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THE INFLUENCE OF POLYPHENOLS ON ATHEROSCLEROSIS DEVELOPMENT

Summary: Polyphenols represent one of the biggest and most widespread groups of secondary plant metabolites with more than 8000 polyphenolic compounds. Fruits, vegetables and beverages such as tea and red wine are the main sources of polyphenols. A significant number of studies indicate the ability of certain polyphenols to delay the development of atherosclerosis. According to the same polyphenols reduce lipid deposition, oxidative stress, inflammation of the blood vessel wall, proliferation of vascular smooth muscle cells and endothelial dysfunction. The widespread use of polyphenols requires further research on bioavailability, absorption and transformation. It is necessary to determine the effect of individual polyphenols as well as the interaction with other bioactive compounds, define the dietary reference intake and the safety of use in certain subpopulations.

Key words: polyphenols, atherosclerosis, cardiovascular diseases

Introduction

Polyphenols are compounds that in their structure contain one or more hydroxyl groups attached directly to one or more aromatic hydrocarbons[1,2]. They represent one of the most numerous and widespread groups of secondary plant metabolites with more than 8000 polyphenolic compounds[2,3]. According to the structure, biological activity and biosynthetic pathway, we distinguish between flavonoids and non-flavonoids[4]. Flavonoids are divided into six main subclasses: flavonols, flavanones, flavanols, flavones, anthocyanins and isoflavones[4-6]. Other groups of flavonoids include less abundant chalcones, dihydrochalcones, dihydroflavonols, flavan-3,4-diols, coumarins and aurones[2]. Non-flavonoids include phenolic acids (benzoic acid and cinnamic acid), stilbenes, lignans, tannins and other polyphenols (curcumin, gingerol)[2]. The main sources of polyphenols are fruits, vegetables and drinks such as tea and red wine[7,8,9].

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Their content in plant products is determined by pedoclimatic and agronomic conditions, as well as the degree of maturity[7]. Absorption of polyphenols is conditioned by phytochemical properties (molecular structure, lipophilicity, dissociation constant and solubility), direct interaction with food components and host factors (intestinal and systemic)[7,9]. The estimated daily intake of polyphenols is 1g[7].

Atherosclerosis is the leading cause of morbidity and mortality in Europe and the United States of America[8-11]. It is defined as a chronic inflammatory disease of the walls of large and medium arteries (predominantly the aorta, carotid arteries, coronary arteries and arteries of the lower extremities)[8]. Risk factors for atherosclerosis are hypercholesterolemia, hypertension, cigarette smoking, obesity, physical inactivity, age, family history, diabetes mellitus, male sex, but also hypertriglyceridemia, hyperhomocysteinemia and hyperfibrinogenemia[9,11,12]. Atherosclerosis is caused by chronic inflammation in the blood vessel wall induced by unbalanced lipid metabolism and impaired immune response[8,9]. Oxidative modification of LDL cholesterol (low-density lipoprotein, LDL) (mediated by reactive oxygen species, myeloperoxidase, lipoperoxidase, nicotinamide adenine dinucleotide phosphate) into oxidized low-density lipoprotein (Ox-LDL) within the extracellular matrix of the subendothelial space induces endothelial dysfunction, formation of foam cells, migration and subsequent proliferation of blood vessel smooth muscle cells (SMC), adhesion and aggregation of platelets[8,10]. Clinical manifestations of atherosclerosis are conditioned by the place of plaque development and the presence of thromboembolic changes (myocardial infarction, transient ischemic attack and stroke, intermittent claudication, intestinal infarction)[9].

A significant number of studies indicate the ability of certain polyphenols to delay the development of atherosclerosis[13-20]. According to the same polyphenols reduce lipid deposition, oxidative stress, inflammation of the blood vessel walls, proliferation of vascular smooth muscle cells and endothelial dysfunction[13-20].

The influence of polyphenols on atherosclerosis development

Polyphenols modify the processes involved in the formation, progression and eventual rupture of atherosclerotic plaque[13-20]. Polyphenols can significantly reduce lipid absorption by inhibiting emulsification in the small intestine, inhibiting pancreatic lipase activity, reducing micellar solubility and precipitation of micellar cholesterol[13-16]. Reduced cholesterol absorption causes increased production of mitochondrial ribonucleic acid for the LDL receptor in the liver[16]. They reduce the production of apolipoprotein B100 in the liver by reducing the formation of cholesterol esters, reducing the activity of Acyl-CoA cholesterol acyltransferase and reducing the activity of microsomal protein for the transfer of triglycerides[15]. Therefore, polyphenols reduce the concentration of LDL in the extracellular matrix of the subendothelial

space[8,23]. They reduce the concentration of triglycerides by reducing the activity of the microsomal protein for the transfer of triglycerides and possibly increasing the activity of lipoprotein lipase[15]. A reduced concentration of triglycerides modifies the delipidation cascade and reduces the concentration of LDL in plasma[15]. Polyphenols exert antioxidant activity in several ways[2]. The most effective involves the neutralization of free radicals (transfer of hydrogen atoms from active hydroxyl groups of polyphenols to free radicals)[2]. The ability to neutralize free radicals is conditioned by the arrangement and total number of hydroxyl groups, the degree of polymerization, glycosidation, O-methylation and 2-3 double bonds in conjugation with the 4-keto group[2]. The anti-inflammatory effect of polyphenols involves the inhibition of pro-inflammatory enzymes (lipoxygenase a, cyclooxygenase-2, inducible nitric oxide synthase, nuclear factor-κB, activating protein-1) and activation of mitogen-activated protein kinase, protein kinase-C, nuclear factor erythroid 2-related factor 2 and phase-II enzymes of antioxidant detoxification[16- 18]. Polyphenols can inhibit the proliferation of vascular smooth muscle cells by arresting the cell cycle in the S phase of mitosis (deoxyribonucleic acid chain breaking in the presence of copper ions) and apoptosis[19]. Independently of their antioxidant effects, polyphenols achieve vasoprotective, antiaggregative, antiatherogenic, vasorelaxant and antihypertensive effects by activating the production of vasodilating factors (nitric oxide, hyperpolarizing factor derived from the endothelium, prostacyclin), by inhibiting the synthesis of vasoconstrictor endothelin-1 in endothelial cells, and by inhibiting the expression of two main proangiogenic factor, vascular endothelial growth factor and matrix metalloproteinase-2 in smooth muscle cells[20]. In endothelial cells, polyphenols increase the level of calcium, induce redox-sensitive activation of the phosphatidylinositol 3 kinase/Akt protein kinase B pathway and increase the expression of nitric oxide synthase[20]. In smooth muscle cells, there is a redox-sensitive inhibition of the activation of the p38 mitogen-activated protein kinase pathway (inhibition platelet-derived growth factor-activated vascular endothelial growth factor gene expression) and redox-independent inhibition of thrombin-induced matrix metalloproteinase-2 formation[20].

Red wine phenols inhibit LDL oxidation, vascular smooth muscle cell proliferation and activate endothelial nitric oxide synthase[21]. Pomegranate polyphenols reduce platelet aggregation[21]. Dark chocolate flavonoids increase plasma antioxidant capacity and cause endothelium-dependent vasodilation[22,23]. Green tea catechins are incorporated into LDL particles and reduce their oxidation[24]. Flavonoids in hibiscus sabdarife leaves inhibit LDL oxidation[25]. Blueberry phenolics reduce the activity of the proliferation signaling pathway[21]. Polyphenols from extra virgin olive oil suppress the formation of reactive oxygen species, promote the formation of nitric oxide, inhibit angiogenesis, migration and proliferation of vascular cells and prevent vascular injuries caused by advanced glycation end products[26]. Resveratrol, isorhamnetin, curcumin and vanillic acid reduce the release of pro-inflammatory cytokines[21]. Resveratrol reduces

platelet activation and aggregation[21]. Curcumin reduces the proliferation of vascular smooth muscle cells and reduces oxidative stress[21].

Method

The literature was searched using the keywords: polyphenols, atherosclerosis and cardiovascular diseases. The search was conducted for the period from 2001. until 2022 within the following databases: PubMed, Emabase, Scopus, SCin-dex and Hrcak. Due to the limited number of available studies, no available filters were used in the database search. After the summaries were read, the papers were studied in more detail and those that did not correspond to the research objective were excluded.

Atheroroprotective effect of polyphenol

A significant number of animal studies confirmed the integral association of polyphenols with the development of atherosclerosis[27-30]. Research in Australia found that specific dietary polyphenols, predominantly quercetin and theaflavin, could slow atherosclerosis in mice with the apolipoprotein E27 gene removed. According to the same, the atheroprotective effect of a diet rich in fruits and vegetables can partly be the result of the effect of flavonoids[27]. Research on mice with the LDL receptor gene removed determined that the consumption of fruits and vegetables equivalent to 8-9 servings of fruits and vegetables in humans slows down the development of atherosclerotic plaque caused by an atherogenic diet[28]. Similar research in Israel confirmed the atheroprotective effect of grape polyphenols[29]. Research with New Zealand rabbits on an atherosclerotic diet in Spain observed the atheroprotective effect of components of extra virgin olive oil[30]. Hydroxytyrosol improved endothelial function, while squalene reduced plaque fibrosis[30].

The atheroprotective effect of polyphenols has been the subject of numerous studies with humans[31-38]. The multicenter, randomized, controlled study PREDI-MED in Spain lasting 8 years in which 7447 people at high risk for developing cardiovascular disease participated found that a Mediterranean diet based on vegetables rich in unsaturated fatty acids enriched with olive oil slows the progression of subclinical atherosclerosis (measured by ultrasound of the carotid arteries)[31]. A substudy of the PREDIMED study in which 1139 individuals at high risk for cardiovascular disease participated observed a significant inverse correlation between one-year intake of polyphenols and circulating inflammatory molecules associated with atherosclerosis[32]. A double-blind randomized crossover

controlled study with 24 female adults with an average age of 26 years confirmed the atheroprotective role of polyphenols[33]. According to the same, a diet rich in polyphenols improves the function of the endothelium, which stimulates the nitric oxide synthase system and reduces the oxidation of LDL (predominantly hydroxytyrosol and its derivatives)[33]. A 23-year prospective cohort study in Denmark involving 53,552 individuals found that polyphenol intake (1000 mg/day) was associated with a 14% lower risk of atherosclerotic cardiovascular disease (9% ischemic heart disease, 9% ischemic stroke and 32 % peripheral artery disease)[34]. The strongest association is the confirmed disease in peripheral artery disease and atherosclerotic cardiovascular disease in smokers and people with alcohol abuse disease[34]. Obese people had a low association, which could be explained by a change in the intestinal microbiota and impaired bioconversion of flavonoids in the large intestine[34,35]. A double-blind randomized controlled study in Hungary among people with myocardial infarction found that resveratrol intake (without alcohol consumption) slows down the development of atherosclerosis in people with coronary artery disease[36]. A study among 558 men aged 40-49 years with elevated serum total cholesterol and/or high coronary risk determined that the consumption of fruits and berries rich in polyphenols can slow down the progression of atherosclerosis of the carotid arteries[37]. A meta-analysis of 7 studies involving 133 participants who used a variety of foods and supplements rich in hydroxytyrosol, quercetin and resveratrol (45-1015 mg/100 g) for up to 145 days found a reduction in lipids and inflammatory markers[38].

On the other hand, a study of mice with the Apolipoprotein E gene removed in the United States of America determined that the polyphenols of red wine do not reduce the size of the formed atherosclerotic plaque, nor the content of collagen in the same[39]. A similar study in Canada observed that catechin in young mice protects against the development of atherosclerosis40. In older mice with developed atherosclerotic plaque, catechin favors further endothelial dysfunction and leukocyte adhesion[40]. A systematic review and meta-analysis of 35 prospective cohort studies in the Czech Republic observed that moderate drinking of black tea, less than 4 cups per day, has an atheroprotective effect, while consumption of 4 to 6 cups per day predisposes to atherosclerosis[40]. This effect is conditioned by the caffeine content in black tea[41]. In the same study, there was a significant inverse correlation between drinking green tea and the development of atherosclerosis in the Asian but not in the Western population4[1]. Research in China found that consumption of fruit rich in polyphenols does not have an atheroprotective effect in people with a high risk of cardiovascular diseases42. One of the possible reasons is that more than a quarter of the mentioned population has hyperglycemia, which is aggravated by high fructose intake[42].

Conclusion

Polyphenols can reduce oxidative stress, inflammation of the blood vessel wall, proliferation of vascular smooth muscle cells and endothelial dysfunction. A significant number of studies indicate the ability of certain polyphenols to delay the development of atherosclerosis. Therefore, supplementation with polyphenols represents a potential alternative to traditional pharmacological agents with relatively limited side effects. The widespread use of polyphenols requires further research on bioavailability, absorption and transformation. It is necessary to determine the effect of individual polyphenols as well as the interaction with other bioactive compounds, define the dietary reference intake and the safety of use in certain subpopulations.

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