Resveratrol Effects on Atherosclerosis Progression

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The beneficial effects of a Mediterranean diet are due to the numerous active compounds in the food and, particularly, the high concentration of compounds with synergistically acting antioxidant properties. Resveratrol, a stilbenoid nonflavonoid phenol, is an antioxidant that is naturally produced by numerous plants as a defensive agent in response to attacks from pathogens, such as bacteria and fungi. Resveratrol has several effects on human health, including on the lipid profile, where it primarily downregulates the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, reducing the synthesis of cholesterol. Resveratrol also increases the expression of low-density lipoprotein (LDL) receptors in the liver, contributing to the reduction in the LDL-cholesterol levels.

diet resveratrol atherosclerosis lipids cholesterol

1. Introduction

The development and progression of atherosclerosis can be attributed to multiple risk factors, such as hypercholesterolemia, hypertension, age, sex, diabetes, impaired glucose tolerance, smoking, obesity, and genetic factors. All these are commonly known as traditional risk factors, which often coexist in the same individual and can aggravate each other, amplifying the mechanism of pathogenesis and the progression of atherosclerotic plaque.

Other risk factors, denominated as nontraditional risk factors, include poor daily lifestyle, infection, inflammation, hyperomocysteinemia, hyperuricemia, clonal hematopoiesis of indeterminate potential (CHIP), dysbiosis of the intestinal flora, depression, metabolic syndrome, hyperinsulinemia, nephrotic syndrome, organ transplantation, hyperfibrinogenemia, hypercoagulable state, obstructive sleep apnea, and extrasystolic arrhythmia, among others [1].

The transforming growth factor/extracellular regulated protein kinases (TGF/ERK) signaling pathway is also involved in the pathophysiological mechanisms that are related to the development of atherosclerosis, such as the vascular smooth muscle cell (VSMC) proliferation, inflammatory response, proliferation of fibroblasts, and accumulation of extracellular matrix [2][3]. Resveratrol (RSV) may also inhibit the TGF/ERK signaling pathway by activating SIRT1, thus potentially playing a role in slowing the development of atherosclerosis [4].

Hypertension is characterized by decreased vasodilator production and increased ROS levels in the endothelium. This leads to a decreased endothelial nitric oxide synthase (eNOS) expression and vasodilator production,

including decreased nitric oxide (NO) levels. Consequently, this leads to increased vasoconstriction and blood pressure.

Several animal model studies have shown that the consumption of resveratrol, by stimulating SIRT1, Nrf2, and the AMP-activated AMPK activity, led to an increased eNOS phosphorylation and expression. This led to increases in the levels of nitric oxide and other vasodilators and a decrease in blood pressure [3].

The effect of RSV in lipid the improving profile could be due to its downregulation of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, thus reducing the total cholesterol (TC) and low-density lipoprotein (LDL) levels. RSV can also increase the expression of the LDL receptors in the liver, contributing to reductions in the LDL concentration [5][6]. Additionally, RSV has antioxidant, antiplatelet, and anti-inflammatory properties [7][8].

RSV improves glucose, lipid, and amino acid metabolism in the endothelial cells (ECs). RSV reduces glucose uptake and glycolysis by inhibiting the expression of the glucose transporter (Glut), monocarboxylate transporter (MCT), 6-phosphofructo-1-kinase (PFK), pyruvate kinase (PK), hexokinase (HK), and lactate dehydrogenase (LDH). In addition, RSV improves fatty-acid-related damage by upregulating the expression of brain and muscle arnt-like protein-1 (Bmal1). It decreases lipogenesis by suppressing the expression of fatty acid synthase (FASN) and activates fatty acid oxidation by suppressing the expression of acetyl-CoA carboxylase (ACC).

Finally, resveratrol increases the uptake and synthesis of glutamine. It upregulates the NO release by elevating the expression of eNOS, suppressing the level of serum asymmetric dimethylarginine (ADMA), and inhibiting the activity of arginase [9][10].

RSV shows a cardioprotective activity both by regulating the ROS production in cardiac cells and changing the lipid profile, and by reducing atherosclerosis progression in animal models, randomized control trials (RCTs), and prospective cohort studies.

2. Resveratrol Effects on Atherosclerosis Progression by Regulating the Trimethylamine N-oxide Synthesis via the Remodeling of Gut Microbiota

The gut microbiota can regulate several metabolic processes in the host, including the lipid metabolism [11][12]. The mechanisms through which dietary fatty acids affect the gut microbiota are poorly known. Most consumed fatty acids are absorbed in the small intestine. However, a minority pass through the gastrointestinal tract and modulate the colonic microbiota composition. Fatty acids have a broad spectrum of antibacterial activity, such as the lysis and solubilization of bacterial cell membranes or the inhibition of ATP production. The antibacterial action of fatty acids is affected by the carbon chain length, saturation, and double bond position. Fatty acids may also be used as metabolic substrates by the gut bacteria, thereby affecting the gut microbiota profile and the production of microbial metabolite [13][14][15][16].

Trimethylamine N-oxide (TMAO) is a phospholipid metabolite related to intestinal microorganisms. It is predominantly sourced from choline, which is found in foods such as red meat, fish, poultry, and eggs, or from L-carnitine, which is found in red meat and dairy products. Both choline and L-carnitine are metabolized by the gut microbiota into trimethylamine (TMA) and then into TMAO through the action of the hepatic enzyme, flavin monooxygenase-3 (FMO3). Studies have recently suggested that TMAO is a new independent risk factor for atherosclerosis. The plasma level of TMAO is reportedly positively associated with cardiovascular risk and mortality in a dose-dependent manner. The higher the concentration of TMAO in the plasma, the higher the probability of malignant cardiovascular and cerebrovascular events. A recent prospective case–control study showed that in a 10-year period, regardless of the level of baseline TMAO, the final increase in TMAO was significantly associated with an increased risk of CHD, and the TMAO–CHD relationship could be improved through dietary changes [17][18][19][20][21][22][23][24][25].

TMAO can hasten the atherosclerosis progression through the mechanisms related to the lipid metabolism and inflammation. More specifically, TMAO promotes oxidative stress and inflammation in the endothelial cells, thus aggravating the vascular dysfunction. TMAO also aggravates the process of the atherosclerotic plaque formation by promoting vascular calcification. It promotes the conversion of macrophages into foam cells and the platelet activation process. In addition, TMAO contributes to increases in the serum cholesterol levels and the progression of atherosclerosis (AS) by reversing the cholesterol transport and by inhibiting bile acid (BA) synthesis [18][20]. TMAO also induces increases in the oxidative stress and inflammation of endothelial cells, leading to an increase in the endothelial-derived NOS expression [26], thus contributing to endothelial dysfunction [27].

Resveratrol is characterized by a poor bioavailability when ingested through red wine, other foods, or food supplements. When taken orally, only 1–8% of free resveratrol is found in the serum, 25% is excreted without absorption, and over 70% is metabolized by the liver and the intestinal microbiota [16][28]. Nonetheless, resveratrol has broad antibacterial activity at concentrations that can be reached even with a dietary intake. Specifically, resveratrol seems to inhibit the bacteria involved in the saccharolytic and proteolytic activities [29].

RSV acts by lowering the TMAO levels and increasing hepatic bile acid synthesis via remodeling the gut microbiota [6]. Specifically, RSV has antibacterial properties against various bacterial species, including opportunistic intestinal pathogens, for example, Escherichia coli, Enterococcus faecalis, and Salmonella enterica [30][31][32]. The bactericidal effect of resveratrol is, however, weaker toward commensal bacterial species such as the Lactobacillus spp. [33]. RSV can, therefore, influence the composition of bacterial species in the intestine in favor of maintaining the state of health.

In summary, by modifying the composition of the intestinal flora, RSV induces reductions in the levels of microbial production of intestinal TMA, subsequently leading to a decrease in the synthesis of TMAO in the liver and, ultimately, to the inhibition of the progression of AS. Additionally, by remodeling the intestinal microbiota, RSV increases the enzymatic activity of bile salt hydrolase (BSH). This induces an increase in the production of unconjugated bile acid (BA) from the conjugated BA. This involves an increase in the fecal excretion and a

contextual induction of hepatic BA neosynthesis, thus contributing to reductions in the serum cholesterol levels and the inhibition of the AS progression [34].

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