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Review

Nutraceuticals: Facts and fiction

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Abstract

Epidemiological studies show a link between the consumption of plant-derived foods and a range of health benefits. These benefits have been associated, at least partially, to some of the phytochemical constituents, and, in particular, to polyphenols. In the last few years, nutraceuticals have appeared in the market. These are pharmaceutical forms (pills, powders, capsules, vials, etc.) containing food bioactive compounds as active principles. The bioactive phytochemicals have become a very significant source for nutraceutical ingredients. Scientific research supports the biological activity of many of these food phytochemicals, but the health claims attributed to the final marketed nutraceutical products have often little or doubtful scientific foundation. This is due to the fact that a lot of the scientific evidence is derived from animal testing and *in vitro* assays, whereas human clinical trials are scarce and inconclusive. Some key issues such as bioavailability, metabolism, dose/response and toxicity of these food bioactive compounds or the nutraceuticals themselves have not been well established yet. Amongst the phytochemicals, several groups of polyphenols (anthocyanins, proanthocyanidins, flavanones, isoflavones, resveratrol and ellagic acid) are currently used in the nutraceutical industry. In this report, we have reviewed the most recent scientific knowledge on the bioavailability and biological activity of these polyphenols ('fact'), as well as the health claims (which are not always supported by scientific studies) ascribed to the polyphenols-containing nutraceuticals ('fiction'). The *in vitro* antioxidant capacity, often used as a claim, can be irrelevant in terms of *in vivo* antioxidant effects. Bioavailability, metabolism, and tissue distribution of these polyphenols in humans are key factors that need to be clearly established in association to the biological effects of these polyphenols-containing nutraceuticals. The future trends of phytochemistry research regarding nutraceuticals are discussed.

Keywords: Phenolic compounds; Polyphenols; Anthocyanins; Flavanones; Isoflavones; Ellagitannins; Ellagic acid; Resveratrol; Proanthocyanidins; Procyanidins; Flavan-3-ols; Biological activity; Bioavailability; Nutraceuticals; Marketing; Health

Contents

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1. Introduction

Epidemiological studies on the relationship between dietary habits and disease risk have shown that food has a direct impact on health. It is generally accepted that plant derived foods such as wine, fruits, nuts, vegetables, grains, legumes, spices, etc. exert some beneficial effects on human health, particularly on age-related diseases. As the human population lives longer, chronic age-related diseases such as cardiovascular diseases, neurodegenerative diseases, type II diabetes, and several types of cancer (e.g. gastrointestinal cancer), known to be related to dietary habits, continue to expand. This fact has encouraged several health organizations around the world to recommend an increase in the intake of plant derived food in order to improve our health status and to delay the development of these diseases. However, it should be noticed that these epidemiological studies generally focus on a narrow range of plant substances in the diet. In addition, where a benefit is suggested, it is usually associated with a decade or so of following that type of diet indicating a modest effect that over a long period accumulates to a modest (but highly desirable) benefit. The magnitude of the effect produced in a short-term intervention study designed supposedly to test the epidemiological association may be too small to detect from purely analytical perspectives (even if the study organisers have focussed on the correct mechanism and measurement required).

The capacity of some plant-derived food to reduce the risk of chronic diseases has been associated, at least in part, to the occurrence of non-nutrient secondary metabolites (phytochemicals) that have been shown to exert a wide range of biological activities. These metabolites have low potency as bioactive compounds when compared to pharmaceutical drugs, but since they are ingested regularly and in significant amounts as part of the diet, they may have a noticeable long-term physiological effect. Phytochemicals that are present in the diet, and have been associated to health benefits, include glucosinolates, sulphur-containing compounds of the Alliaceae, terpenoids (carotenoids, monoterpenes, and phytosterols), and various groups of polyphenols (anthocyanins, flavones, flavan-3-ols, isoflavones, stilbenoids, ellagic acid, etc.). Their bioactivity has been, to some extent, associated to their antioxidant properties (capacity to scavenge free-radicals) which are involved in the onset development of many of the chronic degenerative diseases (LDL oxidation in atheroma plaque development, DNA oxidation and cancer, oxidation and ageing, inflammation, etc.).

Marketing studies carried out by diverse industries have shown the consumers' increasing demand for health-promoting food products as well as for non-food products (i.e. dietetics and pharmaceuticals) containing the active principles present in these health-promoting foods. In the past few years, many food bioactive constituents have been commercialized in the form of pharmaceutical products (pills, capsules, solutions, gels, liquors, powders, granulates, etc.) that incorporate food extracts or phytochemical-enriched extracts to which a beneficial physiological function has been directly or indirectly attributed. These range of products cannot be truly classified as 'food' and a new hybrid term between nutrients and pharmaceuticals, 'nutraceuticals', has been coined to designate them.

This type of health-promoting products is getting more popular amongst health-conscious consumers and, thus, a large list of nutraceuticals containing phytochemicals from foods is now available in the market. For example, the carotenoid lycopene, Alliaceae (garlic, onion) extracts containing sulphur derivatives (i.e. alliin and allicin), glucosinolate extracts, and phytosterol extracts are widely commercialized products. Some of the most common phytochemicals found in the nutraceutical market are polyphenols such as anthocyanins, proanthocyanidins, flavonols, stilbenes, hydroxycinnamates, coumarins, ellagic acid (EA) and ellagitannins (ETs), isoflavones, lignans, etc.

Functional foods are those that when consumed regularly exert a specific health-beneficial effect beyond their nutritional properties (i.e., a healthier status or a lower risk of disease) and this effect must be scientifically proven (International Life Science Institute; http://www.ilsi.org). The new regulation of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods specifically indicates the necessity of scientific support for health claims (http://eur-lex.europa.eu/JOIndex.do?ihmlang=en; Official Journal of the European Journal, OJ L 404, 30/12/2006).

Nutraceuticals are diet supplements that deliver a concentrated form of a presumed bioactive agent from a food, presented in a non-food matrix, and used with the purpose of enhancing health in dosages that exceed those that could be obtained from normal foods (Zeisel, 1999). Nutraceuticals are sold in presentations similar to drugs: pills, extracts, tablets, etc. The Food and Drug Administration (FDA; http://vm.cfsan.fda.gov) regulates dietary supplements under a different set of regulations than those covering conventional foods and drug products. However, no specific regulation exists in Europe to control nutraceuticals.

The boundary between nutraceuticals and functional foods is not always clear. For example, when a phytochemical or phytochemical extract is included in a food formulation, i.e. 300 mg of extract dissolved in 1 L of juice, we have a new potential functional food. The same amount of phytochemical or phytochemical extract included in a capsule will constitute a new nutraceutical. Although consumption of one litre of this functional juice would provide the same dose of bioactive compounds as one capsule of the nutraceutical, the new functional food will be regulated whereas the nutraceutical will be not.

The aim of this work is to critically assess some of the most representative polyphenols-containing nutraceuticals currently available in the market, in particular those in which the main components declared are the polyphenols anthocyanins, proanthocyanidins, flavanones, resveratrol, isoflavones, and EA acid and ETs. We have reviewed the most up to date literature on key issues such as bioavailability and metabolism, as well as bioactivity, for these groups of polyphenols and we have also examined the claims ascribed to the final nutraceutical products for marketing purposes. We highlight some of the weak points and unresolved questions in relation to the promotional labels and health claims found for some of these products. Future trends for phytochemistry research in this area are also discussed.

2. Anthocyanins

2.1. The facts

A growing number of scientific reports suggest that anthocyanins, and anthocyanin-rich berries or derived extracts, exhibit a wide range of protective effects with potential benefits for human and animal health. It has been recognized that some of these effects may be related to the chemical characteristics and inherent associated antioxidant capacity of these compounds, but newly discovered mechanisms of action, such as alteration of gene expression, may be responsible for the observed health benefits (Lila, 2004; Juranić and Žižak, 2005). Most of the evidence accumulated in recent years is based on results from *in vitro* studies and animal testing. Additional data from human trials are slowly emerging. The biomedical properties ascribed to either pure anthocyanins, or to anthocyanin-rich berries or extracts include a large list of beneficial effects on: visual capacity, brain cognitive function, obesity, ulcer protection, cardiovascular risk, and cancer prevention.

Improvement of visual capacity has been attributed to anthocyanins, but only one human study has indicated an apparent improvement of nocturnal vision in myopia subjects after repetitive high doses of a purified anthocyanoside oligomer (Lee et al., 2005a,b), whereas a previous study failed to find any effect of high doses of bilberry capsules on night vision in young males with good vision (Muth et al., 2000). Several animal studies have shown that anthocyanins and berry extracts can increase the cognitive performance, and protect the brain function by reducing oxidative ischemic damage and enhancing memory (Kang et al., 2006; Shin et al., 2006; Barros et al., 2006). Diabetes and obesity can also be prevented in animals fed anthocyanins by decreasing blood sugar levels, or reducing body weight gain and adipose tissue (Tsuda et al., 2003; Guo et al., 2007). Also, chokeberry has been reported to have a gastroprotective effect on ethanol-induced gastric hemorrhagic lesions (Matsumoto et al., 2004), and to inhibit *Helycobacter pylori* growth (Chatterjee et al., 2004).

The prevention of the development of cardiovascular diseases by dietary anthocyanins has been thoroughly studied. Numerous *in vitro* studies have described possible mechanisms of action for anthocyanidins in the vascular system by measuring the response of vascular cell models in terms of gene and protein expression (Kim et al., 2006; Xia et al., 2007). Although a lot has been learnt from these studies, results must be interpreted with caution given the limitations of the *in vitro* experimental conditions. A few *in vivo* animal experiments have confirmed some of the cardiovascular protective effects. The consumption of anthocyanins has been associated to some improvement of diverse cardiovascular risk markers. In dietary-induced hyperlipidemic rats, the intake of chokeberry juice reduced the levels of total plasma cholesterol and of LDL-cholesterol (Valcheva-Kuzmanova et al., 2007). An anthocyanin-rich extract from black rice also decreased serum levels of triglycerides, total cholesterol and non-HDL cholesterol and reduced the area of atherosclerotic plaques in apolipoprotein E-deficient mice (Xia et al., 2006). Administration of a single dose of a mixture of anthocyanins decreased the size of infarct area in a rat model of myocardial injury (Kim et al., 2006). Also, it has been shown that blackcurrant concentrate can decrease peripheral vascular resistance in a hind-limb perfusion rat model (Iwasaki-Kurashige et al., 2006), and that wild blueberry consumption results in alteration of the structural composition of rat aortic tissue glycosaminoglycans (Kalea et al., 2006). Some other recent findings, however, do not support some of these protective effects. An anthocyanin-rich extract from blackcurrant was found to increase plasma and LDL-cholesterol in Watanabe heritable hyperlipidemic rabbits (Finne-Nielsen et al., 2005).

Few controlled human dietary interventions have investigated the anticholesterolemic and antioxidant effects of

anthocyanins or anthocyanin-rich berries, and data are still scarce and inconclusive. In a group of healthy volunteers, a daily intake of a mixed berry juice for a 4-week period led to a decrease in oxidative cell damage and to an increase in the levels of reduced glutathione (Weisel et al., 2006). However, another study in healthy volunteers consuming blackcurrant juice or an anthocyanin drink (from blackcurrant) for 3 weeks showed no effect on DNA damage markers (Moller et al., 2004). Because markers of stress or damage are very low in healthy volunteers, and resulting effects are difficult to measure, other recent studies have looked at effects in groups under stress conditions (physical work or smokers) or groups with enhanced risk. In this context, it has been reported that the intake of blackcurrant capsules slightly increased peripheral blood flow and also improved muscle fatigue in healthy volunteers after repeated typing work (Matsumoto et al., 2005). Daily consumption of chokeberry juice by rowers performing regular physical exercise limited induced oxidative damage, and enhanced endogenous antioxidant defence systems (Pilaczynska-Szczesniak et al., 2005). In chronic cigarette smokers, the levels of lipid hydroperoxides were reduced by daily consumption of blueberries for several weeks (McAnulty et al., 2005). Consumption of a commercial chokeberry extract in combination with statin therapy for six weeks by patients with ischemic heart disease led to a significant reduction of inflammation by reducing levels of serum isoprostanes and oxidized LDL levels, as well as by increasing adiponectin and reducing blood pressure (Naruszewicz et al., 2007). Very recently, it has also been shown that a standardized herbal product from *Hibiscus sabdariffa,* containing high levels of anthocyanins, significantly decreased blood pressure and reduced plasma ACE (angiotensin converting enzyme) activity in hypertensive patients (Herrera-Arellano et al., 2007).

The chemopreventive properties of dietary polyphenols and specifically of anthocyanins, are a lot more complicated to demonstrate, and much of the evidence accumulated so far is based mostly on *in vitro* studies and animal cancer models. In the past few years, a plethora of human cancer cells assays have been used to show the antiproliferative activity of berry extracts or of anthocyanins from berries (Seeram et al., 2006; Wu et al., 2007; Bermúdez et al., 2007). A chemopreventive role of berries or derived extracts has also been shown in animal models, in particular in models of gastrointestinal cancer. The consumption of anthocyanins from bilberry reduced the number of intestinal adenomas in an APC^{Min} mouse model (Cooke et al., 2006). In rats, berries have been shown to decrease the number of induced oesophageal tumours (Stoner et al., 2006), and to inhibit multiple biomarkers of induced colon cancer (Lala et al., 2006).

Although berry-derived nutraceuticals and supplements contain many potentially beneficial anthocyanins, an essential question not yet completely resolved is the bioavailability of these compounds. Some recent reviews (Manach et al., 2005; Prior and Wu, 2006) on human bioavailability of polyphenols show that for different sources of anthocyanins (type of berries), or type of matrix in which the anthocyanins are administered (juice, extract, and capsules), or total amount dosed, the levels of total anthocyanins measured in plasma can vary a lot, and is, in general, very low (in the low nM range, mostly below 0.1 μM). Absorption is rapid and anthocyanins can be detected within less than 1.5 h after intake, indicating that absorption probably occurs from the stomach and (or) the small intestine. In addition, anthocyanins are rapidly eliminated in the urine (in less than 4–6 h). The proportion of absorbed and excreted anthocyanins is less than 0.1% of the ingested amount, indicating that the metabolic fate of a very high percentage of the ingested anthocyanins has not been yet elucidated. The activity of the microflora in the colon and the low stability of anthocyanins at the pH of the intestine are at least partially responsible for the conversion of anthocyanins into more stable small phenolic acids or other molecules of unknown structure. The nature of the anthocyanin metabolites formed and absorbed *in vivo* is another important aspect of the metabolism of anthocyanins. Recent investigations have identified in human plasma the presence of intact mono-, di- and triglycosides of various anthocyanins (cyanidin, peonidin, and delphinidin), some of the aglycones, and some glucuronide and methylated derivatives (Felgines et al., 2005; Frank et al., 2005a,b; Kay et al., 2005; Stoner et al., 2005; Tian et al., 2006; Ohnishi et al., 2006). Incipient information can be found on the presence and distribution of anthocyanins and (or) their metabolites in internal tissues, which is a key issue for understanding the mechanisms of their effects. A few recent studies in animal models fed either a single compound or berry extracts have shown the presence of glycosides, aglycones and both methylated and glucuronide derivatives of anthocyanins in tissues such as stomach, small intestine, liver, bile, kidney, lung and eye (Wu et al., 2005; El Mohsen et al., 2006; Felgines et al., 2006; Ichiyanagi et al., 2006; He et al., 2006; Matuschek et al., 2006). In some particular organs such as the eye or the brain, detection of anthocyanins was very fast (less than half an hour), and total amounts of the detected compounds were between 100 and 200 ng/g (Passamonti et al., 2005).

In spite of the knowledge accumulated in the last few years, a lot of work remains to be done on the nature and detection of possible anthocyanins derivatives formed *in vivo*: metabolites and breakdown products originated under physiological conditions or from the colonic microflora activity, as well as their tissue distribution.

2.2. The fiction

The health-promoting effects of berries and anthocyanins are being increasingly exploited to market products such as nutraceuticals and dietary supplements. These products are commercially available and some information on the composition and health claims is provided

with the product mostly via internet. The main dietary origin of these products is either single berry extracts (e.g. bilberry or wild blueberry) or natural combinations of various berries (blend of blueberry, strawberry, cranberry, wild bilberry, elderberry, and raspberry extracts). Often, they are also combined with other food components and are commercialized as powders, capsules, or tablets. These products are marketed as a source of anthocyanins, and, within the description, the composition is frequently indicated as total mg or percentage of anthocyanins in the product. It is possible to find dietary supplements with a declared content of anthocyanins ranging from <1% to >25%, or tablets containing from 40 mg up to 250 mg of anthocyanins. In addition to anthocyanins, many other compounds are also present in these supplements, and even at higher proportions than those of the anthocyanins themselves. Non specified polyphenols can amount up to 70% of the product. Sometimes, the percentage of other fairly bioactive polyphenols (e.g. proanthocyanidins, hydroxycinnamic acids, or flavonols) is also stated. In addition to compositional information, nutraceutical companies provide information on recommended doses for many of these berry-based products, and it varies from 1 to 2 capsules or 40 to 200 mg daily or twice a day with meals or with water or any other beverage. For most of these berry-based nutraceuticals the composition in anthocyanins or any other components and the recommended doses have not been properly established and standardized.

One of the main claims about these anthocyanins-based nutraceuticals or supplements is their high level of antioxidant capacity. This is usually expressed in terms of their *in vitro* antioxidant activity determined by the ORAC assay. Additionally, the health claims ascribed to berry nutraceuticals comprise a long list that includes statements such as: '*... promotes healthy brain function and mental clarity, healthy vision, cardiovascular health, and healthy blood sugar levels. It also prevents the effects of premature aging...*', '*... reduces oxidative damage and inflammation in the nervous system. It prevents LDL oxidation in blood vessels, reduces the risk of retinopathy and decreases eye fatigue...*', '*...helps maintain healthy brain function...*', '*...Natural vision enhancer that prevents retinopathy; improves capillary fragility and reduces inflammation...*', '*...Supports vision, improves blood glucose levels and memory...*', '*...may prevent some effects of premature aging, healthy brain function and mental clarity, cardiovascular health, healthy vision, provide support for joint discomfort, maintain healthy blood glucose levels and reduce the risk of some cancers.*'

Together with these claims, a final statement is added to clarify that none of the statements have been evaluated by the FDA, that these products are not medically proven to cure, mitigate, treat or prevent any disease, that the information provided is for general knowledge, and that it is up to the consumer to research and make informed decision by obtaining advice from health care professionals.

Both producers and consumers would benefit from having more accurate and comprehensive information on the type, levels, doses, and health benefits that may be expected from the regular consumption of these nutraceuticals and supplements.

3. Proanthocyanidins

3.1. The facts

Proanthocyanidins are the second most abundant natural phenolics after lignin. They are widespread throughout the plant kingdom, and become part of the human diet upon consumption of fruits (grapes, apples, strawberries, etc.), beans, nuts, cocoa, and wine (http://www.nal.usda.gov/fnic/foodcomp/Data/PA/PA.pdf). They are not abundant in vegetables. Proanthocyanidins impart astringency and flavour to these natural sources (Santos-Buelga and Scalbert, 2000).

Proanthocyanidins have been extensively investigated (more than 2700 bibliographic entries from 1945 to early 2007) and they have mainly attracted attention due to their effects on the vascular system, including increase in the antioxidant activity of plasma, decrease of LDL-cholesterol fraction and oxidative stress-derived substances, improvement of endothelium vasodilatation, decrease of blood pressure, maintenance of endothelium function, etc. (Williamson and Manach, 2005). These activities have been mainly reported in grape seed extracts and cocoa derived products. The health-beneficial effects of cocoa consumption have been demonstrated along a number of trials in humans (Heiss et al., 2005, 2007; Schroeter et al., 2006; Wang-Polagruto et al., 2006 among many others). However, the vast majority of these studies have been carried out with procyanidin-rich cocoa derived foodstuffs (milk drinks and other beverages, snack bars, chocolate, etc.). In this context, from the nutraceutical point of view, the most relevant studies available are those involving grape extracts.

Grape seed extracts have shown a number of beneficial effects in humans (Kar et al., 2006) (Table 1), including the increase of plasma antioxidant capacity (Vinson et al., 2001), the prevention of plasma postprandial oxidative stress (Natella et al., 2002), the improvement of blood circulation in legs and the reduction of fluid retention in pre-menopausal women (Christie et al., 2004), and the improvement of endothelial function in subjects at high cardiovascular risk (Clifton, 2004).

Until very recently, the metabolic fate of procyanidins was unknown. Numerous studies in animals and humans show that polymeric procyanidins are not absorbed as such. The majority of polymeric procyanidins pass unaltered through the small intestine after which they are metabolized by the colonic microflora to yield a number of simple phenolic acids including phenylpropionic and phenylacetic derivatives (Depréz et al., 2000). Tsang et al.

Table 1
Human intervention trials of grape procyanidins-derived nutraceuticals

Supplement	Composition	Dose (per day) and assay period	Subjects	Effect	Reference
Grape seed extract	Oligomeric procyanidins	200–300 mg/day; 1 year	3 patients with chronic pancreatitis	Reduction of chronic pancratitis, vomiting and pain	Banerjee and Bagchi (2001)
Grape seed extract	Procyanidins	600 mg/day; 'long-term'	17 healthy and hypercholesterolemic humans	Decrease in plasma cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol concentrations in hypercholesterolemic subjects. No effect on healthy subjects	Vinson et al. (2001)
Grape seed extract	Procyanidins	300 mg; 1 single dose.	8 healthy humans	Prevention of postpandrial oxidative stress	Natella et al. (2002)
Grape seed extract	Procyanidins	300 mg/day; 1 month	24 heavy smokers	Decrease in TBARS. No effect on HDL-cholesterol, LDL-cholesterol, triglycerides and total cholesterol	Vigna et al. (2003)
Grape seed extract	Procyanidins	162 mg/day; 6 months	12 women with chloasma	Reduction and prevention of hyperpigmentation	Yamakoshi et al. (2004)
Mixture of grape, bilberry and cranberry extract (capsules)	Oligomeric procyanidins	320 mg/day;	13 premenopausal women	Reduction of fluid retention	Christie et al. (2004)
Grape seed extract	Procyanidins	1 g/day; 1 month	43 men and women in high cardiovascular risk	Improvement of flow-mediated dilation. No effect on other markers (clotting and fibrinolytic factors, adhesion molecules, serum lipids, urinary isoprostanes and nitric oxide production).	Clifton (2004)
Grape seed extract	Proanthocyanidins	300 mg/day; 6 months, Phase II trial	66 women with radiation-induced breast indurance	No effect on tissue hardness, pain or breast appearance	Brooker et al. (2006)

(2005) reported the presence of catechin glucuronides and methylated glucuronides in rat plasma upon administration of grapeseed procyandins. The same metabolites were found in urine together with sulphate derivatives and dimers B1, B2, B3, B4, the trimer C2, and another unknown trimer. These authors suggested that proanthocyanidins were not depolymerised in the gastrointestinal tract releasing monomeric flavan-3-ols (Tsang et al., 2005). A recent study has reported the presence of oligomers up to the pentamer size in rat plasma upon administration of a procyanidin extract from apple. Interestingly, polymeric procyanidins influenced the absorption of procyanidin oligomers (Shoji et al., 2006).

The data based on the absorption and degradation of proanthocyanidins in humans is somewhat conflicting. *In vitro* assays performed to investigate the metabolism of procyanidins by mimicking gastrointestinal conditions reported the degradation of procyanidin oligomers to yield (bioavailable) monomers (Spencer et al., 2000). However, the results of subsequent *in vivo* assays did not match those from the former *in vitro* approach. No oligomeric procyanidins have been detected in humans upon consumption of high dietary amounts, i.e., from 500 mg to 1 g (Schroeter et al., 2006; Tomás-Barberán et al., 2007). In this case, the main metabolites detected in human plasma upon consumption of cocoa are epicatechin derivatives, mainly the glucuronides and methylglucuronides, whereas the main metabolites detected in urine were sulphate derivatives (Roura et al., 2005; Tomás-Barberán et al., 2007). The bioavailability of cocoa procyanidins seems to be mainly enhanced by the selective enrichment in the content of epicatechin monomers (Tomás-Barberán et al., 2007). The detection of dimers B1 and B2 in human plasma has been reported only in two studies in which the volunteers consumed approximately 2 g of procyanidins (Holt et al., 2002; Sano et al., 2003).

Independently of the concentration of catechin in cocoa products, the bioavailable metabolites are epicatechin derivatives. This could be explained by a difference in the bioavailability of catechin enantiomers. Whereas most fruits, including grapes, contain the (+)-catechin enantiomer, cocoa mainly contains the (−)-catechin enantiomer, which has been reported to be less bioavailable (Donovan et al., 2006).

The main microbial metabolites detected in humans upon consumption of grape procyanidins were 3-hydroxyphenylpropionic acid and 4-*O*-methylgallic (Ward et al., 2004). The production of microbial metabolites derived from procyanidins in humans from other sources, including cocoa, has not been approached in detail.

Regarding the potential toxicity of proanthocyanidins, *in vivo* studies have not reported any major side effects. Grape seed extracts are classified in the USA as GRAS products (Generally Recognized As Safe), and, in Japan,

as an additive for various food applications. Bentivegna and Whitney (2002), as well as Wren et al. (2002), obtained a similar no-observed-adverse effect level (NOAEL) of grape seed extracts in rats. The intake in these experiments was equivalent to an intake of 12 g daily by an adult human for 3 months. A recent study carried out in rats also confirmed the same NOAEL for a procyanidins-enriched commercial extract ingested for 6 months (Fujii et al., 2007). Grape seed proanthocyanidins extract is under study in a Phase I pilot chemopreventive study in healthy women at high risk of developing breast cancer (www.cancer.gov). The intake of 1 g grape procyanidins for one month (Clifton, 2004), or 0.3 g/day for 6 months (Brooker et al., 2006) did not show any adverse effect in humans.

3.2. The fiction

Procyanidins-rich products are one of the most common nutraceuticals in the market. The most popular are those based on grape seed extracts which are usually sold as '95% procyanidins standardized extracts' pills or capsules. The main activity attributed to theses nutraceuticals is their antioxidant activity: ....'*eliminate free radicals immediately*'.....'*antioxidants can be beneficial for protecting against premature aging and degenerative diseases caused by free radical damage*'.....There are many other claims such as: strengthens and repairs connective tissue; helps patients with multiple sclerosis; helps teeth and gums; reduces allergic responses by minimizing histamine production; enhances capillary strength and vascular function; reduces blood pressure and cholesterol levels; helps prevent cancer; strengthens the immune system; increases peripheral circulation, improving vision; reduces skin aging and loss of elasticity.

Wrong information is often provided with these grape seed extract nutraceuticals: .....'*It is distributed to virtually every organ and tissue, and remains in the body for up to 72 hours*'..... '*It is bioavailable and immediately absorbed from the stomach into the bloodstream...*', ...'*Grape Seed extract is water-soluble and extremely well-absorbed into your body, usually within minutes of consumption*'.....

The recommended daily dose can change but it is rather homogeneous: .....'*daily dose of 50 mg for ages from 30 to 40; 100 mg from 40 to 50 and 200 mg for adults over 50*'....., ...'*150 mg for a 70 kg adult person*'..... In general, the average recommended dose is 150–200 mg/day which is in the average of many intervention studies.

There is not enough information regarding the effects of long-term supplementation of procyanidins in humans. Up to now, there are not enough clinical trials carried out by independent researchers to confirm the claims. Most trials have been performed with a small number of volunteers and for short periods of time. In addition, there is a conundrum regarding the true bioactive compounds responsible for the systemic biological activity observed: are the microbial-derived metabolites the real active molecules, the monomers, or the oligomers?

4. Flavanones

4.1. The facts

The most representative and investigated flavanones are the aglycones naringenin and hesperetin, and their corresponding glycosides, naringin and hesperidin, abundant in grapefruits and oranges respectively (Garg et al., 2001; Manach and Donovan, 2004). A less studied flavanone, eriodictyol, and its glycoside eriocitrin are also abundant in lemon peel (Garg et al., 2001). As reported in numerous animal experiments and *in vitro* studies, these compounds exhibit a wide range of biological and pharmacological activities including antioxidant, hypocholesterolemic, hypoglycemic, prevention of bone losses, and anti-tumor, which indicates they may have potential beneficial effects in humans against diseases such as cardiovascular diseases, diabetes, osteoporosis, or cancer.

Several *in vivo* studies looking at cardioprotective effects of flavanones have been conducted in animal models. Dietary supplementation with naringenin in high-cholesterol fed rats effectively improved cholesterol metabolism by lowering the levels of plasma and hepatic cholesterol, plasma TG and increasing levels of HDL. Also, lower plasma and hepatic TBARS, as well as higher levels of superoxide dismutase (SOD) and glutathione peroxidase indicated an improvement in antioxidant status (Jeon et al., 2007). However, very recently it was shown that supplementation with naringenin in rats enduring high oxidative stress had no antioxidant effect (Andrade and Burgess, 2007). In a model of myocardial infarction-induced rats, oral administration of several doses of naringin for 56 days inhibited lipid peroxidation and improved antioxidant status (Rajadurai and Stanely Mainzen Prince, 2006), as well as modulated several cardiac markers, indicating some cardioprotective effects (Rajadurai and Stanely Mainzen Prince, 2007a,b). Mice fed experimental diets containing naringenin for 21 days exhibit an increase in hepatic fatty acid oxidation mediated by regulation of the expression of several hepatic enzymes, and lowered the levels of serum TG, cholesterol, phospholipids, and fatty acids (Huong et al., 2006). Other biomedical properties attributed to the flavanones naringin and hesperidin are their capacity to ameliorate the glucose and lipid profiles in diabetic animals by regulating hepatic metabolism (Jung et al., 2004, 2006), and to reduce bone losses and decrease serum and hepatic lipids in an animal model of osteoporosis (Chiba et al., 2003). Hesperidin and naringenin have also been reported to exert some protective effects in experimental animals against induced toxicity in the liver (Kaur et al., 2006; Pari and Gnanasoundari, 2006), or in the kidney (Badary et al., 2005), and to protect against induced arthritis (Kawaguchi et al., 2006).

Besides the evidence on the hypocholesterolemic activity of flavanones in animals, only a few human clinical trials have been carried out so far with flavanone-containing orange juice or flavanones. In a study accomplished in

healthy men and women with moderate hypercholesterolemia (elevated plasma cholesterol and LDL-cholesterol but normal TG) the consumption of 750 mL of orange juice daily for 4 weeks led to an increase in HDL- cholesterol, and to a concomitant decrease in LDL-HDL cholesterol ratio (Kurowska et al., 2000). However, in a more recent study also carried out with mildly hypercholesterolemic subjects, the consumption of 480 mL daily of orange juice for 10 weeks had no significant effects on the plasma lipids profile (total cholesterol, total TG, LDL- and HDL-cholesterol) (Devaraj et al., 2004). The intake of 700 mL of orange juice daily for three weeks by healthy subjects had little effect on cholesterol levels but significantly raised the levels of plasma TG (Franke et al., 2005). Administration of a water soluble hesperidin derivative, glucosyl-hesperidin or G-hesperidin, to hypertriglyceridemic subjects at 500 mg/day for 24 weeks resulted in a significant decrease of the serum triglycerides (TG) levels, as well as a reduction of the levels of several apolipoproteins and improvement of the VLDL/LDL ratio (Miwa et al., 2005). A study conducted in hypercholesterolemic subjects, who received naringin capsules in a dose of 400 mg/day for 8 weeks, also showed that naringin supplementation lowered plasma cholesterol, LDL- cholesterol concentration, and apolipoprotein-B levels, but did not affect the levels of TG or HDL. In addition, it was also found that in erythrocytes the levels of SOD and catalase activities were increased, indicating some antioxidant regulating capacity of the naringin supplementation (Jung et al., 2003).

Like other flavonoids, the antiproliferative and anticarcinogenic properties of flavanones have been investigated extensively using a wide range of human cancer cell models (Fenton and Hord, 2004; Lee et al., 2005; Kanno et al., 2006; Gao et al., 2006), but only a few studies in animals have been reported. Oral administration of the non naturally-occurring flavonoids, flavanone and 2′-OH flavanone (Hsiao et al., 2007) or naringenin and naringin (Kanno et al., 2005) suppressed tumour growth in xenograft mice models. Recently, it has also been shown that dietary naringin supplementation protected against azoxymethane-induced aberrant crypt foci (ACF) in rats by suppressing proliferation and elevating apoptosis through anti-inflammatory activities in the colon (Vanamala et al., 2006).

There are only a few studies on the bioavailability of flavanones in humans, some of which were recently reviewed (Manach et al., 2005; Mennen et al., 2006). In general, and as for many other flavonoids, the efficiency of absorption for flavanones is poor. Although values may fluctuate depending on the source of flavanones and on the doses, maximum measured plasma concentrations of these compounds are in the nM to low μM range. This was corroborated by a late report in humans that demonstrated that daily consumption of 236 mL of orange juice for 3 weeks led to an increase of the plasma concentrations of hesperetin and naringenin up to about 22 and 69 nmol/L, respectively (Franke et al., 2005). However, in a very recent study it was shown that bioavailability of hesperidin can be enhanced (plasma values up to the low mM range) by consuming either hesperidin-fortified orange juice or glycosidase-treated juice (Nielsen et al., 2006). There are also some recent reports on the absorption of pure flavanones orally administered to experimental animals. The total plasma concentrations detected of these compounds were in the low μM range (El Mohsen et al., 2004; Silberberg et al., 2006; Yamada et al., 2006). In humans, administration of a single dose of hesperetin and naringenin (135 mg each) in the form of capsules led to a very rapid (20 min) detection of the aglycones with maximum concentrations of approximately 3.0 and 7.0 μM (Kanaze et al., 2007). Aglycones appear to be absorbed more rapidly (T_{max} 2–4 h) than the glycosides, for which the time to reach maximum concentration may be extended up to 6–7 h (Manach et al., 2005; Nielsen et al., 2006; Yamada et al., 2006). The lag time has been explained as the time needed by the microflora to hydrolyze the rhamnosides before absorption of the aglycone (Nielsen et al., 2006).

The *in vivo* reported metabolites of flavanones are typically the glucuronide- and (or) sulfo-conjugates detected after enzyme treatment in urine or plasma samples (Silberberg et al., 2006). Only the 5- and 7-*O*-β-glucuronides of naringenin have been structurally elucidated in plasma and in several rat tissues (El Mohsen et al., 2004). Microbial derived metabolites such as 3-(4-hydroxyphenyl) propionic acid have also been identified in rats (El Mohsen et al., 2004). In humans, the absorption of eriodictyol from lemon peel has been reported lately, and the glucuro- and (or) sulfo-derivatives of eriodictyol and homoreiodictyol have been detected in plasma with a maximum peak at approximately 1 h after intake (Miyake et al., 2006).

4.2. The fiction

Supplements containing flavanones such as hesperidin or naringenin as main components are less represented in the current market of nutraceuticals than are isoflavones- or anthocyanins-containing products. At present, most flavanones-containing supplements are prepared from citrus fruits extracts, marketed mostly as citrus bioflavonoids complex and often mixed with large quantities of vitamin C and a blend of other flavonoids such as flavonols. There are also some tablets available that contain the flavanone hesperidin but it is also found mixed with other compounds such as the flavone diosmin, or even mixed with enzymes such as the proteolytic enzyme bromelain, apparently to aid in the absorption of hesperidin. Like other supplements, doses are not properly standardized and may vary from one product to another. Health claims are less clearly stated than for other nutraceuticals, and, thus, some of the claims are either very general: '*...For maintaining proper health...*', or cover an often too wide range of biological effects: '*...Immunity booster and powerful antioxidant; prevents heart diseases; reduces the effects of aging; reduces capillary permeability; protect blood vessels; lower*

cholesterol levels; and have anti-inflammatory activities…'. Flavanone-based nutraceuticals represent a good example of new products being marketed and claimed to exert some benefits for which there is little or almost not existent scientific support.

5. Resveratrol

5.1. The facts

Stilbenes are a group of polyphenols widely distributed in the plant kingdom, although their presence in the diet is rather occasional. Amongst the stilbenes, resveratrol (3,5,4'-*trans*-trihydroxystilbene) is by far the most relevant compound (2,678 bibliographic entries from 1945 to early 2007; Isi Web of Knowledge™). It was first isolated from the roots of hellebore (*Veratrum grandiflorum* O. Loes) in 1940 (Takaoka, 1940). The interest in this compound begun when it was detected in wine (Siemann and Creasy, 1992) and it was attributed some cardioprotective effects (Bertelli et al., 1995). But it was after the publication in *Science* by Jang et al. (1997) on resveratrol anticancer potential that the scientific community became really interested in resveratrol and the number of scientific reports on the effects and properties of this compound increased exponentially. Overall, most studies indicated a clear positive health-beneficial effect upon resveratrol administration. Resveratrol has been described as a compound that can prevent or reduce a wide range of diseases such as cancer (Jang et al., 1997; Asensi et al., 2002), cardiovascular diseases, and ischemic damage (Bradamante et al., 2004), as well as increase the resistance to stress and prolongs the lifespan of various organisms, from yeast (Howitz et al., 2003) to vertebrates (Valenzano et al., 2006; Baur et al., 2006). The biological activities above mentioned have been detailed in a large amount of publications, including some reviews (Delmas et al., 2005; Signorelli and Ghidoni, 2005; de la Lastra and Villegas, 2005; Bau and Sinclair, 2006) where many of the main mechanisms of action of this stilbene have been described: inhibition of ornithine decarboxylase and cyclo-oxygenases; inhibition of angiogenesis; selective inhibition of some Phase-I pro-carcinogenic activator isoenzymes; cell cycle alteration; cell death promotion; free radical scavenging capacity that prevents lipid peroxidation; inhibition of platelet aggregation; vasodilatation; estrogenicity/anti-estrogenicity; anti-bacterial, antiviral and antihelminthic; increase of the cognitive capacity; sirtuins activation; neuroprotection; etc.

The vast majority of studies on the effects of resveratrol have been carried out using the pure compound (either purified or synthetic) since resveratrol and other stilbenes are not very abundant in the diet. The resveratrol content in red wine ranges from undetectable to 14 mg/L with a mean value of 1.9 ± 1.7 mg (Stervbo et al., 2007). There are, however, many important factors that may affect the content of resveratrol in wine and have not been properly evaluated (i.e. production of wine from different years, aging of particular wine, etc.). Other less significant sources of resveratrol are peanuts, 0.02–1.8 mg/g (Sanders et al., 2000) or some berries of the genera *Vaccinium* with some μg/g dry weight (Rimando et al., 2004).

In addition, numerous studies in animals and humans have shown that the bioavailability of resveratrol is very low. Once it is absorbed, resveratrol is readily metabolized to form mainly glucuronide and sulfate derivatives. The colon microflora can also produce the metabolite dihydroresveratrol (Walle et al., 2004). Resveratrol metabolites reach their maximum concentration in plasma approximately 30 min after intake (Wenzel and Somoza, 2005). Plasma concentration of resveratrol and its metabolites depends on the administered dose (Marier et al., 2002). In the plasma of rats administered with a high dose of pure resveratrol, high levels of resveratrol metabolites were detected whereas the aglycone did not reach concentrations higher than 7 μM (Marier et al., 2002), and exhibited a relatively short life of about 8–14 min (Marier et al., 2002; Asensi et al., 2002). These results suggest an intense Phase-II metabolism (due to the action of detoxifying enzymes) (Walle et al., 2004), and support the fact that at higher administered doses, higher levels of derivatives (not the aglycone) can be detected in plasma. The enterohepatic circulation of resveratrol has also been described in rats (Marier et al., 2002). But the metabolism in rats differs substantially from the metabolism in humans, which has not been established yet. In humans, the bioavailability of resveratrol does not seem to be critically affected by food matrix. Goldberg et al. (2003) did not find differences in the urine excretion of resveratrol upon administration with vegetable juice, wine and grape juice. However, although the same maximum peak was detected in plasma, a longer plasma accumulation was observed upon consumption with grape juice (Goldberg et al., 2003).

There are a number of studies on the toxicity of resveratrol. Most of them describe the lack of adverse effect unless extremely high (unrealistic) doses are administered. Juan et al. (2002) did not find adverse effects in rats after consumption for 28 days of the quantity of resveratrol equivalent to 1,000-fold the content of this compound in red wine. Similarly, Crowell et al. (2004) did not observe renal toxicity in rats fed with a dose of 300 mg resveratrol/kg/day for 4 weeks (equivalent to 21 g of resveratrol for an adult human of 70 kg). A recent report (Horn et al., 2007) described the lack of oncogenicity in mice of a dose of 4 g of resveratrol/kg/day for 28 days (equivalent to 280 g resveratrol/d for an adult human of 70 kg). However, this dose caused mild anaemia and an increase in liver weight and serum cholesterol. To date, there is only one published report that has investigated resveratrol safety in humans. Single (one day only) oral doses of 1.0, 2.5 and 5.0 g of resveratrol were given to 29 volunteers. No serious adverse events were noted (Boocock et al., 2006). At present, resveratrol is under Phase-II clinical trials that look at the prevention of colon cancer (www.cancer.gov)

which indicate that, Phase-I trials (to test the safe dose range, side effects and how the body copes with the drug) have been passed.

To summarise the above exposed, resveratrol is currently one of the plant phytochemicals with a great potential to be used as a pharmacological drug in order to prevent and reduce the risk of some diseases. However, its role in human health as a dietary non-nutritional bioactive compound is not yet clear due to, its low abundance in the diet and its low bioavailability.

5.2. The fiction

Resveratrol-containing nutraceuticals are often prepared from *Vitis vinifera* extracts or grape pomace extracts. Resveratrol is a phytoalexin and, therefore, the normal levels of this compound in grapes or derived products (i.e. wine) are very low and very variable. The content of resveratrol depends on factors such as the grape cultivar, the agronomic conditions, the geographic region and the oenological procedure. Importantly, the infection of wine grapes by the fungus *Botrytis cinerea* previous to the vintage causes the so-called bunch rot or gray mold and induces the production of resveratrol in the grape. The wine made from these infected grapes may have a higher content of resveratrol. Up to now, however, there is not a standardized procedure to obtain resveratrol-enriched grapes that may be subsequently used to prepare nutraceuticals with a high content of this compound. Instead, many of the current resveratrol-containing nutraceuticals are enriched in this compound by adding purified resveratrol that has been extracted from the root of the Japanese knotweed *Polygonum cuspidatum*. In some cases this is specified on the labels:. . .'*Vitis vinifera* extracts enriched in resveratrol*. . ..(*from *Polygonum cuspidatum* extracts)'.

Claims attributed to resveratrol-based nutraceuticals are continuously evolving according to new reports and findings on resveratrol health effects. Some years ago, the main claim was . . ..'*discover the benefits of red wine*'. . .., the (daring) claims evolved to, ...'*the World Health Organization declares that resveratrol decreases by 40% the cardiovascular risk*'. . .., '. . ..*anti-aging, anti-cholesterol, anti-cancer*. . ..', and many more. Usually (not always), all these claims are followed by an asterisk that heads declarations at the bottom of the dossier such as . . .'**The statements made have not been evaluated by the U.S. Food & Drug Administration. Our products are not intended to diagnose, cure or prevent any disease*. . .' (consumers should be aware of the need of obtaining proper advise on the consumption of these products).

Resveratrol supplements are mainly sold as capsules or pills with different contents of the compound, from a few milligrams to 500 mg per capsule! The 'recommended daily dosage' is also very variable, from 3 mg ('. . ..*the equivalent to 1 bottle of red wine*. . .') to 1 g/day ('. . .*drink 1000 glasses of wine*. . ..'). The content of the nutraceuticals can be based exclusively on pure resveratrol or also combined with other grape polyphenols and/or other phytochemicals from many different plants in bizarre combinations whose effects have never been explored.

At this point we should point out that in order to understand the benefits in humans derived from consuming resveratrol, some essential questions remain to be answered: (i) what are the actual quantities of resveratrol that should be consumed to induce a health benefit? (ii) what are the risks, if any, derived from long-term supplementation with high doses of resveratrol? Common sense and precaution should prevail.

6. Isoflavones

6.1. The facts

Isoflavones are flavonoids belonging to the so-called phytoestrogens and one of the most investigated polyphenols so far (2906 bibliographic entries from 1945 to 2007; Isi Web of Knowledge^{TM}). Phytoestrogens have been considered to be weakly estrogenic and serum levels of isoflavones and their metabolites can reach the low micromolar level (about 100–1000 times that of estradiol). Therefore, even with a weak potency, isoflavones could potentially exert biological effects *in vivo*.

Isoflavones have attracted attention mainly due to their role in the amelioration of postmenopausal symptoms such as hot flushes and osteoporosis (Williamson-Hughes et al., 2006; Ikeda et al., 2006; Howes et al., 2006). Other important biological activities are related to effects on cardiovascular diseases, cognitive function, and breast and prostate cancer (Lee et al., 2005; Verheus et al., 2007).

Amongst all polyphenols, isoflavones are the compounds most frequently tested in humans. Many epidemiological studies, clinical and dietary intervention trials have evaluated the effects of isoflavones on menopausal symptoms, cardiovascular function, and endocrine regulation of the menstrual cycle. Overall, results are strongly contradictory. Some studies show positive effects such as the reduction of hot flushes (Williamson-Hughes et al., 2006), the excretion of bone resorption biomarkers (Uesugi et al., 2002; Harkness et al., 2004), the increase in bone mineral density, the lower LDL and total cholesterol (Jayagopal et al., 2002; Zhuo et al., 2004), the improvement of the cognitive function (Lee et al., 2005), the reduction of colon cancer (Cotterchio et al., 2006; Verheus et al., 2007), and the modulation of the immune function (Ryan-Borchers et al., 2006). Other studies clearly report the lack of effects (Cassidy et al., 2006a) on antioxidant activity (Heneman et al., 2007), serum lipoproteins levels (Dewell et al., 2002, 2006; Tormala et al., 2006), bone mineral density (Anderson et al., 2002), endothelium function (Simons et al., 2000; Chan et al., 2006; Hallund et al., 2006), or colon cancer (Adams et al., 2005). Various meta-analyses have also been published reporting either the lack or doubtful effects (Gardner et al., 2001; Weggemans

and Trautwein, 2003), very low or modest effects (Trock et al., 2006) or clear positive effects (Reynolds et al., 2006) of isoflavones.

The bioavailability of isoflavones is usually higher than that of many other polyphenols but results are also conflicting. Some studies have reported that isoflavone aglycones are absorbed more efficiently than isoflavone glycosides (Izumi et al., 2000; Kano et al., 2006; Casssidy et al., 2006b), while other data suggest that the bioavailability of daidzein and genistein glucosides is larger than that of the corresponding aglycones (Setchell et al., 2001). In another study no difference was found in the bioavailability of aglycone or glucoside isoflavone tablets (Zubik and Meydani, 2003). The influence of the food matrix and the chemical form (aglycone or glucoside) of the compound on the bioavailability and pharmacokinetics of isoflavones has been recently investigated (Casssidy et al., 2006b). A liquid matrix, such as soy milk, causes a faster absorption rate and a higher plasma concentration peak of the isoflavone than a solid matrix does. Aglycones in a fermented food are absorbed faster than the glucoside conjugates. In addition, an influence of gender is suggested whereas no major influence of age was inferred.

In humans, isoflavones are transformed into the colonic-derived metabolites equol and *O*-desmethylangolesin (ODMA) (30–50% population are equol producers and 80–90% are ODMA producers). The involvement of these colonic metabolites in the observed health benefits of isoflavones has also been explored but the correlation of the effects with the production of these metabolites is not clear (Atkinson et al., 2005).

Isoflavone-based nutraceuticals are one of the most widely tested polyphenol supplements so far. Table 2 shows some representative intervention trials using isoflavone supplements. As described above, the results are not conclusive yet.

The possible adverse effects derived from isoflavone consumption are also a matter of debate. Some studies have reported the induction of alterations of the reproductive development in female mice (Takashima-Sasaki et al., 2006), in pregnant and lactating rats, as well as in suckling pups consuming high doses of isoflavones (1 g/kg) (Ikegami et al., 2006). Some clinical studies suggested that soy phytoestrogens stimulate epithelial cell proliferation in breasts of pre-menopausal women (McMichael-Phillips et al., 1998). A placebo-controlled trial in post-menopausal women found that isoflavone tablets caused endometrial hyperplasia, after 5 years, in 6 out of 154 women compared with none in women having a placebo (Unfer et al., 2004). Due to the possible adverse effects of isoflavones and the lack of consensus regarding the health benefits derived from isoflavones consumption, The American Heart Association does not recommend the use of isoflavone supplements in food or pills (Sacks et al., 2006).

Despite the strong controversy related to the effects of isoflavones on human health, there is an increasing interest in these compounds as dietary protective agents which has prompted the emergence of many isoflavone-based functional foods and nutraceutical preparations. Another important reason for the development of these isoflavone-derived products is the scarce presence of these flavonoids in Western diets since the main isoflavone sources are soy-derived products which are abundant in Asian diets.

6.2. The fiction

There are many isoflavone-based supplements commercially available. These nutraceuticals are mostly prepared from fermented or unfermented concentrated soybean extracts or red clover extracts. The main claim is the amelioration of postmenopausal symptoms (…'*maintain your hormonal balance*'…'*reduce annoying hot flushes*'..,) but other much more daring claims are used (…'*effective cancer prevention*'…). As already stated, the existing literature concerning the biological activity and bioavailability of isoflavones is not fully clear, and data examining the clinical effectiveness in humans of specific isoflavone-derived preparations are very limited.

Despite the lack of definite scientific foundations, there is a general belief in the beneficial effect of isoflavones amongst health-conscious consumers. This is due, at least in part, to the uncontrolled Web propaganda. Isoflavones-based nutraceuticals readily include in their propaganda claims extracted from the most recent discoveries and that suit their marketing objectives:… '*Isoflavones in the their aglycone form are absorbed faster and in bigger amounts from soy milk than the glucoside form, reports a new study from……..*'. It is rather common to find claims such as '*….. Isoflavones effectively prevent cancers and reduce risk of heart disease*'. Often, a list of scientific references is included to support the claim. However, these reports are not always appropriate since most of them refer to *in vitro* studies or even studies that are not related to the claim at all. Although isoflavones are widely recognised as phytoestrogens, the use of the term *phytoestrogen* is a bit manipulated by manufacturers. Some nutraceutical companies use this term in their own interest claiming things like: '*…the main constituents in soy that are helpful are genistein and daidzein. These are NOT "phytoestrogens" as many so-called experts will allege as there is no estrogen, or testosterone, progesterone, DHEA, melatonin in any plant*'….

Isoflavone nutraceuticals are sold in different forms: pills, tablets, extracts, etc. The declared content of isoflavones is variable: '*50 mg*'…'*135mg*'…'*500 mg*'…'*40% isoflavones*', and different daily doses are recommended. At present, no specific dosage of isoflavones has been established to exert a beneficial effect.

There is not a current consensus regarding the actual effects of isoflavones on human health. This controversy may be partially due to the many differences between studies: (i) the use of different types and doses of isoflavones (from soy, red clover); (ii) the use of different administration vehicles (foods, supplements, pure compounds);

Table 2
Human intervention trials of isoflavone-based nutraceuticals

Supplement	Composition	Dose (per day) and assay period	Subjects	Effect	Reference
Red clover extract	Genistein, daidzein, biochanin, formononetin	40 and 80 mg (6 weeks)	27 women	Improvement of arterial compliance. No effect on plasma lipids	Nestel et al. (1999)
Soybean tablet	Isoflavones	80 mg (2 months)	20 postmenopausal women	No effect on endothelium function or plasma lipids	Simons et al. (2000)
Soy protein extract	Isoflavones	132 mg (3 months)	32 postmenopausal women with diabetes-2 type	Improvement of serum lipid profile, glycemic index	Jayagopal et al. (2002)
Genistein supplement	Genistein	54 mg (1 year)	30 women	Increase of bone mineral density	Morabito et al. (2002)
Capsules	Isoflavones	61.8 mg (1 month)	23 perimenopausal women	Beneficial effects on bone metabolism and on serum lipids	Uesugi et al. (2002)
Red clover extract	Isoflavones	86 mg (4 months)	25 premenopausal women	No effect on serum lipid profile. No effect on glucose or insulin	Blakesmith et al. (2003)
Soy protein extract	Isoflavones (daidzein, genistein, glycitein and their respective glycosides or 69 mg in aglycone form by weight)	118 mg (3 months)	106 postmenopausal women	No effect on bone resorption. Decrease of LDL. No effect on HDL and triglycerides	Dalais et al. (2003)
Soya supplement	Isoflavones	60 mg (3 months)	33 postmenopausal women	Significant cognitive improvement	Duffy et al. (2003)
Red clover extract	Isoflavones	86 mg (1 month)	16 pre- and 7 postmenopausal women	Increase in HDL, no effect on cholesterol and triglycerides	Campbell et al. (2004)
Red clover-tablets	Isoflavones (26 mg biochanin, 16 mg formononetin, 1 mg genistein, 0.5 mg daidzein)	43.5 mg (1 year)	205 women with Wolfe P2 or DY mammographic breast patterns	No increase in mammographic density. No effect on menopausal symptoms	Atkinson et al. (2004a)
Red clover extract	Isoflavones	43.5 mg (1 year)	177 perimenopausal women	No effect on serum lipid profile, blood pressure and PAI-1	Atkinson et al. (2004b)
Capsules	Isoflavones	100 mg (6 months)	30 postmenopausal women	Hypogycemic	Cheng et al. (2004)
Soy extract	Isoflavones	60 mg (6 weeks)	50 postmenopausal women	Cognitive improvement in frontal lobe function. No effect on memory	File et al. (2005)
Red clover supplement	Isoflavones	80 mg (90 days)	60 postmenopausal women	Decrease of menopausal symptoms. Positive effect on vaginal cytology and triglycerides	Hidalgo et al. (2005)
Soy protein powder	Isoflavones	83 mg (1 year)	150 patients with adenomatous polyps diagnosed	No reduction of colorectal epithelial cell proliferation and height of polyps. Increase of sigmoid colon cell proliferation	Adams et al. (2005)
Soy extract	Isoflavones	120 mg isoflavone glycosides and aglycones (6 months)	79 postmenopausal women	No effect on vaginal mucosa and endometrium	Kaari et al. (2006)
Isoflavone tablets of soy protein	125 mg protein extract with 50 mg isoflavone (35.5 mg genistein and 14.5 daidzein)	100 mg and 200 mg, (1 year)	43 postmenopausal women	No dose–response effect. Prevention of estrogen-related bone loss. Lack of undesirable side effects	Huang et al. (2006)
Soy protein extract	Isoflavones	97.5 mg and 135.5 mg, (50 days)	13 postmenopausal women	No effect on bone resorption at any dose	Cheong et al. (2007)

(iii) the different groups of people selected for the clinical trials (healthy, pre-menopausal, post-menopausal, high-risk post-menopausal, hypertensive, etc.) and (iv) the inter-individual variability (e.g. differences in the production of the colonic microflora-derived metabolites equol and *O*-desmethylangolesin (ODMA).

7. Ellagic acid and ellagitannins

7.1. The facts

Ellagic acid (EA) was first studied in the 1960s for its effects on blood pressure and clotting (Botti and Ratnoff, 1964; Bhargava and Westfall, 1969). Afterwards, many studies in cell cultures and animal models found that EA may slow the growth of some tumours caused by certain carcinogens. The dietary administration of ETs-containing foods such as strawberries and raspberries to rats has proved to inhibit events associated with both the initiation and promotion/progression of chemically-induced colon and oesophageal cancers (Harris et al., 2001; Chen et al., 2006). However, a more recent study showed the lack of effect on the number or size of adenomas in the small intestine of Apc-mutated Min mice upon administration of pure EA (1.5 g/kg), or cloudberry diets containing ETs (approx. 0.8 g) and EA (34 mg) (Paivarinta et al., 2006). These contradictory results may be due to the fact that, the possible cancer chemopreventive effects of EA and related molecules may differ depending on the type of tumour, the animal model, etc.

Pomegranate juice is currently recognized as one of the most powerful *in vitro* antioxidant food. This remarkable activity has been associated to ETs, such as punicalagin, that are characteristic of this fruit (Gil et al., 2000). The antioxidant activity and the punicalagin content have been suggested as the possible mediators of the different health effects reported for pomegranate juice. These effects include: protection against cardiovascular diseases (decrease in atherosclerosis risk factors such as hypertension, platelet aggregation, oxidative stress, and blood lipid profiles) (Aviram et al., 2000, 2002, 2004; Rosenblat et al., 2006), and cancer prevention (Pantuck et al., 2006).

The bioavailability and metabolism of ETs and EA are key issues that need to be resolved in order to understand the biological role of these phytochemicals and their *in vivo* effects. In general and due to their large molecular size, ETs are not absorbed (Cerdá et al., 2003a, 2005a). However, small amounts of punicalagin were detected in the plasma of rats following long term administration with pomegranate ETs at high doses (Cerdá et al., 2003b). ETs are mostly hydrolysed to EA under the physiological conditions in the small intestine (Larrosa et al., 2006a). A few reports have shown that free EA is rapidly absorbed within 30–90 min after the intake suggesting a direct absorption from the stomach or the proximal small intestine (Seeram et al., 2004; Stoner et al., 2005, 2006). These authors reported the presence of free EA in plasma at nM concentrations. However, other authors did not find absorption of free EA after the intake of EA-containing juices (Cerdá et al., 2004, 2006). Various different factors may have a critical effect on the absorption of EA: (i) the influence of the food matrix; (ii) the dose of free EA and/or (iii) the inter-individual variability. In addition, it is known that EA can bind extensively to the intestine epithelium (Whitley et al., 2003) which could also affect EA absorption.

Once the ETs or EA reach the distal part of the small intestine and the colon, they are largely metabolized by the gut microflora to render hydroxy-6H-dibenzo[*b,d*]-pyran-6-one derivatives known as urolithins A and B (Cerdá et al., 2005b), and these are then absorbed, conjugated and detected in plasma at concentrations in the μM range (up to 10 μM) (Cerdá et al., 2004). These metabolites are then excreted in the urine where they can be detected even after three days following ETs intake, suggesting that these metabolites enter the enterohepatic circulation (Cerdá et al., 2005a). EA methyl ether glucuronides have been detected in human plasma and urine showing that free EA is absorbed and extensively metabolized by Phase II enzymes (Seeram et al., 2004).

All the above results indicate that EA and (or) ETs may exert some biological effects already in the GI tract, whereas the urolithins and (or) the EA methyl-glucuronide derivatives may be the main compounds responsible for the potential systemic effects.

There are a few reports available that investigate the toxicity of ETs. It has been shown that punicalagin can cause liver necrosis and nephrotoxicity in cattle (Doig et al., 1990; Filippich et al., 1991; Oelrichs et al., 1994). In rats, punicalagin exerts some antioxidant and hepatoprotective effects against acetaminophen-induced liver damage but some harmful effects were detected at high doses of the compound (Lin et al., 2001). However, no toxic effects were observed in rats upon consumption of 4.8 g of punicalagin/kg body weight/day for 5 weeks (approximately 350 g/day of punicalagin for a 70 kg-person) (Cerdá et al., 2003b).

Extracts from red raspberry leaves or seeds, pomegranates, or various other sources containing high levels of EA are commercially available as dietary supplements in capsules, powders, tablets or liquid forms. Since they are sold as dietary supplements and are derived from foods, they are generally recognized as safe (GRAS) by the FDA. Manufacturing companies are not required to prove effectiveness or additional safety, as long as they do not claim that their products can prevent, treat, or cure a specific disease. However, the claims are still posted in the Web. Similar to other supplements, these EA extracts may contain variable quantities (between 1 and 40 % or more) of the compound but the best potentially health-promoting dose of these preparations has not been established. In addition, high concentrations of EA have not been tested in humans and the potential toxic effects are not known. Once again, a call of caution should be made to all potential consumers (Lansky, 2006; Lansky and Newman, 2007).

Since EA is a powerful antioxidant agent, absorption of intact EA (even at low concentrations) may provide some beneficial effects *in vivo* but this can not be easily inferred and has not been demonstrated so far (Cerdá et al., 2006; Lansky and Newman, 2007). To the best of our knowledge, there is only one study that reports the administration of

purified EA to humans (Falsaperla et al., 2005). The main aim of the study was to counteract the side-effects of chemotherapy by using EA. These researchers found that EA slightly reduced the side effects of chemotherapy in men with advanced prostate cancer. However, EA did not help to slow the disease progression or to improve survival. The patients ingested 180 mg of EA daily for 6 weeks. The most successful outcome was the reduction of neutropenia after chemotherapy in the EA-treated patients but these results needed further confirmation.

While research on EA as an anticancer agent is promising (Aggarwal and Shishodia, 2006), at present, there is no reliable evidence from human studies showing that EA, in any form, may prevent or cure cancer.

7.2. The fiction

In the mid 1990s, EA and EA-containing supplements began to be advertised as cancer preventing and (or) cancer therapy products. This type of information was spread not only by the direct manufacturers of these supplements but also by fruit growers who claimed the goodness of the EA-containing fruits.

The main natural sources of ETs and EA supplements are berry extracts (mainly red raspberry). Berry extracts can be commercialized either as a source of anthocyanins or as a source of EA, depending on the extraction procedure. Another important source of EA supplements is pomegranate extract. Often, it can be found that, the terms ETs and EA are not properly differentiated by the manufacturers. For example, for a product named 'EA extract', it can be read: '*...EA is an ET found in red raspberry...*' or '*...EA is a phenolic antioxidant compound found in many fruits. Studies have shown that the highest concentrations of these condensed tannins (ETs) may be found in meeker red raspberries. These powerful antioxidants have been shown to support many positive functions of cellular activity...*'. Apart from wrongly defining ETs as 'condensed tannins', no difference is made between ETs and EA.

In the current nutraceutical market, the main claims for EA and related molecules are those related to the high content of these compounds in the supplements and, of course, their cancer preventive properties: '*...contains high concentrations of ETs...*', '*...1000 mg pharmaceutical grade...*', '*...may support DNA integrity...*', '*...promote overall cell health...*', '*...anti-cancer EA extract...*', etc. There are exceptions and some honest declarations can also be found: '*...Important Notice: As we will never mislead you, we make absolutely NO claims on EA for cancer treatment or prevention. Instead, we have findings listed for your convenience and education. We'll always encourage you to do more research!* Relying on this type of treatment alone, and avoiding conventional medical care, may have serious health consequences...' Many web informative pages on the benefits of EA quote that The Hollings Cancer Institute at the University of South Carolina is conducting a double blind study on 500 cervical cancer patients. According to the information available on these pages, unpublished research at this institute shows that '*one cup of raspberries per week will stop prostate cancer growth for a period of up to one week*'. At the time of submission of this review, we have not found results of this study.

Most studies about the cancer preventive action of EA are based on *in vitro* assays or animal testing. Some of the most interesting studies in animals have shown positive effects of lyophilized fruit (berries) extracts. These extracts contain many other compounds that can have an important participation in the observed effects. No definite proof has yet been obtained that unequivocally attributes the positive observed effects of berry extracts to their EA content. There are not evidences based on clinical human trials that support any benefit or protective role of EA.

8. Discussion

A large number of phytochemicals-containing nutraceuticals with various compositions and health claims are now widely distributed and available in the market. However, the scientific evidence supporting their health benefits is still insufficient and it is mostly based on *in vitro* or animal model assays. Clinical trials that evaluate the actual physiological effects in humans are scarce and results are controversial. This is not unexpected. There are many confounding factors that may have an impact in the final outcome of the trials, i.e., the stability of the bioactive compounds in the different pharmacological forms available and (or) in the gastrointestinal tract. Any chemical alteration of the original bioactive compound that may take place during storage or digestion may modify severely the bioavailability and bioactivity of the compounds. Another important factor is the inter-individual variability for bioavailability and metabolism as well as for the biological response.

Many of the human age-related degenerative diseases are associated to oxidative processes. It has been well established that many of the phytochemicals present in plant derived foods have antioxidant capacity, i.e. are able to remove damaging radical species, as shown by a range of *in vitro* assays. The measurement of antioxidant capacity using *in vitro* tests is extensively used to define and claim the 'goodness' of some of these nutraceutical products. The ORAC assay appears to be preferred by many scientists and manufacturers. There are, however, other tests to measure the total antioxidant capacity of a food product or nutraceutical (FRAP, ABTS, DPPH, lipid peroxidation, etc.), and that evaluate the ability of these products to scavenge artificially originated radical species under certain reaction conditions. The word 'antioxidant' on a label sells the product and is now well accepted amongst producers and consumers. The values provided by these tests may be, however, misinterpreted by both producers and consumers. Scientists in the field have now agreed that, the *in vitro* antioxidant activity of a certain compound may

not reflect its activity *in vivo*, especially in view of its *in vivo* transformation into metabolites and (or) other derivatives which are the true bioactive compounds (Cerdá et al., 2004, 2005a; Larrosa et al., 2006b). *In vitro* antioxidant activity may be used as a quality indicator of a particular product, but cannot be an indicator of its 'goodness' to the human body (consumer's perception). To illustrate this, the case of pomegranate ETs is a good example. The high antioxidant power of ETs makes pomegranate one of the most powerful *in vitro* antioxidants (Gil et al., 2000). This has, however, little relevance *in vivo* since these compounds are not absorbed and are extensively metabolized by the colon microflora to urolithins. Urolithins are very bioavailable but have lost the original antioxidant capacity of the ETs (Cerdá et al., 2004). These metabolites, however, can be responsible for the health benefits associated to the consumption of the ET-containing food or nutraceutical preparation (Larrosa et al., 2006b).

Many of the studies that investigate the biological activity of the phytochemicals have been carried out using *in vitro* tests and (or) animal models. *In vitro* assays are frequently performed in human cultured cells where often, the concentrations tested are unrealistic in comparison to the *in vivo* situation. Also, the compounds assayed are the original phytochemicals present in the plant and not the metabolites relevant *in vivo* (mostly because these metabolites are not commercially available). For instance, it is inadequate to evaluate the apoptotic effect of proanthocyandin oligomers on breast cancer cell lines and at mM concentrations. These compounds are poorly absorbed and mostly metabolized to render simpler phenolic derivatives. These derivatives are often found conjugated with methyl ethers, glucuronides and (or) sulphates, and, if present at the mammary tissues, the concentration is expected to be in the range of 1000 to 10,000 lower than the concentration usually assayed *in vitro*. It is known that, the direct extrapolation of the results obtained in an animal model to humans is not entirely appropriate due to differences in the physiology between animals and humans and, in particular, to differences in the bioavailability and metabolism of the active compounds. These differences also occur between different animal models (i.e. between mice and rats) which may explain contradicting experimental results.

Clinical studies with both healthy and unhealthy volunteers have shown a large inter-individual variability and lack of consistency in the results. This may be attributed to various factors: (i) differences in the chemical composition of the nutraceutical tested (a full characterization of the phytochemicals included in the tested mixture is needed); (ii) differences in the pharmaceutical form used (pills, capsules, gels, etc.) which can affect stability and bioavailability of the compounds; (iii) physiological status of the volunteers. It has become well established that, in general, absorption of the phenolic phytochemicals is poor, and that most of the ingested products reach the colon where they are broken down by the colon microflora to produce metabolites. The transformation of soybean isoflavones into equol and desmethylangolesin (ODMA), the metabolism of lignans (secoisolariciresinol) to render the active compounds enterolactone and enterodiol, the transformation of hops isoxanthohumol to render prenylnaringenin (much more estrogenic), the transformation of EA into urolithins, or the transformation of anthocyanins and procyanidins into phenyl acetic and phenyl propionic metabolites are good examples of this degradation and transformation of polyphenols by the microflora in the colon. These transformations are largely affected by the nature and characteristics of the colon microflora. For example, depending on the microorganisms present in the colon the individual can be an 'equol producer' or a 'non-equol producer', an 'urolithin-producer' or 'non-urolithin producer' and consequently the biological activity can be very different after the intake of these phytochemicals (Cerdá et al., 2005a). Colon microflora differences among individuals contribute to explain the large inter-individual variability and discrepancies in the outcome of clinical assays. Microbial transformations need to be thoroughly addressed and taken into consideration when claiming health benefits for specific nutraceutical products.

The metabolites can be then absorbed or further transformed by the human cells and distributed to the different tissues. The tissue distribution of the absorbed metabolites is an additional relevant issue but the available information is in general very scarce. It is difficult to evaluate the compounds and (or) metabolites distribution to the different tissues in humans (only certain samples may be removed after surgery in patients). Alternatively, animal models such as pigs, physiologically more similar to humans than rodents, may be used for the evaluation of tissue distribution.

Another important aspect that remains to be elucidated is the interaction of the phenolic phytochemicals and (or) their *in vivo* relevant metabolites, with proteins (plasma and cell proteins), lipids (lipoproteins) and DNA, as these interactions may play an important part in the biological role of these compounds.

The biological activity of metabolites is also a hot topic of research. In particular, deconjugation of circulating metabolites at specific target tissues is critical to determine the bioactivity exerted in that tissue.

Studies on long-term supplementation to evaluate the biological effect after regular intake of these nutraceutical supplements are generally missing and studies on possible adverse effects, accumulation and toxicity are urgently needed (Walker, 2004).

Most nutraceuticals available in the market display a recommended dose. It is not clear what the scientific basis of this dose recommendation is. Also, it is not known what consequences may be derived from a high intake of polyphenols-containing supplements. For example, the estimated daily intake of dietary anthocyanins may range from several hundred up to a thousand mg. Extra consumption of 1 or 2 tablets a day of berry supplements may provide almost up to 1 additional g of these compounds. Consumers should be

aware of the risk of ingesting high doses of these supplements, since for most of these natural extracts the possible toxic effects have not been examined. Also, increasing doses of these compounds may not necessarily result in an increase in their absorption (as some suppliers state in their claims). Therefore, another important question that remains to be answered is: what is the 'right dose' of a certain polyphenol or mixture of polyphenols that would yield the 'right quantity of metabolites' that may, in turn, exert a beneficial effect?

Most commercially available nutraceuticals contain a mixture of compounds since they are usually prepared from raw extracts from different food products. Often, the non-declared compounds are present in the supplement even at higher quantities than the actual declared bioactive polyphenol. Health claims are based on reported/known bioactivities of individual components and (or) of whole extracts, but the possible synergistic or inhibitory effects in complex mixtures have not been investigated. Also, interferences between compounds during uptake (bioavailability) are not known. Nutraceuticals may have captured the full health beneficial potency of a plant extract (multiple components, synergistic effects) but it is not known yet. If we believe all the rumours flying around the Web, the cure for many diseases would be at hand... For most phytochemicals and nutraceuticals preparations, there is some truth in all and also a lot of nonsense.

The nutraceuticals field offers a good opportunity to phytochemical research. Many of the research needs pointed out above will benefit of phytochemists helping in the following topics: a full and detailed characterization of the content of the extracts and nutraceutical products as well as their stability; the application of phytochemical analysis to the bioavailability, metabolism and tissue distribution of the metabolites; evaluation of the protein/, lipid/ and DNA/phytochemical interactions; a collaboration with microbiologists to evaluate the transformation of phytochemicals by the colon microflora is also needed; the synthesis of microbial metabolites from phytochemicals and the conjugates with glucuronic acid and (or) sulphate will allow the quantification of the metabolites in biological fluids, and the determination of the biological activity of the metabolites bioavailable *in vivo*.

The search for specific health-effects associated with diets rich in foods of plant origin is a difficult task. It appears that these effects are manifested through multiple mechanisms mediated by a wide range of substances and their metabolic transformation products, and that these benefits are only recognisable after long-term exposure to the diets. This scenario would imply particular difficulties for investigators seeking answers to rather intractable questions (Clifford and Brown, 2005).

To conclude it can be stated that, there is already some scientific basis to support biological activity of phytochemicals but the task is far from completed and further research is needed. More and better designed clinical trials should be carried out in order to prove the benefits of phytochemicals consumption in humans. Importantly, the bioavailability and metabolism of phytochemicals need to be clarified to understand the actual health benefits of food phytochemicals and their use in the nutraceutical market. As a final remark, the public should avoid to follow the advice of doubtfully qualified 'doctors' that proliferate on the Web (the so-called 'Web-doctors'). It is not easy, however, to precisely identify who should be consulted for advice on this matter for various reasons. The current knowledge on this topic is: (i) scarce and inconclusive regarding the effects in humans and, (ii) fragmented amongst the scientific community working in the field. At present, there are already some health care professionals, such as physicians, nutritionists and pharmacists who prescribe and/or give advice on the consumption of some nutraceuticals (e.g. isoflavone-containing nutraceuticals), but most of them may not have the necessary knowledge on these compounds to give a convenient advice to both consumers and producers. Therefore, there is a gap between the scientific community who has the most updated knowledge on nutraceuticals and the health care professionals. So, the question is open for debate: do we need to define a new professional qualification to cover this gap? Or, should we ask the health care professionals to keep themselves updated on the continuously developing knowledge on phytochemicals and health provided by the scientists?

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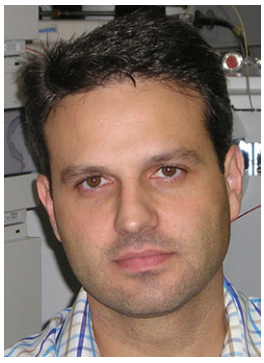

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