Biomedicine & Pharmacotherapy 71 (2015) 102–107

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Review

Flavonoids at the pharma-nutrition interface: Is a therapeutic index in demand?

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ARTICLE INFO

Article history:
Received 1st February 2015
Accepted 21 February 2015

Keywords:
Flavonoids
Pharma-nutrition
Recommended daily allowance
Therapeutic index

ABSTRACT

The consumption of flavonoid-rich foods could have beneficial effects on health. However, different classes of flavonoids have different effect on disease risk and the relationship between flavonoid intake and risk of disease appeared to be non-linear. Furthermore, contrarily to vitamins, there are no symptoms of deficiency for flavonoids; therefore, our body treats them like other xenobiotics. Therefore, a therapeutic index should be determined. Despite flavonoids are at the pharma-nutrition interface, drugs and foods are subject to different regulatory frameworks and there is no recommended daily allowance (RDA) for flavonoids. Relatively little is known about the efficacy, safety and underlying mechanisms of these bioactive compounds, especially when taken in concert with drugs. Flavonoids could act both as drugs and pro-drugs with pharmacological and toxicological promiscuity. Due to the low bioavailability, the gastrointestinal tract could be the primary target of flavonoids and metabolites. Different effects have been observed after acute and chronic consumption and bioavailability and bioactivity have high inter-individual variability. Furthermore, the difficulties in the design and in the interpretation of human intervention studies make difficult the establishment of a therapeutic index for flavonoids. Probably the concept of 'personalized nutrition' previously proposed could be the better approach. However, despite more studies are needed in order to establish a therapeutic index for each flavonoid subclasses, at the moment RDA of total flavonoids could be between 250–400 mg/d, respecting the seasonality of food sources.

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1. Introduction

1.1. Flavonoids at the pharma-nutrition interface

Nutrition and pharmacology are complementary disciplines in several areas of disease. Traditionally, macronutrients and micronutrients are the subjects of nutrition, whereas pharmacology is aimed to the study of xenobiotic compounds with potential therapeutic effects [1,2]. Therefore, the most difference between food and drugs is that the former should provide energy and maintain health, whereas the latter are developed to treat or to prevent disease. However, this does not imply that there is no role for nutrition in preventing disease. In particular, some foods contain several xenobiotics, such as the secondary plant metabolites flavonoids, that reduce the risk of disease development [3].

Furthermore, several of the drugs in use have been derived from natural products including those to which humans have been exposed via the diet. In particular, micronised purified flavonoid fraction supplements are commonly used, as phlebotonics and venoactive drugs, in the management of venous edema [4], venous leg ulcers [5] and haemorrhoidal disease [6]. From that, the definition of nutraceutical develops as the hybrid of 'nutrition' and 'pharmaceutical' [7]. The recognized therapeutic active level of substances may be used as a cut-off point to differentiate between a food item and a medicine [1]. Products with a recommended daily dosage that is higher than this cut-off point would be

Abbreviations: ADI, acceptable daily intake; AhR, aryl hydrocarbon receptor; AP-1, activation protein-1; AUC, area under the concentration–time curve; Cmax, maximum concentration; CVD, cardiovascular diseases; CYP450, cytochrome P450; EC50, concentration required for 50% of a maximum effect; FMD, flow-mediated dilation; GALT, gut-associated lymphoid tissue; IC50, concentration required for 50% inhibition; LOAEL, lowest observed adverse effect level; MDR, multidrug resistance efflux transporters; NF-κB, nuclear factor κB; NOAEL, no observable adverse effect level; Nrf2, nuclear erythroid 2-related factor 2; PXR, pregnane X receptor; RCT, randomized controlled trials; RDA, recommended daily allowance; RDI, recommended daily intake; T2D, type 2 diabetes; Tmax, time to reach the maximum concentration.

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http://dx.doi.org/10.1016/j.biopha.2015.02.028
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classified as drugs, whereas products with a recommended daily intake (RDI) or allowance (RDA) that is lower than this cut-off point would be regarded as dietary supplements [1]. However, Gaine et al. [8] pointed out that there are many obstacles in the determination of RDA for flavonoids. In particular, the bioavailability and bioactivity of flavonoid subclasses differ.

1.2. Food sources and bioavailability

Flavonoids are polyphenolic compounds that are distributed widely in the plant kingdom and include several subclasses, such as flavonols, flavones, flavanols, anthocyanins, flavanones and isoflavones [9].

The mean intake of flavonoids range between 344.83 mg/d [10] and 897 mg/d [11] (Fig. 1). Differences in polyphenol intake may depend on country-specific food preferences and, consequently, on preferences for main dietary sources. In fact, despite flavonoids are abundant in fruits and vegetables, recently tea has been identified as the most important source, especially for flavanols and flavonols, contributing almost 300 mg of daily flavonoid intake in the Polish population [11]. On the other hand, the highest concentrations of catechin polymer (proanthocyanidins) forms are found in cocoa and dark chocolate (1500–3400 mg/100 g) [9], whereas the main dietary sources of flavonols (quercetin and kaempferol) are spinach and onions (120–160 mg/100 g) [9].

The most common dietary sources of the other classes of flavonoids are artichokes, black olives and celery leaves (60–130 mg/100 g) for flavones (luteolin and apigenin), lemon, orange and grapefruit juices (5–60 mg/100 ml) for flavanone (naringenin and hespertine), red fruits (up to 1300 mg/100 g) for anthocyanins, whereas isoflavones (genistein and daidzein) are found almost exclusively in soy products (100,400 mg/100 g) [9].

Contrarily to vitamins, there are no symptoms of deficiency for flavonoids, therefore our body treats them like other xenobiotics (drugs, carcinogens, pro-carcinogens and toxic substances in general). For this reason, their bioavailability is low because once ingested, they are extensively metabolized.

Flavonoids are substrates of the enzymes of phase I and phase II detoxification, which operate the transformation of xenobiotics, and phase III transporters, resulting in poor bioavailability [12].

The metabolism of flavonoids generally begins in the lumen of the small intestine at the level of the enterocytes [12]. Phase II enzymes, which are present in the small intestine and liver, are responsible for the phenomena of conjugation [12]. Most of the protein of phase III is able to mediate the transport of the flavonoids and/or their metabolites, reducing absorption [12]. Although enterocytes and hepatocytes have a primary role in the metabolism, due to the low absorption of flavonoids also the microbial flora generates metabolites, which are absorbed in the colon [12]. From that, not only genetic polymorphisms of the detoxification systems but also differences in gut microbiome and interactions of flavonoids with probiotics and prebiotics could affect inter-individual variability [13].

1.3. Flavonoids and risk of disease

Data from a meta-analysis suggested that total flavonoids, flavonols, flavones, flavanones and flavonols exert protective effects on the risk of smoking-related cancers (lung, oesophagus, and larynx) in smokers, whereas no association was observed in non-smokers, except for flavanones [14]. Although total dietary flavonoid intake was significantly associated with aero-digestive tract cancer risk (risk: 0.67) [14], it was not associated with a reduced risk of colorectal or stomach cancer [15]. However, among flavonoid subclasses, the intake of flavonols, flavanols, anthocyanidins and proanthocyanidins (risk: 0.71, 0.88, 0.68 and 0.72, respectively), but not of flavones and flavanones, showed a significant inverse association with colorectal cancer risk [15]. On the other hand, a significant inverse association was found only between flavonols intake and stomach cancer risk (risk: 0.68)

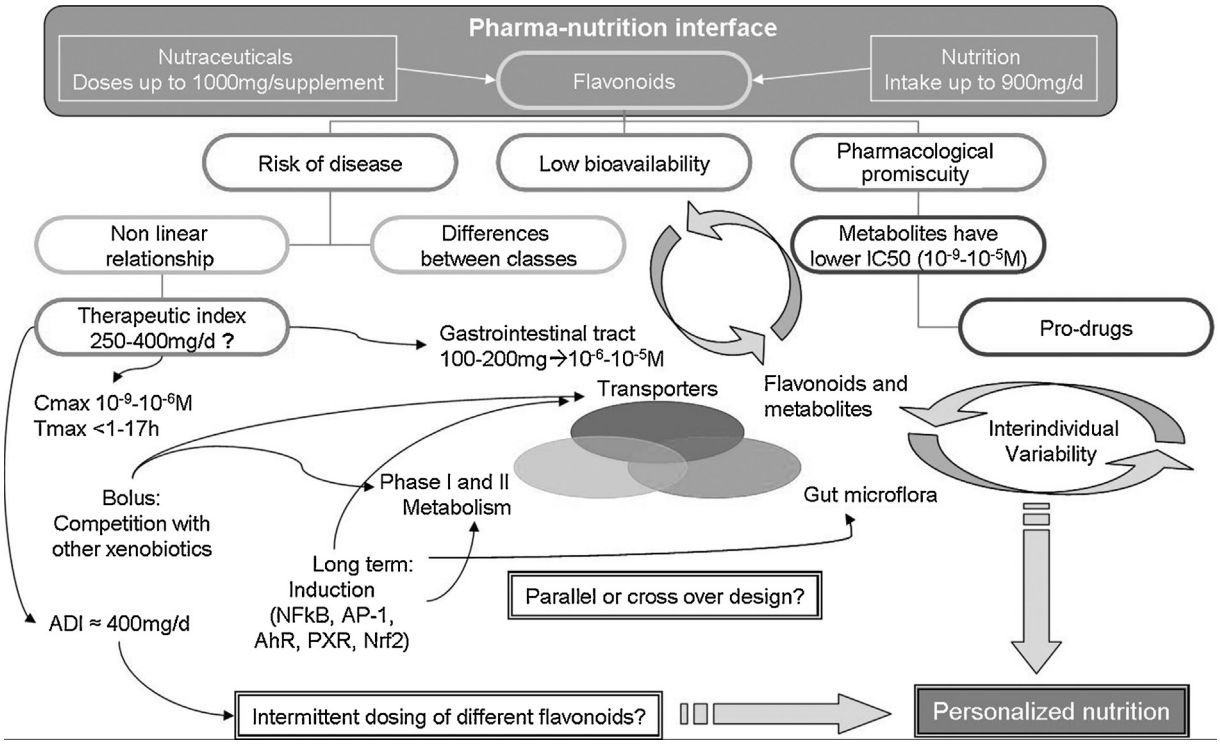

Fig. 1. Flavonoids at the pharma-nutrition interface. ADI: acceptable daily intake; AhR: aryl hydrocarbon receptor; AP-1: activation protein-1; Cmax: maximum concentration; IC50: concentration required for 50% inhibition; NF-κB: nuclear factor κB; Nrf2: nuclear erythroid 2-related factor 2; PXR: pregnane X receptor; Tmax: time to reach the maximum concentration.

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