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Current Opinion in Food Science

Flavonoid intake and cardiovascular disease risk

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Emerging evidence from epidemiological and randomized controlled trials (RCTs) support protective effects of foods and dietary supplements rich in flavonoids against cardiovascular disease (CVD). Epidemiological studies provide valuable information in this field but the estimation of flavonoid intake is still prone to bias due to limitations of food-frequency-questionnaires and lack of biomarkers. Advancements in mass spectrometry led to more accurate flavonoid quantification in foods and biological fluids and development of comprehensive metabolomic databases. Current research is still struggling with the establishment and validation of new biomarkers of flavonoid intake. Efforts to create adequate standardized materials and well-matched controls used in RCTs have also improved data robustness. However, the relationship between flavonoid intake and CVD is still not fully established.

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Current Opinion in Food Science 2015, **2**:92–99

This review comes from a themed issue on **Functional foods and nutrition**

Edited by **Chi-Tang Ho**

For a complete overview see the Issue and the Editorial

Available online 23rd February 2015

http://dx.doi.org/10.1016/j.cofs.2015.02.006

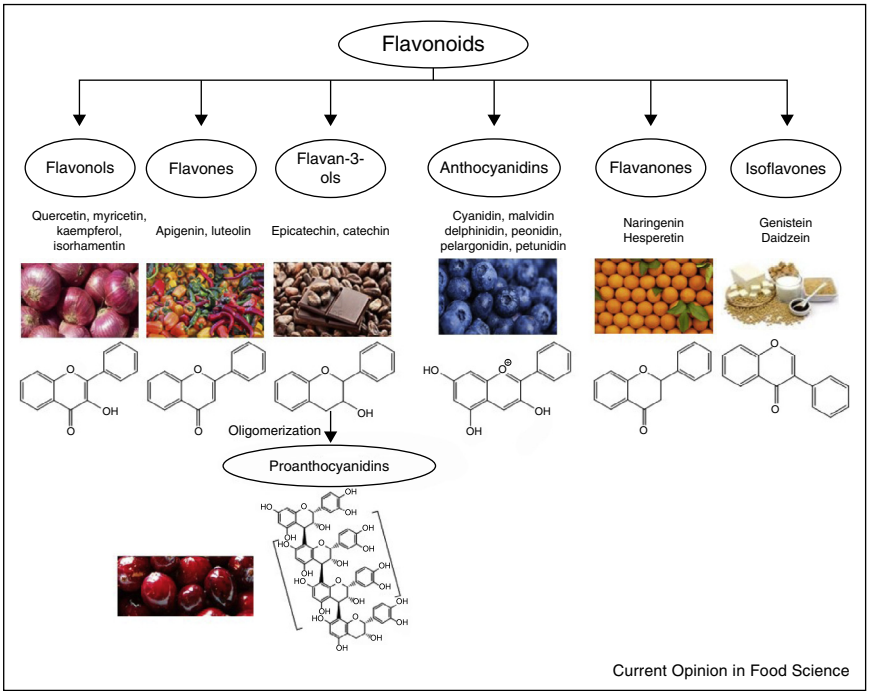
Introduction

A diet rich in fruits and vegetables is essential for a healthy lifestyle and it is conceived that such diets lead to a risk reduction in hypertension, coronary heart disease, and stroke [1]. Fruits and vegetables are rich sources of (poly)phenols, in particular flavonoids, which are considered the putative compounds responsible for the cardiovascular benefits reported in epidemiologic studies [2]. Flavonoids comprise a vast family of ubiquitous plant secondary metabolites with large structural heterogeneity. These compounds are classified based on their hydroxylation pattern and unsaturation degree on the C-ring [3] (Figure 1). Flavones (e.g. apigenin and luteolin) are commonly found in parsley, oregano and artichokes, while high concentrations of flavonols (e.g. quercetin, kaempferol, isorhamnetin and myricetin) are detected in capers, radishes, and onions [4]. Other major flavonoid classes correspond to flavanones (e.g. naringenin and hesperetin), found almost exclusively in citrus, anthocyanidins (e.g. cyanidin, peonidin, petunidin, pelargonidin, malvidin and delphinidin) which are mainly found in berries, red cabbage, and red wine [4], and isoflavones (e.g. daidzein, genistein) which reach high concentrations in soybeans. Tea, chocolate, and cocoa are major sources of flavan-3-ols, such as catechin and epicatechin, which are the building blocks of proanthocyanidins (Figure 1). These highly complex flavonoids can be found in sorghum, cinnamon, and berries. In cranberries, proanthocyanidins with 26 flavan-3-ol units were detected by mass spectrometry [5].

Human intervention studies rely on administering flavonoids via whole foods, dietary supplements, or as individual compounds. As novel data from epidemiological and intervention studies accumulate, the knowledge of the exact composition of the flavonoid rich-foods or supplements to be tested is of paramount importance to support claims with regards to biological activities and to design appropriate controls. Although several studies still use unspecific assays (e.g. Folin–Ciocalteu) to determine total phenolic concentrations of the treatments, there has been tremendous progresses in the detection and quantification of flavonoids using analytical techniques such as ultra high-performance liquid chromatography coupled to mass spectrometry, allowing single compounds quantification and strengthening data quality. A thorough understanding of flavonoid physical–chemistry properties is needed from an analytical standpoint, not only in foods but also in biological fluids obtained after flavonoid intervention. A poor understanding of the flavonoid complexity undermines the validity of both *in vivo* and *in vitro* studies that are conducted in cardiovascular research.

The quantity and the quality of randomized controlled trials (RCTs) investigating the effects of flavonoid-rich foods on cardiovascular function significantly increased in recent years. Currently, many standardized foods with nutrient-matched controls are available for use in RCTs and the synthesis of metabolites and isotopically labeled food grade compounds is becoming more common [6,7], allowing for a better correlation between clinical outcomes and flavonoid metabolism. It is imperative to understand flavonoid metabolism since most compounds, except proanthocyanidins, are extensively metabolized

Figure 1



Flavonoid classes.

and display poor bioavailability [8••,9••]. Ultimately, this factor is extremely important to understand flavonoids' health benefits [10]. The concept of bioavailability is intimately related with the concentration of flavonoids at the target cell/tissue after absorption, metabolism, distribution, and excretion. After absorption, molecules are mainly sulfated, glucuronidated, and/or methylated and transferred to either the bloodstream or back to the colon via the bile. In the colon, these metabolites are further transformed by the gut microflora into smaller phenolic acids, whose effects on cardiovascular physiology and cardiovascular disease (CVD) are still unknown. In a recent review, it was suggested that flavonoid metabolites can even be more bioactive then their precursors [11]. Therefore, pharmacokinetic information is vital to solve the ongoing discussion on the potential cause–effect relationships between flavonoid intake and CVD.

The interpretation of intervention studies is complex because, on the one hand, standardized and validated analytical and biological methodologies to detect putatively biologically active compounds both before and after ingestion are still missing; and, on the other hand, the effects on cardiovascular outcomes depend on population variability, intervention length, and administered amount, which likely hinges on the biological mechanisms of action that is currently not defined. As a consequence of this vicious circle, the role of flavonoids in risk reduction for CVD is still not fully understood [8••]. This review discusses the current knowledge on the role of flavonoids as cardioprotective agents focusing on recent evidence from epidemiological and RCTs.

Epidemiological evidence

Although the number of epidemiological studies investigating the association between flavonoid intake and CVD has increased over the last years, there are still inconsistencies when comparing different studies published in the literature [12••]. Flavonoid intake assessment is generally performed with food frequency questionnaires, diet histories, or self-reported dietary recalls, all of which vary with regards to extend and degree of detail and inherently suffer from considerable sources of error [13••]. Alternative methods to estimate flavonoid intake are necessary. In this regard biomarkers, that can be used to measure the exposure of different flavonoid classes, could provide a better tool to estimate flavonoid intake. Because of the complex nature of flavonoids, this field still presents tremendous challenges. Nonetheless, the discovery and validation of novel dietary biomarkers is emerging [14–16], mainly due to the combination of high-resolution and ultra-high resolution mass spectrometry and multivariate analysis [15,17].

Advances in high-resolution mass spectrometry have enabled accurate identification and quantification of flavonoids in foods [18], which led to the development of comprehensive databases that compiled published data,