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Review

Flavonoids as detoxifying and pro-survival agents: What's new?

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ABSTRACT

The role of flavonoids in the survival machinery of cells has come in the spotlight due to the recent evidence of their effect on the relationship mitochondria-ER stress-proteasome, including the intracellular mechanisms of autophagy and apoptosis. Numerous experimental animal investigations and even human clinical studies have highlighted the major role of these natural compounds in the economy of life and their deep relationship with autotrophic organisms in the evolutionary space. Their role as anti-oxidant and oxidative stress preventive molecules has to date been investigated extensively in the literature. Despite this great amount of promising evidence, many concerns, however, remain, most of which dealing with biochemistry, bioavailability, pharmacokinetics, and interaction of flavonoids with gut microbiome, issues that make difficult any good attempt to introduce these molecules in the human healthcare systems as possible, encouraging therapeutic substances. This review tries to address and elucidate these items.

1. Introduction

In recent years flavonoids have become the major subject of extensive investigations on cell survival and stress response, mostly due to their well-known health-promoting properties. Toxins that enter the body from the environment are transported into the liver or stored in tissues. In the organism, a complex assortment of various enzymes, mainly working in the liver, contribute to excrete and neutralize the different toxins and molecular stressors coming from diet and metabolism as bile salts, thanks to the major role of cholesterol. Compounds that stimulate the bile, like cynarine, increase the elimination of toxins from the bile into the digestive tract for elimination in the feces (Daniel et al., 1988; Aksu and Altinterim, 2013). Due to its relationship with the gastrointestinal tract, the liver is a critical target for toxicity caused by drugs, xenobiotics, and oxidative stress. Reactive oxygen species (ROS) derived from chemicals or drugs, which are exposed to liver cells, appear to indirectly mediate liver injury, although the mechanisms of free radical toxicity in the liver are not yet well understood. Probably, it is important to understand the role of antioxidants during drug-mediated toxicity to discuss if they can be used to reduce oxidative stress caused by reactive intermediates produced by various drugs and chemicals, besides physical stressors (Bakir et al., 1973; Korkina and Atanas'ev, 1997; Rice-Evans, 2001). Yet, ROS might be of major interest for their role as signaling molecules in adjusting the pro-survival mechanisms of the cell, and this issue is a very recent novelty in the field. In this sense, quite recently researchers are wondering if ROS may help the cell to keep its survival activity, by acting as regulators in the modulation function of mitochondrial and endoplasmic reticulum (ER) (Chirumbolo and Bjørklund, 2017).

Chronic ethanol intake (6 g/kg/day × 60 days) causes liver damage characterized by elevated biomarkers of liver dysfunction and a decline in liver glycogen (Aherne and O'Brien, 2002). The administration of ethanol-induced the activities of cytochrome P450 and cytochrome-b5 and reduced the activities of glutathione-S-transferase and cytochrome-c reductase. Moreover, ethanol has been shown to induce hepatocyte apoptosis and to reduce the viability of isolated hepatocytes (*ex vivo*) (Massey et al., 2015; Dinis-Oliveira, 2016). In general, flavonoids are considered as good free radical scavengers. The liver is a functional model of major importance to investigate the effect of xenobiotics and phytochemicals (flavonoids) in medicine. There are flavonoids for which this research appears particularly promising. For example, silymarin has numerous pathways for hepatoprotective effects such as antioxidant activity. Silymarin has been found to be more effective than vitamin E in the liver of about ten times (Takei et al., 1988; Vargas-Mendoza et al., 2014; Sanghai et al., 2017). Furthermore, silymarin inhibits detoxification of cytP450 pathways and prevents metabolism of toxic integrates, including tetrachloride, acetaminophen and thioacetamide (Baumann et al., 1980; Baker, 1998; Gabor, 1988; Hegui et al.,

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1990; Trnovsky et al., 1993; Justesen et al., 2000; Malterud and Rydland, 2000; Bektur et al., 2016). This evidence should encourage the study of plant-derived flavonoids as detoxifying agents. The polyphenols could activate detoxification enzyme through the antioxidant/electrophile response element (ARE/EpRE) in the promoter domain (Mullinck and van Blomberg, 1980; Miller et al., 2000; Day and Williamson, 2001; Slama et al., 2017). Interestingly, the effects that flavonoids, in general, have on enzymes depend on the levels the latter have inside the cell, their tissue distribution, and flavonoids bioactivity and bioavailability, besides their chemistry. Many flavonoids have low bioavailability orally, and the variation in the enzyme activity between different species can be considerable. Moreover, due to environmental and genetic factors, a great interindividual variability in drug- and xenobiotic-metabolizing enzymes has been reported (Ezzikouri et al., 2010; Crawford et al., 2012; Janicka et al., 2013). This review tries to address the state of art of flavonoids in medicine, taking into account new emerging hypotheses on their function.

2. An introduction to flavonoid biochemistry and function

As it is well known that flavonoids constitute a large class of chemical compounds possessing a chromone (benzo (pyron) or similar open structure as the main chemical backbone). Depending on the positions of the benzene ring and substituents, flavonoids can be subgrouped in several classes, the main of which is represented by anthocyanidins, flavonols, isoflavonols, flavones, isoflavones, flavanones, isoflavanes, flavans, chalcones and dihydrochalcones (Ross and Kasum, 2002). Coumarins also are structural and functional closely related to the flavonoids (Borges Bubols et al., 2013). The substituents of the flavonoid may be hydroxyl, methoxyl, ethoxyl or prenyl groups, and the hydroxyl groups may be conjugated with, for example, monosaccharides, oligosaccharides, sulfates or phosphates. Therefore, they should be stored in the dark and at low temperatures. Most flavonoids are highly colored and emit lively and characteristic fluorescence colors, which is used for the identification and separation of them, for example by thin-layer chromatography or high-performance liquid chromatography (HPLC). Such methods are widely used among botanists for taxonomic classification of plants. (Kumar and Pandey, 2013). Furthermore, they are easily oxidized, and they are efficient free radical eliminators. The latter property is utilized in many medical applications of flavonoids.

3. Flavonoid-rich food and medicinal plants

Flavonoids (more than 8000) represent the largest and most valuable groups of polyphenolic integrates in fruits, cocoa, wine, vegetables, and tea. They are very important parts of the daily human diet. Humans usually consume the largest amount of flavonoids via tea, onions, and apples (Havsteen, 2002; Jun et al., 2016). These compounds are present in all green plant cells in which they carry important hormone functions (Pérez-Gregorio et al., 2014). It is therefore not surprising that flavonoids can also have hormone functions in animals. The most important function of the flavonoid in plants was originally considered an enhancement of the growth of the auxins by the increase of length (Gabor, 1988; Brunetti et al., 2013). This could happen by genetic induction or control of membrane pores, which otherwise allows indolyl-acetic acid to leave the cell. The detailed mechanism is not yet known, but it is believed that flavonoids inhibit the formation of COX2-dependent eicosanoids, leading to their well-known anti-inflammatory property (Yoon and Baek, 2005). In the recent years, however, other hypotheses have been put forward (Gabor, 1988; Simmonds, 2001; Chirumbolo and Bjørklund, 2017). The intake of flavonoids with a usual dietary habit for humans was initially estimated at 1–2 g/day, but recent studies show that the amount is much less (Gabo, 1988; DiCarlo et al., 1999; Justesen et al., 2000; Sebastian et al., 2017). Therefore, their toxicity must be very low. This fits well with the dietician's century-long recommendation for the population to consume abundant amounts of fresh vegetables and fruit daily, even though the deeper cause has only become apparent recently. Beneficial health effects of flavonoids are mainly ascribed to their antioxidant activity (Li et al., 2015). However, recent studies highlighted the role of flavonoids in inducing ROS as signaling molecules in the modulation of cell survival, mainly through the activity of mitochondrial and ER (Frank et al., 2012; Murakami et al., 2017). In this sense, one can explain how potentially toxic molecules such as flavonoids exert beneficial action on organisms. Many studies have suggested that flavonoids exhibit biological activities, including anti-allergenic effects (Li et al., 2014; Liang et al., 2017), antiviral (Friedman, 2014; Sithisarn et al., 2013), anti-inflammatory (Chirumbolo, 2010; Sithisarn et al., 2013; Chen et al., 2017), vasoactive and cardiovascular protective action (Lee et al., 2017). These pharmacological effects have been most frequently associated with the antioxidant properties of flavonoids; thug new evidence has emerged about their actual activity in a cell. The antioxidant ability was related not only to the flavonoids but also generally to the polyphenols. This antioxidant activity is particularly difficult to be assessed *in vivo*. A further concern is the possibility that food components like flavonoids can change the metabolism of drugs in the human body (Garg et al., 2001). Flavonoids consumed *per os* are hydrolyzed in the intestine of bacterial enzymes (e.g., fecalase) and about 15% of the aglycones (nuclei) are absorbed in the intestinal epithelium of bile complexes and chylomicrons (Gabor, 1981; DiCarlo et al., 1999; Day and Williamson, 2001; Cassidy and Minihane, 2017). Some of them are found in conjugates that have retained their antioxidant properties. The rest of the flavonoids leave the intestine with feces. Some of the flavonoids bind to serum albumin. The half-life of the flavonoid in the body is usually 2–3 h but may reach 18–28 h in some cases. The short residence time of the flavonoids in the body and their aglycones, poor water solubility are likely explanations of their low toxicity. The long-term toxicity of the flavonoids is very low as these substances do not accumulate in the body (Middleton, 1998; Lairon and Amiot, 1999; Skibola and Smith, 2000; Tapas et al., 2008; Pang and Liu, 2017). A lethal dose of flavonoids can only be obtained by compulsion of rats with these substances in pure form at an unrealistic high dose of $>$ 1.0 g/kg body weight. In that case, hepatocyte membranes will break down after exposure to this treatment for approximately three weeks (Havsteen, 2002). However, some flavonoids may have a toxic effect on humans as specific antibodies to these substances have been found in patients' blood. This antigenic effect may cause allergy in patients (approximately 4% of the population) (Hegui et al., 1990). Some flavonoids, such as quercetin, exhibited another toxic effect in the bacterial Ames test, namely mutagenicity, though not always confirmed (Ames et al., 1975; Harwood et al., 2007). The genotoxicity of flavonoids may appear obvious, as plants produce these substances as a defense mechanism against phytopathogens, but not all the experimental reports seem to support this view in humans (Harwood et al., 2007; Okamoto, 2005). Some flavonoids have antimicrobial properties (Babii et al., 2016).

However, the role of flavonoids in the cell biology might be much more intriguing than expected before. Usually they enter the cell via the arylhydrocarbon receptors (ArHR) (Chirumbolo, 2010) and induce the formation of a low levels of ROS that helps mitochondria to oscillate between the pro-apoptotic activity and the pro-autophagic/pro-survival activity, depending on how much the cell is under stress and needs to be removed by an apoptotic event or “adjusted” by an autophagic mechanism (Chirumbolo and Bjørklund, 2017). This subtle activity of low concentrated flavonoids might explain their pro-beneficial role in cell physiology and medicine (Fig. 1).

In addition, some widely used medicinal plants such as *Aloe vera* (Asphodelaceae) with luteolin, *Betula pendula* (Betulaceae) with quercetrin, *Mentha longifolia* (Lamiaceae) with luteolin-7-*O*-glycoside, *Calendula officinalis* (Compositae) with isorhamnetin, *Citrus medica* (Rutaceae) with flavonoids from hesperidin, *Passiflora incarnate*