inflammation and endothelial activation [5,6]. Oxidative stress [7,8], is also found to be associated with some risk factors [9,10], of atherosclerosis, such as hypertension, diabetes mellitus, hyperlipidemia, obesity, and cigarette smoking [11-14].

Oxidative stress is defined as a state in which the imbalance between the production of reactive oxygen species (ROS), and the antioxidant defense mechanisms favors oxidation, either via overproduction of ROS or decrease in antioxidant capacity. ROS can denature or inactivate proteins, as well as oxidize lipids, especially phospholipids and low-density lipoproteins (LDL), to produce lipid peroxides and oxidized LDL (oxLDL). The oxidation of LDL is a complex process in which both the protein and the

lipids undergo oxidative changes and form complex products. Oxidative stress can damage cells and tissues and impairs biological functions, which can result in arteriosclerosis [15], cancer [16], various lifestyle-related diseases [17], Alzheimer's disease, Parkinson's disease [18], and many other diseases. Oxidative stress has also been reported to be involved in the aging process.

Strong evidence about the close relationship between oxLDL and atherosclerosis exists [19-21]. Atherosclerosis is a chronic inflammatory disease in which formation of atherosclerotic plaque is observed inside the artery [3,22,23]. ROS are generated by biological systems in instances of homeostatic disruption, such as in the case of hypertension, dyslipidemia, diabetes, obesity, acute conditions, including sepsis and respiratory failure, and following xenobiotic triggers like drugs and cigarette smoke [24,25]. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and myeloperoxidase (MPO) are among the most established enzymatic systems involved in atherosclerotic progression [25], and are also involved in the formation of ROS such as the superoxide anion [26,27]. In the early stage of atherogenesis, LDL oxidized by ROS (oxLDL), starts to accumulate in the subepithelial tissue and monocytes differentiate into proinflammatory macrophages, and further become foam cells due to the increased uptake of oxLDL [28-30]. Oxidative stress and LDL oxidation might play a pivotal role in atherosclerosis by modulating NF- κ B signaling pathways [31]. Abnormal proliferation of vascular smooth muscle cells is also observed [32, 33]. It has been reported that a large amounts of reactive oxygen species (ROS) and cytokines are produced in the course

of the onset of these pathological conditions [34], overproduction of which can also cause lipid peroxidation, protein denaturation, and enzyme inhibition leading to various pathological conditions [35].

The side effects of currently prescribed synthetic drugs and their high cost for the treatment of atherosclerosis has led us to investigate alternative herbal medicines, dietary supplements, and antioxidants, which may have fewer side effects in treating atherosclerosis [36,37]. As the production of ROS and oxidized LDL can contribute to the progression of atherosclerosis, the utilization of antioxidants may represent a rational therapeutic strategy to prevent disease progression [37]. Several antioxidants have demonstrated positive effects in various animal models of atherosclerosis. However, experiments in humans are limited or have not shown efficacy. Antioxidant combination therapies have been reported to be more effective overall, as antioxidants may ameliorate oxidation caused by drug therapies [38].

We investigated the effect of antioxidant-rich diet on the vascular, especially endothelial cells in the brain under the strong oxidative stress and hypoxia associated with arteriosclerosis. The AO diet reduced not only the production of lipid peroxide, but also suppressed and MMP-9 production (Figure 1).

It has been shown that polyphenols may reverse the observed decrease in endothelial nitric oxide synthase (eNOS) phosphorylation and intracellular nitric oxide (NO) levels induced by the stimulation of ROS production. This can lead to an

increase in cyclic GMP, a mediator of NO-induced vascular smooth muscle relaxation via increased biological activity of NO [39,40]. Vitamin E, the most comprehensively studied lipid-soluble antioxidant in humans, can have protective effects against atherosclerosis via preventing endothelial dysfunction related to cholesterol, modulating the expression of adhesion molecules, such as VCAM-1 and ICAM-1 on endothelial cells, and preserving endothelial NO release.

Vitamin C is a water-soluble and ubiquitous antioxidant [36,41], with the ability to scavenge peroxy radicals and HOCL [41,42], enhance the NO production, inhibit LDL peroxidation [43], and recycle other endogenous antioxidants such as vitamin E [44]. Vitamin C can also scavenge ROS, such as superoxide, hydroxyl radicals, and peroxy radicals [45,46].

DISCUSSION & CONCLUSION

Atherosclerosis is the leading cause of morbidity and mortality worldwide. Low side-effect dietary supplements and antioxidants such as AO diet may be excellent therapeutic strategies to prevent disease progression for the factors that the productions of ROS and oxidized LDL contribute to the progression of atherosclerosis.

The use of this kind of multiple antioxidants with different mechanisms of action may be more effective for the treatment of atherosclerosis via simultaneous suppression of LDL oxidation, reduction of ROS generation, inhibition of cytokine secretion, and prevention of atherosclerotic plaque formation (Figure 2).

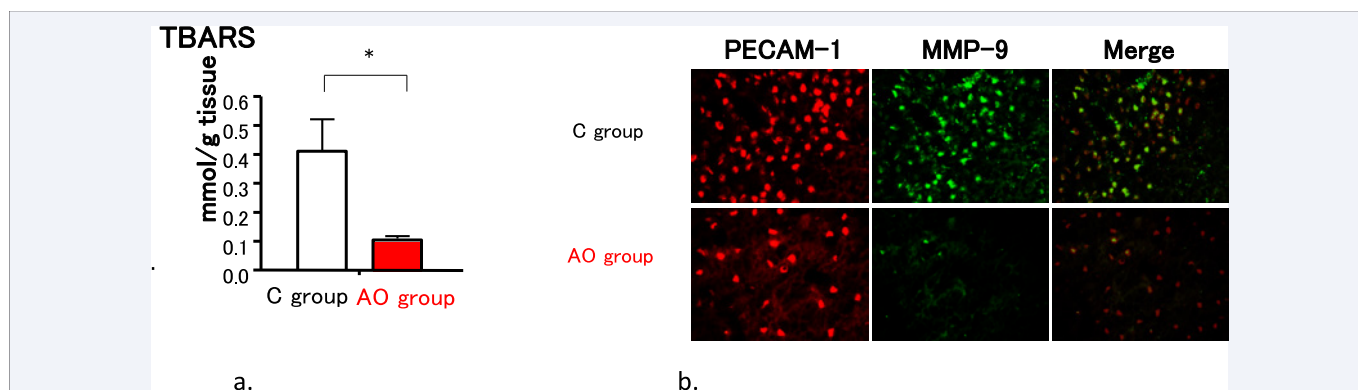


Figure 1 Establishment of a transient middle cerebral artery occlusion (MCAO) model.

a.-the production of TBARS b.-expression of MMP-9 in the brain endothelial cells

Data are expressed as the mean \pm SD. *p < 0.01

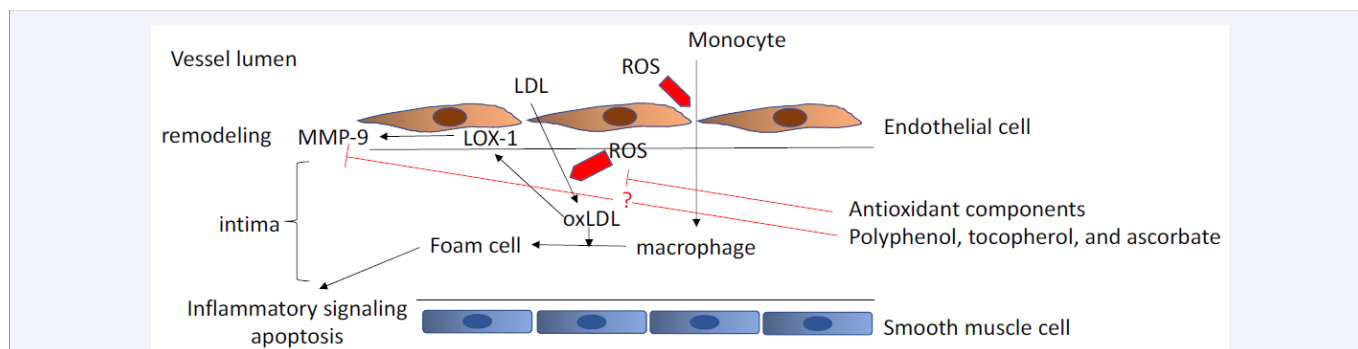


Figure 2 Effects of antioxidant components on the vascular cells.

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