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Review

Mechanisms of endothelial cell protection by hydroxycinnamic acids

Eduardo Fuentes *, Iván Palomo *

[a] Faculty of Health Sciences, Department of Clinical Biochemistry and Immunohaematology, Interdisciplinary Excellence Research Program on Healthy Aging (PIEI-ES), Universidad de Talca, Talca, Chile
[b] Centro de Estudios en Alimentos Procesados (CEAP), CONICYT-Regional, Gore Maule R09I2001, Chile

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ABSTRACT

An endothelial dysfunction generates a proatherogenic environment characterized by stimulating thrombus formation. Epidemiological studies have provided evidence of a protective role of healthy diets in the prevention of cardiovascular diseases. Hydroxycinnamic acids constitute abundant polyphenols in our diets as they are present in high levels in many widely consumed foods, such as fruit, vegetables and beverages. Therefore, it can be established that due to the hydroxycinnamic acid content (caffeic, chlorogenic, feluric and *p*-coumaric acids), fruit, vegetables and beverages contribute to endothelial protection (attenuates oxidative stress, improved nitric oxide bioavailability and decreased E-selectin, ICAM-1 and VCAM-1 expression, among others). In this article, we systematically examine the mechanisms of endothelium protection of hydroxycinnamic acids.

Contents

1. Introduction

Cardiovascular diseases (CVD) (acute myocardial infarction, cerebrovascular disease and peripheral arterial disease) represent the clinical manifestation of an underlying atherothrombotic process produced by a chronic deterioration of the endothelial function [1,2].

Under physiological conditions, endothelial cells are able to exert important regulatory functions, such as maintaining the balance between procoagulant and anticoagulant factors, vascular tone regulation and control of vascular permeability [3–5]. Normally, endothelium is a dynamic interface that normally provides a non-adhesive, non-thrombogenic surface for blood cells and clotting factors [6]. However, several factors may alter this balance, establishing what is known as endothelial dysfunction [7]. An endothelial dysfunction generates a proatherogenic environment characterized by facilitating platelet/endothelium interaction, where communication on various levels is the key in the response to vascular damage and the principle cause of atherothrombosis [8]. A common characteristic of endothelial dysfunction is decreased nitric oxide (NO) bioavailability at a vascular level, increased production of reactive oxygen species (ROS) and induced endothelial cell expression of adhesion molecules (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1] and E-selectin, among others) [9–11]. It is well known that cardiovascular

* Corresponding authors at: Immunology and Haematology Laboratory, Faculty of Health Sciences, Universidad de Talca, Casilla 747, Talca, Chile. Tel.: +56 71 200493; fax: +56 71 20048.
E-mail addresses: edfuentes@utalca.cl (E. Fuentes), ipalomo@utalca.cl (I. Palomo).

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risk factors (CVRF), such as hypertension [12], diabetes [13], smoking [14] and hypercholesterolemia [15], are associated with endothelial dysfunction [16].

Epidemiological studies have provided evidence of the protective role of healthy diets in the prevention of CVD [17–20]. More specifically, a number of natural bioactive compounds from fruit, vegetables and beverages, among others, have shown endothelial protection [21]. In this way, polyphenolic compounds acutely improve endothelial function in patients with coronary heart disease [22]. To this respect, Fuentes et al. [23] have recently identified a group of hydroxycinnamic acids (chlorogenic, caffeic, ferulic and *p*-coumaric acids) from red tomatoes, tomato products (sauce, ketchup and juice) and pomace (by-products of tomato paste processing) with antithrombotic activity.

Since the antithrombotic properties of bioactive compounds could be directly associated with endothelial protection [24], the mechanisms of endothelium protection of hydroxycinnamic acids (caffeic, chlorogenic, ferulic and *p*-coumaric acids) are systematically examined in this article.

2. Endothelial protection

Vascular endothelium plays a key role in the control of hemostasis and thrombosis. The function of endothelial cells goes beyond providing a non-thrombogenic inner layer of the vascular wall, which maintains blood fluidity [25,26]. An important rationale for this approach has been the observation that endothelium-derived NO; a major mediator of endothelium-dependent vasodilation has important anti-inflammatory and antithrombotic properties. Antithrombotic effects of endothelium-derived NO may be related to the inhibition of plasminogen activator inhibitor-1 (PAI-1) expression, a prothrombotic protein [27–29]. Thus, endothelial protection may represent a novel target for antithrombotic strategies in cardiovascular pathologies.

3. Phenolic acids and endothelial protection

The Mediterranean diet is characterized by a high consumption of fruit, vegetables, pulses, olive oil and a moderate consumption of red wine [30,31]. Epidemiological studies have shown that a higher intake of fruit and vegetables is associated with a lower risk of CVD [32]. Nanri et al. [33] demonstrated an inverse correlation between the consumption of fruit, vegetables and serum markers of inflammation. This effect has been seen not only in adults but also in teenagers and in several populations [33,34]. In this way, studies have established that after an increased consumption of a Mediterranean-type diet serum c-reactive protein (CRP) concentrations, interleukin (IL)-6, IL-7, IL-8, insulin and homocysteine are significantly reduced [35–38]. Also, it decreases blood pressure and improves blood flow in adults [39,40]. It may be concluded that this diet has a positive effect on the endothelial function [41].

Strawberry consumption significantly lowers levels of proinflammatory cytokines (IL-1β and IL-6) and increases anti-inflammatory cytokines like IL-10 [42,43]. Furthermore, we recently found that strawberry significantly decreases sP-selectin, sCD40L, CCL5 and IL-1β levels [44]. The compounds found in the strawberry relating to endothelial protection are polyphenols [45].

Polyphenols were able to localize into the endothelial cells subsequently reducing endothelial cell vulnerability to oxidative stress at both the membrane and cytosol level [46,47]. It has been shown that polyphenols activate endothelial nitric oxide synthase (eNOS) through the activation of the estrogen receptor α of the endothelial cells mediated by the inhibition of the p38 MAPK and PI3K/Akt pathways [48,49]. In this way, protection against oxidative stress, and inhibition of angiogenesis, platelet activation and cell migration/proliferation are generated by increasing the NO levels [50–56]. Also the increase in NO bioavailability inhibits nicotinamide adenosine dinucleotide phosphate (NADPH) oxidase activity and reduces the release of endothelin-1 (ET-1) [57–59]. Polyphenols also reduced tumor necrosis factor-α (TNF-α)-induced up-regulation of various inflammatory mediators (IL-8 and ICAM-1) involved in the recruitment of leukocytes to sites of damage or inflammation along the endothelium [60].

4. Hydroxycinnamic acids

The most common groups of polyphenols in our diet are phenolic acids (Table 1) [61,62]. Phenolic acids can be further distinguished into two groups, hydroxybenzoic and hydroxycinnamic acids. Among the most common and well-known hydroxycinnamic acids are caffeic, chlorogenic, feluric and *p*-coumaric acids (Fig. 1). Hydroxycinnamic acids constitute abundant polyphenols in many diets because they are present in high levels in many widely consumed foods, such as fruit (blueberries, grapes, pears, cranberries, apples, oranges, lemons, grapefruits, peaches and cherries), vegetables (such as potatoes, lettuce, brassica, broccoli, spinach and cabbage) and beverages (tea, coffee, cherry, orange and apple juice) [63–66]. The types of fruit with the highest content of polyphenols contain 0.5–2 g hydroxycinnamic acids/kg when fresh [67].

Caffeic and quinic acid combine to form chlorogenic acid, which is found in many types of fruit and in high concentrations in coffee: a single cup of ground coffee may contain 70–350 mg chlorogenic acid [63]. Caffeic acid is abundant in carrots and various berries [68]. Moreover, the current growing interest for natural antioxidants has led to renewed scientific attention to the artichoke, due to not only its nutritional value but also its polyphenolic content with strong antioxidant properties [69]. The highest constituents of artichoke extracts are hydroxycinnamic acids such as chlorogenic, caffeic and ferulic acids [70].

Ferulic acid is the most abundant phenolic acid found in cereal grains, which may represent up to 90% of total polyphenols (0.8-2 g/kg dry weight) [71,72]. The radix of *Angelica sinensis* (RAS) is used in traditional Chinese medicine to enrich the blood and invigorate blood circulation [73]. Chuanxiong, the rhizome of *Ligusticum chuanxiong* Hort (RLC) (Umbelliferae), another well-known traditional Chinese herb, is widely used in China to treat cardiovascular disorders such as strokes, hypertension and arrhythmia [74]. The concentration of ferulic acid was 0.46 mg/g in the extract of RAS and 0.51 mg/g of RLC [75].

Blueberries have as a rich source of antioxidants [76]. The highest amount of ferulic acid was found in rabbit eye blueberries. The lowest concentration (1.38 mg/100 g) of caffeic acid was found in the choctaw blackberry cultivar [77].

5. Hydroxycinnamic acids and endothelial protection

Antithrombotic properties of bioactive compounds could be directly associated with endothelial protection [78]. Our findings suggest that hydroxycinnamic acids protect against thrombus formation or atherosclerotic lesion development through endothelial protection. Here we systematically examine the mechanisms of endothelial protection by hydroxycinnamic acids, suggesting its potential role in the prevention of atherothrombosis (Fig. 2).

5.1. Caffeic acid

Caffeic acid is a component of garlic, fruit and coffee and is widely used as a phenolic agent in beverages [79]. Furthermore, caffeic acid inhibited hyperhomocysteinemia (HHcy)-elicited leukocyte rolling and adhesion, decreased ROS production and activation of cyclooxygenase-2 (COX-2) in endothelial cells. Also, caffeic acid was seen to reduce the E-selectin and ICAM-1 expression on cerebrovascular endothelium and CD11b/CD18 on leukocytes caused by HHcy [80,81]. In the endothelial cell lipopolysaccharides (LPS)-induced oxidative stress, caffeic acid inhibited NF-κB activation via the c-Src/ERK and NIK/IKK signal transduction pathways [82].

Caffeic acid and some of its derivatives such as caffeic acid phenetyl ester (CAPE) are potent antioxidants which present important anti-