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REVIEW

Flavonoids and arterial stiffness: Promising perspectives

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Abstract *Background and aims:* Flavonoids are a group of polyphenol compounds, ubiquitously found in plants. Great emphasis has been given to their possible benefits for cardiovascular health. These beneficial effects may be mediated by a specific action on arterial walls. Arterial stiffness is a marker of vascular aging, increasingly used in the clinical setting and assessed by pulse wave velocity. It has shown to be a robust predictor of cardiovascular events and mortality. This review aims at providing a comprehensive evaluation of available intervention and observational studies examining the relationship between flavonoid consumption and arterial stiffness.
Data synthesis: A Medline® literature search was performed using the keywords "arterial stiffness" and "flavonoids". As a result, 2 cross-sectional and 16 intervention studies assessing the relationship between flavonoids intake and arterial stiffness were retained. Four intervention trials reported a significant decrease of arterial stiffness after a flavonoid-based intervention, independently from blood pressure changes. The two observational studies reported significant associations between a higher flavonoid consumption and a lower arterial stiffness. In this review, isoflavones, anthocyanins and to a lesser extent cocoa flavan-3-ols appeared to be the more efficient to improve vascular function.
Conclusions: Despite their heterogeneity, preliminary data seem to support an improvement of the arterial stiffness related to flavonoid intake. However, further research on absorption and dose–response effects of the specific flavonoid subclasses on arterial structure is warranted.

Introduction

The "French paradox" was proposed as an attractive concept to illustrate the contrast between a low rate of coronary heart disease in France, in spite of a high prevalence of cardiovascular risk factors, and an important consumption of saturated fats [1]. One of the features of the French diet, is the frequent consumption of red wine, containing high levels of polyphenols. Even though moderate ethanol consumption may explain this cardioprotective role [2], non-ethanol components of wine, and in particular flavonoids, which are a class of polyphenolic compounds, may provide additional health benefits. Flavonoids have especially shown a variety of beneficial actions on cardiovascular health [3,4]. However, their effectiveness on arterial function has not been fully appreciated yet.

The aim of this article is to provide a comprehensive evaluation of intervention and observational studies over the last ten years, evaluating the association between

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flavonoid consumption and arterial stiffness, which is a marker of arterial function and a strong predictor of cardiovascular outcomes and mortality [5].

Firstly, an overview of the flavonoid subclasses and metabolism is presented, as well as their main physiological effects on arteries. Secondly a brief description of arterial stiffness and its potential implications is provided, supplemented by an overview of other vascular assessment methods. Finally, a summary of the current evidence examining the impact of flavonoid consumption on vascular function will be discussed.

Flavonoids

Dietary flavonoids constitute a large class of bioactive polyphenolic compounds, commonly consumed in plant foods and beverages [6]. This large family consists of about 7000 molecules, characterized by a phenyl benzopyrone structure. According to the different patterns of this nucleus they are categorized into 6 main subclasses: flavan-3-ols (e.g. catechin, epicatechin), flavonols (e.g. quercetin, myricetin, kaempferol), anthocyanidins (e.g. cyanidin, delphinidin), flavones (e.g. apigenin, diosmin), and flavanones (e.g. naringenin, hesperetin). The bioavailability of flavonoids is generally low and may vary drastically among different flavonoid classes as well as individual compounds in a particular class. Isoflavones, flavonols, flavanones and flavan-3-ols, may be absorbed sufficiently to exert possible cardio-protective effects *in vivo* [7].

Firstly, several biological mechanisms have been indicated to support a beneficial effect of flavonoids on endothelial function. After ingestion, flavonoids are extensively metabolized to various phenolic acids, some of which still possess a radical-scavenging ability. Besides, flavonoids are competitive inhibitors of oxidases (e.g. xanthine oxidase) responsible for superoxide anion production. Therefore, both the absorbed flavonoids and their metabolites may display an anti-inflammatory and antioxidant activity, and the reduced production of reactive oxidant species, may in turn contribute to an enhanced endothelial function [8]. Secondly, flavonoids may reduce LDL-cholesterol oxidation, increase insulin sensitivity and decrease pro-thrombotic and pro-atherosclerotic molecules expression and thus slow down the progression of early atherosclerotic lesions to advanced plaques [9]. Thirdly, polyphenols present antihypertensive effects which can be explained not only by an increase in nitric oxide (NO) production but also by a direct inhibition of angiotensin-converting enzyme. Fourthly, constitutive production of NO by the endothelial cells inhibits the recruitment and adhesion of inflammatory cells, but also reduces ADP/collagen activated platelet-related primary hemostasis [10]. Inhibition of platelet activation combined with inhibition of prothrombotic molecules may be efficient to prevent ischemic diseases (e.g. myocardial infarction or stroke). Finally, anti-angiogenic effects of flavonoids have also been reported, modulating several protein kinases (e.g. protein kinase-C, serine–tyrosine kinases), vascular endothelial growth factor receptors (VEGFRs), fibroblast growth factor and cyclin-dependent kinases (CDKs) which play important roles in both arterial remodeling and cancer pathogenesis [11].

These pharmacological effects have suggested a potential role of flavonoids in clinical trials aiming at improving arterial function and reducing the incidence of cardiovascular events. The effectiveness of flavonoids on predictors of cardiovascular outcomes, has been supported by three meta-analyses of randomized controlled trials [12–14].

Arterial stiffness

Central elastic arteries undergo major age-related modifications and tend to stiffen gradually. In fact, arterial aging may be considered as an integrator of the long-term effects caused by traditional cardiovascular risk factors on the arterial walls [5]. As the arterial tree stiffens, the propagation of the pressure waves speeds up and may overlap with reflected pressure waves, increasing in turn central pulse pressure [15]. These hemodynamic consequences may also damage the microvasculature and lead to end-organ dysfunction. Thus, aortic stiffness has been indicated as a marker of vascular dysfunction and a major predictor of cardiovascular outcomes, including mortality, independently of other cardiovascular risk factors [5,16,17]. Accordingly, growing interest has been given to noninvasive assessment of arterial stiffness in clinical practice. To date, the gold standard to assess aorta stiffness is the measurement of carotid-femoral pulse wave velocity (PWV) usually estimated with applanation tonometry [15]. Briefly, pulse waves are recorded with an applanation tonometer at two arterial sites (carotid and femoral) and the delay in the onset of the wave between these two locations is measured using registration with a simultaneously recorded electrocardiogram. The PWV is calculated by dividing the distance between the two measurement points by the time difference. Various other methods have been validated to estimate regional arterial stiffness noninvasively such as echotracking, magnetic resonance imaging or oscillometric devices. Although arterial stiffness is a consequence of vascular aging, this condition has been shown to be a reversible process. Several pharmacological and non-pharmacological interventions have been proposed, aiming at improving vascular stiffness [15].

Other arterial function measurements

In parallel with arterial stiffness assessment, several biological measures of arterial function have been used over the last decades. Although they provide additional information on arterial structure and/or function, they are no substitute for PWV [15].

- Aortic pulse pressure also reflects aorta's stiffness, calculated by subtracting the central diastolic pulse pressure from the central systolic pulse pressure. Its association with cardiovascular outcomes was reported