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Mini review

Natural products—friends or foes?

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HIGHLIGHTS

- Food supplements may change the pharmacokinetic profile of drugs.
- Food supplements may change the efficacy of drugs.
- Food and food supplements might induce toxic outcomes in combination with drugs.

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ABSTRACT

A trend in the general population has been observed in recent years regarding the orientation toward preventive measures in health; in this context the increased interest from the users and researchers concerning the active effect of food supplements on the health state and on longevity, is noticeable. All over the world, the consumption of natural foods and of vegetal supplements has increased spectacularly over the last 5–10 years. The decreased prevalence of cardio-vascular diseases associated with Mediterranean diet, as well as the French paradox convinced researchers to scientifically document the beneficial outcomes pointed out by traditional use of plants, and to try to develop supplements that would have the same positive effects as these noticed for diet components.

The intense research dedicated to this topic revealed the fact that food supplements are linked to some problematic aspects, such as toxicological side effects when associated with classical synthetic drugs. The food supplement–drug interactions are submitted to complex issues regarding pharmacokinetic interactions leading to changes in absorption, distribution, metabolism and excretion processes with direct impact on effect and toxicological potential.

The present review based on recent literature aims at discussing the food–drug interactions with direct impact on efficacy and toxicity of drugs.

Contents

Abbreviations: ADME, absorption, distribution, metabolism and excretion; ROS, reactive oxygen species; MDA, malondialdehyde; OATP, organic anion transporting polypeptide; QQ, quercetin–quinone; GSH, glutathione; RLE, rat lung epithelial cells; LDH, lactate dehydrogenase; ABC, ATP binding cassette; P-gp, P-glycoprotein; MRP 2, multidrug resistance- associated protein 2; TMD, transmembrane domain; NBD, nucleotide-binding domain; BCRP, breast cancer resistance protein; SGLT1, Na^+- dependent Na1/glucose co-transporter 1; HCC, hepatocellular carcinoma cells; UGT, UDP-glucuronyltransferase; SULT, sulfotransferase.

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1. Introduction

Recent research pointed out an increasing interest concerning the health benefits of a diet rich in natural products and/or vegetal/food supplements. Certain controversies regarding the role of food stuff in promoting health have been registered worldwide both in the research community and in the common population. All over the world, the consumption of natural foods and vegetal supplements has increased spectacularly over the last 5–10 years.

The consumers from developed countries manifest an interest regarding the active role of food on the health state and longevity, specifically on preventing cardio-vascular diseases as well as malignant diseases. Vegetable based diets are considered to reduce the incidence of some chronic diseases (atherosclerotic based cardio-vascular disease, hypertension, type 2 diabetes mellitus, malignancies, hepatic disorders, etc.). For example, the Mediterranean diet, rich in flavonoids, is nowadays considered an effective tool for improving the general health status. In addition, the French paradox is discussed with respect to the ability of red wine polyphenols to reduce the incidence of cardio-vascular disease even in a population consuming a lipid rich diet.

However, as a coin has two sides, there are also some problematic issues, regarding the toxicological aspects that are obviously linked to the use of vegetal supplements and vegetal components of diet, especially when associated with classical medicines. In addition, there are complex issues regarding pharmacokinetic interactions leading to changes of important ADME (absorption, distribution, metabolism and excretion) processes under the effect of natural compounds from diet or food supplements.

Subjects usually consuming rich polyphenols diet are characterized by concentrations of the respective compounds ranging between 2.5 and 10 μM; subjects using natural supplements can reach blood levels of over 20 μM polyphenols. (Tribolo et al., 2008; Winterbone et al., 2009; Margina et al., 2013). Several reports underlined the pro-oxidant effects induced by polyphenols (generally known for their antioxidant effects), whereas some natural compounds have a major influence on P-glycoprotein-mediated transport, thus interacting with anti-cancer therapies. Compounds encountered in cruciferous vegetables (such as polyphenols) modulate the activity of other membrane transporters such as glucose transporter. Moreover, some vegetal extracts generally used in traditional medicine (Devil's claw) or even tea components (epigallocatechin gallate) are listed as inhibitors of CYP enzymes, thus interfering with drug metabolism.

Another important aspect is related to the capacity of some fruit juices (*e.g.*, grapefruit juice) to inhibit the activity of enzymes involved in drug metabolism, thus having an important impact on the pharmacokinetic data and toxicity of these drugs. Other fruit juices (apple, orange) have an inhibitory effect on organic anion transporting polypeptide (OATP) 2B1, thus interfering with the absorption process. As a result concerns are raised regarding the potential interactions of vegetal supplements in patients undergoing chronic therapy, possibly leading to changes of bioavailability, distribution, metabolism, elimination and toxicity of the drugs. The present review aims at discussing certain food–drug interactions with direct impact on efficacy and toxicity of drugs.

2. Polyphenols–antioxidants becoming pro-oxidants

Flavonoids are natural polyphenols, best known as pigments responsible for a diversity of colors found in vegetables (yellow, orange, red, etc.—their name being derived from the Latin word *flavus*, meaning yellow). They are secondary plant metabolites, important for the plant physiology, ensuring the growth, development and defense mechanisms of the plant. Even if their bioavailability is low, dietary intake of flavonoids is correlated with important health benefits (Fraga et al., 2010; Weng and Yen, 2012; Karewicza et al., 2011; Androutsopoulos et al., 2010).

Most of the polyphenolic compounds are found in plants and foods in their glycosylated forms; at the intestinal level, they undergo different biotransformations (depending on the nature of the sugar residue), generally hydrolysis, either in the small intestine (with enzymes such as lactase phlorizin hydrolase or β-glucosidase) or in the colon (under the effect of gut microbiota), the sugar moieties are cleaved and the aglycones are absorbed (Marín et al., 2015). For certain compounds, there are particular features for the biotransformation. For example, flavan-3-ols, (such as (−)-epicatechin), are not glycosylated but acylated with gallic acid and are absorbed at the enterocyte level without any deconjugation or hydrolysis. The absorbed compounds may further undergo hepatic transformations and then reach target organs, *via* blood toward urine excretion.

The bioavailability of polyphenols is also strongly influenced by the nature of the attached sugar, due to interindividual differences regarding the microbiota and digestive enzymes and/or the "associated food matrix" (*e.g.*, dietary fiber divalent minerals, viscous and protein-rich meals, digestible carbohydrates, dietary lipids, etc.). All these factors are reviewed elsewhere (Scholz and Williamson, 2007; Bohn, 2014).

It is important at this point to stress that the bioavailability of hydroxylated flavonoids is a major factor that determines their biological activity *in vivo*. The general consensus suggests that hydroxylated flavonoids, such as quercetin, are subjected to extensive phase II biotransformation reactions that reduce the concentration of the free aglycone in plasma. Since hydroxylated flavonoids are present in very small amounts in their aglycone form in dietary products, the form of flavonoid glucosides is the predominant form of flavonoid compounds that enter the body through food or beverages (Androutsopoulos et al., 2010). Flavonoid glucosides contain one or more sugar groups attached to phenolic hydroxyl groups by a glycosidic bond (Androutsopoulos et al., 2010). The enzyme lactate phlorizin hydrolase (LPH) located in the brush border of the small intestine is capable to catalyze the hydrolysis of certain glucosides, such as quercetin glucosides, to their aglycone (Androutsopoulos et al., 2010; Murota and Terao, 2003). Further conjugation reactions by UGT or SULT enzymes may occur before the

aglycone reaches systemic circulation. A percentage of those metabolites is excreted in the bile and returns to the intestinal lumen (Androutsopoulos et al., 2010).

The most important feature discussed for polyphenols is their antioxidant activity (Boots et al., 2008; Spanou et al., 2012; Stagos et al., 2012); nevertheless, flavonoids (like many other antioxidants), can act, under certain circumstances, as pro-oxidants, for example in systems containing redox-active metals (copper, iron, etc.). However, *in vivo*, most transition metal ions are sequestered in forms unable to catalyze free radical reactions. In certain conditions, this situation can be changed, as very low levels of free copper ions may be released following tissue injury (*e.g.*, atherosclerotic lesions) and possibly hepatic Cu(II) overload diseases (Wilson disease), thus being able to promote pro-oxidant effects in association with vegetal compounds (Halliwell and Gutteridge, 1990; Smith et al., 1992; Galati and O'Brien, 2004).

The pro-oxidant activity of dietary phenolics is linked to the total number of hydroxyl groups in a flavonoid molecule. Certain structural features (Fig. 1) directly influence the pro-oxidant ability, increasing the risk for production of radical/nonradical reactive species (hydrogen peroxide, hydroxyl radicals) in Fenton reactions: multiple hydroxyl groups, especially in the B-ring, or 2,3-double bond and 4-oxo arrangement of flavones (Cao et al., 1997; Hanasaki et al., 1994; Heim et al., 2002; Procházková et al., 2011). Some authors state the possibility that flavonoid pro-oxidant function could be related also to their beneficial functions; one example is epigallocatechin gallate which reduces O_2 to yield H_2O_2 thus promoting apoptosis and exerting cytotoxic activity against bacteria (Nakagawa et al., 2004).

The extent to which flavonoids are able to act as anti- or pro-oxidants *in vivo* is still poorly understood (Procházková et al., 2011), all the more most studies have focused on the beneficial effect of natural compounds with complex composition. Table 1 summarizes certain findings of studies performed *in vitro* (cell models) or using animal models.

Studies have also shown that some individual flavonoids, for example quercetin, particularly at high-dose levels, have potentially toxic effects, including pro-oxidant activity, which could be related to mutagenicity and mitochondrial toxicity. For example, Boots showed that quercetin efficiently protects against H_2O_2-induced DNA damage in rat lung epithelial (RLE) cells, but this protection comes in exchange with a reduction in GSH level, an increase in LDH leakage as well as an increase of the cytosolic free calcium concentration (Boots et al., 2007), therefore quercetin acts as a toxicant.

Quercetin contains a catechol B-ring and has been shown to be oxidized by tyrosinase, hydrogen peroxide, horseradish peroxidase, or other peroxidases, to quinone/quinone methide intermediates, with subsequent reactions with GSH resulting in quercetin glutathionyl adducts (Awad et al., 2000; Awad et al., 2002; Galati and O'Brien, 2004). The two electron oxidation of quercetin yields quercetin–quinone (QQ) that has four tautomeric forms (an orthoquinone and three quinonemethides). This oxidation product is very reactive toward thiols, including GSH. When the GSH concentration is low, QQ will react with other thiol groups, *e.g.*, protein sulfhydryls or -SH enzymes thus explaining the consequent redox toxicity (Fig. 2). This phenomenon has been defined as "the quercetin paradox", (the conversion of quercetin into a potential toxicant while offering protection by scavenging ROS) (Boots et al., 2007; Jacobs et al., 2010). These studies might lead to the conclusion that, in subjects with elevated oxidative stress associated with pathological conditions (diabetes mellitus, obesity, malignancies, etc.), the generation of oxidized quercetin will be intense, in the case of antioxidant therapy treatment. Additionally, in these subjects GSH levels might be low, making them even more susceptible to damage by quercetin oxidation metabolites. So quercetin may become toxic as a result of its involvement in antioxidant reactions (Boots et al., 2007, 2008).

This mechanism is confirmed by *in vitro* experimental results. In human cells (embryonic fibroblasts, umbilical vein endothelial cells, red blood cells) quercetin at a concentration of 300 μM proved to be moderately cytotoxic, contributing to an increase of ROS generation. Quercetin was shown to oxidize oxyhemoglobin, producing methemoglobin, without an increase of hemolysis (Galati et al., 2002). In animal studies (male Sprague–Dawley rats), Choi et al. (2003) pointed out that 4–6 weeks oral treatments with quercetin (up to 20 mg quercetin/rat/day), lead to a significant decrease of hepatic levels of GSH, compared to controls, while quercetin treatment decreased the glutathione concentration and glutathione reductase activity (40 and 34%, respectively) in the liver in vitamin E-deprived and undeprived rats. Animal studies revealed elevated levels of renal MDA in male Wistar rats receiving quercetin in diet for a period of 21 days (285 or 1133 mg/kg body weight/day) (Rangan et al., 2002).

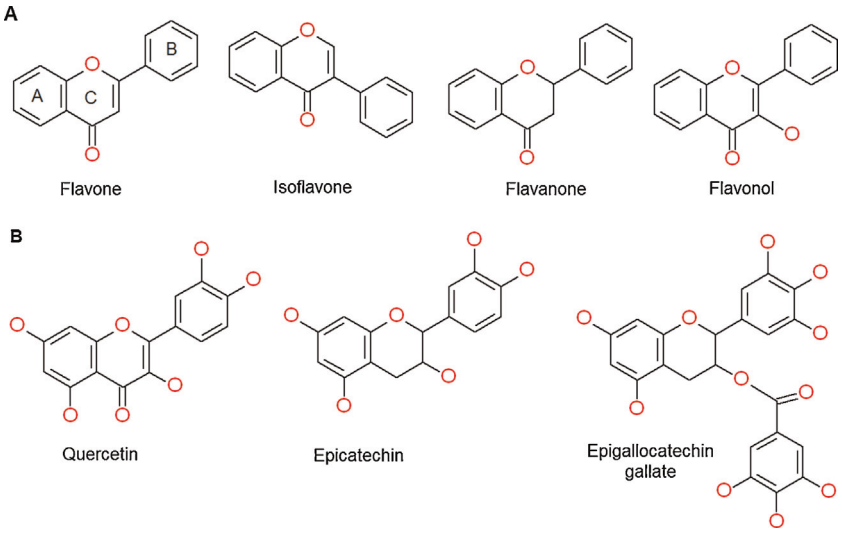

Fig. 1. Flavonoid family subclasses (A), examples of flavonoid structures (B).

Table 1
Effects induced by natural compunds in animal/cell model.

Effect	Study model/doses	Reference
Pro-oxidant toxic effect of flavonoids		
Apoptosis promotion	Jurkat T cells/12.5–50 μM epigallocatechin gallate	Nakagawa et al. (2004)
DNA damage due to oxidative stress	Human lymphocytes/ 200 μM quercetin, morin, naringenin, hesperetin	Yen et al. (2003)
	Rat liver microsomes/ 100 μM gossypol, quercetin, myricetin	Laughton et al. (1989)
	Human leucocytes/ 100 μM quercetin	Wilms et al. (2008)
Mutagenicity	Flavonoids (review)	Harwood et al. (2007)
	Cultured tubular epithelial cells/75–100 μM quercetin	Kuhlmann et al. (1998)
GSH level reduction via formation of glutathionyl quercetin adducts	In vitro/quercetin	Awad et al. (2000)
	B16F-10 melanoma cells/quercetin	Awad, et al. (2002)
GSH reduction level, LDH leakage increase	Flavonoids	Boots et al. (2007), Jacobs et al. (2010)
GSH level, glutathion reductase activity reduction	Vitamin E-deprived and -undeprived Sprague–Dawley rats/2–20 mg/ day quercetin	Choi et al. (2003)
Pro-oxidant beneficial effect of flavonoids		
Inhibition of carcinogenesis	Flavonoids (review)	Galati and O'Brien (2004)
Protection against genotoxicity and apoptosis	Gingsenoids (review)	Wang et al. (2009)
Cytotoxic activity against bacteria	In vitro/epigallocatechin gallate	Nakagawa et al. (2004)
Interaction with medicines		
Protection against cyclophosphamide-induced toxicity	Mouse bone marrow cells/60–140 mg ginsenosides from Panax ginseng/ kg b.w.	Zhang et al. (2008)
Protection against cisplatin-induced toxicity	Cultured tubular epithelial cells (LLC-PK1)/10–100 μM quercetin	Kuhlmann et al. (1998)
Potentiation of adriamycin effect	MCF-7 adriamycin-resistant cells/1–10 μM quercetin	Scambia et al. (1994)
Increased uptake, decreased efflux of paclitaxel	Rat/3.3 mg genistein/kg or 10 mg genistein/kg	Li and Choi (2007)

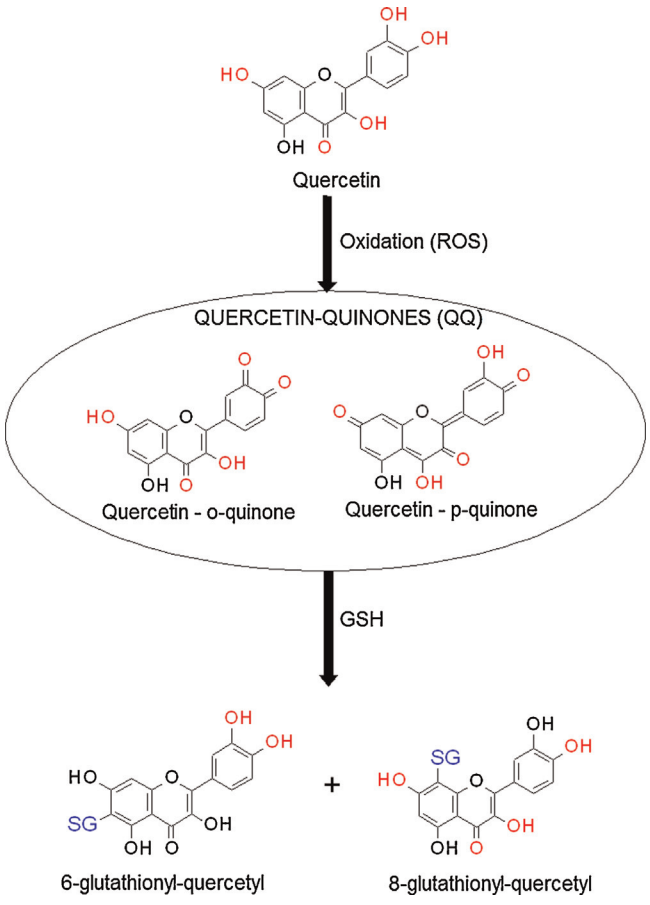

Fig. 2. Quercetin oxidation.

Quercetin as well as morin increase H_2O_2 production in human lymphocytes, (concentration range of 25–200 μM and 125–200 μM, respectively), leading to increased generation of lipid peroxidation products. These compounds were also able to induce DNA strand breakage in a concentration-dependent manner, as assessed by the comet assay. The pro-oxidant effect seems to be connected to the concentration range, given that gossypol, quercetin and myricetin have antioxidant properties in rat liver microsomes experiments, at low micromolar concentrations (1.5 μM), whereas at 100 μM concentration they became generators of hydroxyl radical. Quercetin at concentrations lower than 50 μM exhibited antioxidant properties in human leucocytes, while at concentrations over 100 μM the amount of oxidative DNA damage superoxide-induced was increased (Yen et al., 2003; Laughton et al., 1989; Wilms et al., 2008).

However, in a review study, trying to resolve the apparent conflict existing between *in vitro* results attesting mutagenicity of quercetin and *in vivo* studies showing the absence of carcinogenity, Harwood et al. (2007) concluded that quercetin use is rather safe.

3. Natural compounds as modulators of the cell membrane protein transporters

Molecules cross the cellular membranes by passive or active mechanisms; in the first case, the transport involves no energy expense (the molecules are driven by their concentration gradient), but in the second case (molecules are driven against their concentration gradient) the crossing of the membrane is facilitated by transporters, using energy-coupling mechanisms such as ATP hydrolysis. Among them there are the proteins belonging to the ATP binding cassette family (ABC) transporters, including importers (carriers delivering the molecules to the cell) end efflux transporters (which function as pumps to expel the unwanted molecules out of the cells).

Among efflux transporters, P-glycoprotein (P-gp) is a plasma membrane system consisting of two homologous parts, each having a transmembrane domain (TMD) responsible for drug binding and efflux, and a cytosolic nucleotide-binding domain (NBD) responsible for ATP binding and hydrolysis (Ravishankar et al., 2013). Due to its main role in physiological settings—to protect the cells from toxic/unknown substances and to ensure their clearance, it is found mostly in tissues involved directly in managing the contact of the human body with xenobiotics: the epithelium of the gastro-intestinal tract (the polarized apical membranes of enterocytes), the renal proximal tubule (at the brush border level), the canalicular surface of the hepatocyte, the endothelial cell surface of the blood brain barrier (Kitagawa, 2006; Chieli et al., 2010).

Cancer cells can often develop resistance not only to anti-cancer agents which they have been exposed to, but also to other drugs and chemicals that they have not yet been in contact with. In most cases, an over-expression of the ATP efflux pumps induces the multidrug resistance (MDR) state, leading to an increased "excretion" of most active substances from the target cells and thus preventing their effect to be reached (Kitagawa, 2006; Sak, 2012). The most significant efflux pumps found to confer chemo-resistance in cancer are members of the ABC transporter family: P-glycoprotein (or ATP-binding cassette sub-family B member 1-ABCB1), multidrug resistance-associated protein 1 (MDR1, or MRP1), multidrug resistance-associated protein 2 (MDR2, or MRP2), breast cancer resistance protein (BCRP or ABCG2), etc. (Szakacs et al., 2006; Abraham et al., 2012; Estudante et al., 2013).

The inhibitors of ABC transporters, also called MDR modulators, chemosensitizers, or MDR reversal agents, are able to reverse resistance against anticancer drugs (Abraham et al., 2012).

Research performed over the last years pointed out the ability of known pharmacologically active substances (such as verapamil, dihydropyridine analogs, quinidine, cyclosporin A, some vitamins), some endogenous compounds (hormones or cytokines) and also dietary components (some polyphenols, capsaicin, curcumin derivatives, etc.) to inhibit the activity of P-gp thus diminishing or even reversing the P-gp-mediated multidrug resistance (Kitagawa, 2006; Chieli et al., 2010). Various plant-derived agents, such as genistein, curcumin, epigallocatechin gallate, resveratrol, indole-3-carbinol, proanthocyanidin, tangeretin etc., have been also shown to alter the efficacy of traditional chemotherapeutic agents.

3.1. Polyphenols

Polyphenols, alone or in complex vegetal extracts, inhibit the activity of membrane transporters and thus increase the intracellular concentration of certain drugs. In the context of high toxicity exhibited by anti-cancer agents, the use of natural compounds may constitute the solution to improve the efficiency of cytotoxic agents, by means of decreasing the cell resistance to their action and lowering their toxic side effects. Dietary components may act either by protecting the organism from the adverse effects of intervention or as modifiers of biological response exerting additive, synergistic or antagonist effects with pharmaceutical agents. Inhibition of ABC transporters *via* co-administration of natural products with anti-cancer agents may lead to reduced drug resistance, providing a possible mechanism to improve chemotherapeutic effects (Sak, 2012).

There is a strong interrelation between the P-gp inhibitory action and the structure of polyphenols. Compounds with double bonds between the 2- and 3-position in the C ring (found in the structures of flavone and flavonol molecules) are generally planar, so they can intercalate between the hydrophobic amino acid residues of P-gp and can also easily interact with MRP1 and MRP2 (Kitagawa, 2006).

Flavonoids might modulate cell multidrug resistance mediated by P-gp through different mechanisms: inhibition of the multidrug resistance gene-1 (MDR1) over-expression, direct binding to NBDs with high affinity or inhibition of ATPase activity, nucleotide hydrolysis and energy-dependent drug interaction with membrane transporters (Ren et al., 2003). Polyphenols may also inhibit other membrane transporters, such as multidrug resistance associated proteins (MRPs) and breast cancer resistant protein (BCRP).

Quercetin, which is found in many vegetables (onion, apples, tomatoes, etc.), was shown to inhibit P-gp activity, down-regulate P-gp expression and decrease ABCB1 mRNA (in a wide range of concentrations10–100 μM) in different experimental models (cancer cell lines such as HK-2, MCF7, etc.) and thus enhances the sensitivity to anti-tumor agents (cisplatin, tamoxifen, paclitaxel) (Chieli et al., 2010). Experiments performed on cell lines of human pancreatic carcinoma, exposed to selected concentrations of quercetin and daunorubicin, confirmed that the polyphenol affects the expression and function of P-gp in a concentration dependent manner. Moreover, it decreases the expression of ABCB1 (Borska et al., 2010).

Quercetin is also found in mango (*Mangifera indica*) stem bark extract, together with other biocompounds: phenolic acids (gallic acid, 3,4-dihydroxy benzoic acid and benzoic acid), phenolic esters (gallic acid methyl ester, gallic acid propyl ester and benzoic acid propyl ester), flavan-3-ols (catechin, epicatechin and quercetin) and xanthones (mangiferin) (Berardini et al., 2005; Chieli et al., 2009). Experimental research has suggested a series of pharmacological properties for the mango stem bark extract: antioxidant, analgesic, anti-inflammatory and immunomodulatory (Chieli et al., 2009; Garrido-Garrido et al., 2007; Nunez-Selles et al., 2007). The corresponding standardized extract is used in Cuba and surrounding countries for its beneficial properties. Some of the components of mango stem bark extract (mangiferin, its aglycone norathyriol, or quercetin) as well as the whole extract, are able to significantly inhibit, in a dose dependent manner, the activity of ABCB1/P-gp multidrug transporter (as proven by experiments performed on Caco-2 cell line as well as HK-2 cells); however, other phenolic compounds from the extract (catechin or gallic acid) do not show significant effects (Chieli et al., 2009).

In contrast to hydroxylated flavonoids, studies by Walle et al. (2007) suggest that fully methoxylated dietary flavonoids can be regarded as a superior anticancer flavonoid subclass, due to particularly desirable pharmacokinetic properties and chemical stability that result from reduced phase II reactions occurring in the liver and intestine. Notably, the flavones 5,7-dimethoxyflavone and 5,7,4′-trimethoxyflavone, which are the fully methoxylated analogues of chrysin and apigenin, have been shown to possess improved metabolic stability and half-life compared to their hydroxylated analogues, as demonstrated by *in vitro* and *in vivo* models (Wen and Walle, 2006; Walle at al., 2007; Androutsopoulos et al., 2010). Methoxy substitution is believed to protect these compounds from undergoing conjugation reactions in O-atoms by UDP-glucuronosyltransferase enzymes (Androutsopoulos et al., 2010).

Some polyphenols, such as epigallocatechin gallate (EGCG), also down-regulate MDR1 gene expression and improve the action of daunorubicin and irinotecam (Kitagawa, 2006; Sak, 2012).

Johnson and Gonzalez de Mejia (2013) proved that pretreatment of human pancreatic cancer cells with apigenin and/or luteolin, for 24 h, at concentrations of 10–15 μM significantly enhances gemcitabine (a nucleozide analogue) activity through inhibition of the GSK-3b/NF-kB signaling pathway, leading to the induction of apoptosis. Thus exposure of cancer cells to polyphenol action may have a sensitizing effect for the activity of classical

tumor agents, through other cellular pathways, except membrane transporters.

3.2. Curcuminoids

Curcumin, a yellow-colored dietary pigment derived from a traditional herbal remedy (*Curcuma longa*), has a variety of beneficial pharmacological properties, including anti-inflammatory, anti-cancer (especially in tumors that are resistant to conventional chemotherapy) and antioxidant (with consecutive inhibition of vascular hyperpermeability following hemorrhagic shock) (Ingolfsson et al., 2007; Margina et al., 2012). Curcumin accumulates in biological membranes and is known as a membrane-destabilizing agent at concentrations of approximately 100 μM. These observations lead to the hypothesis that curcumin at low μM concentrations (that are used in most of the studies) could alter membrane protein function by modulating the lipid bilayer properties (Sun et al., 2008; Fraga and Oteiza, 2011). Previous studies have reported that curcumin has potent anti-MDR activities in some tumor cells (Lu et al., 2012; Tang et al., 2005; Zhang et al., 2010; Efferth et al., 2002). Lu et al. (2012) proved that P-gp protein level was significantly reduced by treatment with curcumin in MDR K562/A02 cells and thus, it might be used in combination therapy with other drugs that are the substrates of P-gp, in order to improve cell sensibility to treatment. Curcumin has a positive effect regarding the sensitivity of human colorectal cancer HCT-116 and human squamous cell lung carcinoma H520 cells to 5-fluorouracil and vinorelbine (Sak, 2012). Curcumin further increased the sensitivity of primary hepatocellular carcinoma (HCC) cells to some anti-cancer treatment, the effect being slight for cisplatin and very remarkable in the case of doxorubicin (D'Alessandro et al., 2007).

3.3. Carotenoids

Carotenoids are natural antioxidants widely distributed in plants that interfere with the activity of membrane transporters. The ability of carotenoids to prevent biological oxidation comes from the polyene system which is extremely susceptible to oxidative degradation and to isomerization under the effect of light, heat or extreme pH. Carotenoids belong to the large class of terpenoids, and constitute the precursors of vitamin A, but there are studies proving that some of these biomolecules, for example lycopene, inhibit the proliferation of several types of cancer cells such as prostate and breast cancer cells. In addition to their antiproliferative effects, carotenoids (capsanthin, capsorubin, lycopene, lutein, antheraxanthin, violaxanthin, etc.) exhibit MDR reversal properties, therefore acting as possible resistance modifiers in cancer chemotherapy (Gyémánt et al., 2006). As in the case of polyphenols, their MDR reversal properties are due to a structure-activity relationship. It seems that the (9Z) configuration ((9′Z)-neoxanthin, (9Z)-violaxanthin, (9Z)-zeaxanthin) displays a stronger binding capacity toward the P-gp compared to the linear (all-E) forms (neoxanthin, violaxanthin, zeaxanthin). Moreover, the presence of 3-hydroxy group on the right six-membered ring (a 3-hydroxy-b-end group) is associated with a moderate MDR reversal effect. The polarity, the shape and the size of the carotenoid molecule also influences its ability to interact with the cell membrane and thus to exhibit MDR activity. Polar carotenoids (lutein or zeaxanthin) are generally better incorporated in the cell membrane compared to non-polar like carotene, and as a result they have higher MDR reversal activity (Gruszecki et al., 1999; Parker, 1996; Socaciu et al., 2002a; Gyémánt et al., 2006). This effect on P-gp also correlates with the effect of carotenoids on membrane fluidity (carotenoid retention in the cancer cell membrane causes a decrease in lipid fluidity, thus sterically impairing the diffusion of drugs and decreasing the kinetics of drug excretion—Socaciu et al., 2002b; Hendrich and Michalak, 2003; Gyémánt et al., 2006).

3.4. Other natural compounds

Resveratrol, a natural stilbene encountered in red wine, has documented antitumor function but also acts synergistically with other agents from the same class (Apostolou et al., 2013). Several studies show that resveratrol reverses the multidrug resistance of the cancer cells through downregulating the MDR-1 gene and P-glycoprotein expression levels, enhancing the cytotoxicity of doxorubicin within solid tumor cells (MCF-7) (Kim et al., 2014; Huang et al., 2014). Cellular studies show that resveratrol also contributes to the inhibition of genistein-induced MRP2 expression (Kim et al., 2011). Capsaicin (from hot and red chili pepper—*Capsicum annuum*) and [6]-gingerol (responsible for the spicy taste of ginger *Zingiber officinale*) can partially reverse multidrug resistance in human cells that express P-glycoprotein (Nabekura et al., 2005; Nabekura, 2010).

The ability of traditional Chinese medicine herbs or of natural products derived from them to interfere with P-gp, either by functionally inhibiting P-glycoprotein (interference with efflux activity of the drug pump) or by down-regulating P-glycoprotein/MDR1 expression, thereby re-sensitizing multidrug-resistant cells, has been reported by several studies in the literature. Most frequently mentioned in the literature are: *Panax ginseng*, *Camelia sinensis* (rich in EGCG), *Glycorrhiza glabra*, *Salvia miltiorrhiza*, *Ginkgo biloba*, *Schisandra chinensis*, *Coptis chinensis*, *Scutellaria baicalensis*, *Radix Astragali*, *Sho-saiko-to* (Xiao-Chi-Hu-Tang), *Paeonia lactiflora* and *Hippophae rhamnoides* L. (Eichhorn and Efferth, 2012).

Among the natural products found in diet that may act as MDR reversal agents, marine-derived compounds are also mentioned in the literature. Studies have shown that agosterol A (from *Spongia* sp.), the aqueous extracts of the Caribbean tunicate *Ecteinascidia turbinata*, sipholane triterpenoids (isolated from the Red Sea sponge *Callyspongia siphonella*), bryostatin 1 (isolated from the marine bryozoan *Bugula neritina*) and welwitindolinones from the blue-green alga *Hapalosiphon welwitschii*, are only a few of the compounds isolated from marine sources, that act as P-gp inhibitors, thus contributing to the increased sensitivity of tumor cells to classical therapy (Abraham et al., 2012).

Table 2 summarizes the most important findings regarding the interference of natural compounds in the MDR syndrome.

Similar to the case of flavonoids acting as pro- or antioxidants, depending on concentration and/or process type, some natural products induce the opposite effect on P-gp. For example, in the case of drugs with a narrow therapeutic window or toxic compounds, modulation of P-gp could also result in enhanced toxic susceptibility, or renal disorders, such as those observed in P-glycoprotein deficiency (Alvarez et al., 2010).

Devil's Claw (*Harpagophytum procumbens*), a plant from Southern Africa, is an important traditional medicine which is consumed as a general health tonic and for its analgesic and anti-inflammatory action. Scientific studies revealed that Devil's Claw exhibits analgesic, anti-oxidant, anti-diabetic, anti-epileptic, anti-microbial and antimalarial activities amongst others. The anti-inflammatory and analgesic effects are due mainly to the inhibition of enzymes involved in the inflammatory pathway, through similar mechanisms to those exhibited by non-steroidal anti-inflammatories (Anauate et al., 2010). The active components in Devil's Claw are iridoid glycosides, mainly harpagoside (Qi et al., 2006). Romiti et al. (2009) proved that prolonged exposure (3 days) to pure harpagosides as well as to the Devil's Claw extract produced a significant dose-dependent increase in P-gp expression, whereas

Table 2
Natural compounds as down-regulators and/or inhibitors of efflux transporters.

Compound (plant)	Medicine	Model/dose	Reference
Quercetin, Mango stem bark extract	Cisplatin, tamoxifen, paclitaxel	Cell lines HK-2, MCF-7/10–100 μM	Chieli et al. (2010)
	Daunorubicin	Human pancreatic carcinoma	Borska et al. (2010)
Epigallocatechin gallate	–	Cell lines Caco-2, HK-2	Chieli et al. (2009)
Curcumin (*Curcuma longa* extract)	Daunorubicin, irinotecam		Kitagawa (2006), Sak (2012)
	–	MDR K562/A02 cells	Lu et al. (2012)
	5-fluorouracil; vinorelbine	Human colorectal cancer HCT-116 cells, human squamous cell lung carcinoma H520 cells	Sak (2012)
	Doxorubicin	HCC cells	D'Alessandro et al. (2007)
Resveratrol	Doxorubicin	MCF-7	Kim et al. (2014), Huang et al. (2014)
Capsaicin, 6-gingerol	Daunorubicin	Human multidrug-resistant carcinoma KB-C2	Nabekura et al. (2005), Nabekura (2010)
Traditional Chinese medicine herbs	–	Inhibitory activity toward P-glycoprotein	Eichhorn and Efferth (2012)

standardized extracts of Devil's Claw inhibited P-gp activity *in vitro* but harpagoside was almost inactive. This is important because Devil's Claw is traditionally used for chronic diseases, therefore in long-term treatments which increase the probability of secondary reactions and drug interactions, with an increased risk of drug resistance. The long time treatment with Devil's Claw from food supplements leads also to high blood concentrations of the active ingredients similar to those used for the *in vitro* tests (0.5–200 μM harpagosides).

In contrast to Devil's Claw, soy isoflavones induce contradictory effects in conjunction with chemotherapy. While genistein can potentiate the action of tamoxifen to inhibit tumor cell growth in estrogen receptor-negative human breast cancer cells, the same isoflavone can also attenuate the tumoricidal activity of tamoxifen in estrogen-dependent breast carcinoma cells. In addition, the therapeutic effect of tamoxifen can be fully blocked by tangeretin, a flavone derived from tangerine and other citrus peels. Due to these adverse effects, flavonoid compounds should be avoided as nutritional supporting programs of breast cancer patients treated with tamoxifen (Sak, 2012; Lamson and Brignall, 1999; Lamson and Brignall, 2000; Ju et al., 2002; Bracke et al., 1999).

St. John's wort (*Hypericum perforatum* L.) is a vegetal remedy widely used for the treatment of mood disorders, especially in cases of mild to moderately severe depression. The effect of the latter on membrane transporters is conflicting. Hypericin, the main active ingredient from St. John's wort induces the expression of two ABC transporters MRP1 and BCRP in ovarian adenocarcinoma cell lines. Studies also show that St. John's wort extract (60 μg/ml), but not hypericin, induced the reversal of the antiproliferative action of P-gp substrates paclitaxel and daunorubicin in Hvr100-6 cells 72 h after treatment. It is noticeable that pure herbal constituents of St. John's wort (hypericin, kaempferol, quercetin and silibinin) can cause a significant increase in P-gp-mRNA expression. Thus it can be expected that St. John's wort would alter the effectiveness of anti-cancer therapies *in vivo* (Jendželovská et al., 2014; Pal and Mitra, 2006).

Natural products may also interact with a number of drugs in the intestinal absorption process, modulating their pharmacokinetic behavior. For example, grapefruit juice reduces the absorptive transport of drugs in the small intestine because of an inhibition of organic anion transporting polypeptide (OATP); consequently, the bioavailability of fexofenadine (OATP substrate) is reduced. In addition to grapefruit juice, apple and orange juice have the same type of effect on OATP, reducing the bioavailability and the efficacy of associated drugs (Dresser et al., 2002a; Bailey et al., 2007; Shirasaka et al., 2010, 2013; Choi et al., 2004).

Polyphenols modulate intestinal absorption of nutrients and drugs through the influence on organic cation transporters (OCT) and also contribute to the reduction of glucose absorption through the inhibition of apically located high-affinity and Na^+- dependent Na1/glucose co-transporter 1 (SGLT1), responsible for glucose uptake in the luminal membrane. Green tea extracts, grape seed extracts and wine polyphenols induce 1-methyl-4-phenylpyridinium (MPP^+) uptake into Caco-2 cells; MPP^+ absorption in Caco-2 cells constitutes a model for the function of the organic cation transporter 1 (OCT1) and the organic cation transporter 3 (OCT3). On the other hand, there is evidence that shows that tea extracts and specifically (1)-catechin and catechins with galloyl residues such as epicatechin gallate and EGCG inhibit intestinal glucose uptake. Quercetin, EGCG, the apple polyphenol phloretin, myricetin and gossypin can decrease GLUT-2 mediated intestinal glucose uptake, thus being able to interfere with hypoglycemic drugs (Welsch et al., 1989; Cermak et al., 2004; Johnston et al., 2005).

4. Interactions between natural compounds and complex mixtures with metabolizing enzymes

Cytochrome P450s constitute a superfamily of enzymes (encoded by the gene CYP) that are involved in the metabolism of xenobiotics and endogenous compounds (Jáuregui-Garrido and Jáuregui-Lobera, 2012). The first 3 families, CYP1, CYP2 and CYP3, participate in the phase I metabolism of all clinically encountered drugs. The relative abundance of different CYP450 in human hepatic smooth endoplasmic reticulum was evaluated to be: 30% CYP3A4, 13% CYP1A2, 7% CYP2E1, 4% CYP2A6, 2% CYP2D6, 20% CYP2C9, and 1% CYP2B6 (Zhou et al., 2003). This means that CYP3A4, CYP1A2 and CYP2C9 the major liver enzymes involved in phase I metabolism of drugs and xenobiotics.

Two very important points need to be considered regarding the ability of natural compounds to modulate the activity of metabolizing enzymes: the capacity of natural compounds to interfere with metabolic enzymes as a mechanism for their health preventing actions and the influence of natural compounds on the biopharmaceutical profile of associated drugs.

In the first case, we can mention flavonoids acting as chemopreventing agents: one of the mechanisms responsible for this effect is their ability to inhibit phase I metabolizing enzymes, such as cytochrome P450 (CYP), which metabolically activate procarcinogens to reactive/highly toxic intermediates that further induce carcinogenesis. CYP1A1 and CYP1B1 are overexpressed in tumors and contribute to the metabolism of procarcinogens to epoxide

intermediates, which are further activated to diol epoxides by the epoxide hydrolase, thus inducing tumorigenic effects.

4.1. Polyphenols

Galangin (3-hydroxy chrysin) inhibit CYP1A1, thereby preventing the toxic activation of polycyclic aromatic hydrocarbons; apigenin and acacetin strongly inhibit CYP1A1 and CYP1A2 enzymatic activities (Androutsopoulos et al., 2011; Doodstdar et al., 2000). Ellagic acid inhibits CYP1A and CYP2E1 and prevents lung tobacco-induced tumorigenesis; capsaicin inhibits CYP2E1, CYP1A and 2B and reduces skin carcinogenesis. Gingo Biloba extract containing flavonoids, was demonstrated to inhibit benzo [a]pyrene (extensively studied for its carcinogenicity) hydroxylation; kaempferol, quercetin and isorhamnetin are also potent CYP1B1 inhibitors. Luteolin was also reported to be a potent inhibitor of CYP1A1 (Sousa et al., 2013; Chang et al., 2006; Androutsopoulos et al., 2010, 2011). All these examples are likely to lead to the conclusions that natural compounds are at least efficient anti-cancer agents.

However, in addition to inhibition of carcinogens by CYP1A1 and CYP1B1, flavonoids may also influence the metabolism of certain anticancer drugs by CYP1A1 and CYP1B1. It has been shown that the tumor specific enzyme CYP1B1 can metabolize the anticancer drug flutamide to 2-OH flutamide resulting in its deactivation (Rochat et al., 2001). Flavonoids that inhibit CYP1B1 can reduce activation of flutamide in tumors, thus influencing the clinical outcome of chemotherapy.

Furthermore, recent data regarding the interactions of dietary flavonoids with CYP1A1 and CYP1B1 enzymes have revealed that flavonoids may directly act as substrates for these enzymes. This causes the metabolism of flavonoids to more biologically active molecules that results in flavonoid-mediated-bioactivation in cancer cells that express active CYP1A1 and CYP1B1 (Androutsopoulos et al., 2008, 2009; Androutsopoulos and Tsatsakis, 2014; Androutsopoulos and Spandidos, 2013). In this sense, flavonoids are considered cancer therapeutic instead of chemopreventive molecules, as CYP1A1/CYP1B1 mediated metabolism yields products that inhibit cancer cell growth (Androutsopoulos et al., 2010). Whether this effect is possible in humans after ingestion of a natural product extract containing high amounts of flavonoids remains undiscovered, although preliminary *in vitro* and *in vivo* data suggest that CYP1-activated metabolism of dietary flavonoids is a possible novel mechanism of dietary chemotherapeutic action.

Moreover, flavonoids and other natural compounds induce activation of phase II metabolizing enzymes such as glutathione S-transferase (GST), NAD(P)H:quinone oxidoreductase (NQO), and UDP-glucuronyltransferase (UGT), by which carcinogens/toxic metabolites may be conjugated, detoxified and eliminated from the body (Galati and O'Brien, 2004; Hodek et al., 2002; Ahn et al., 1996; Surh and Lee, 1995; Sousa et al., 2013).

Some natural compounds modulate the activity of drug metabolizing enzymes, including CYP450 isoforms, and this effect could be responsible for undesired variations in plasma concentration of many drugs, after association of herbal supplement or even diet components with these enzymes. Several studies have shown that both green tea and black tea derivatives may influence the activity of several drug metabolizing enzymes, including those involved in anti-cancer drugs. Catechins, the main polyphenol constituents of green tea, inhibit the activity of CYP 3A4, 2A6, 2C19, and 2E1, while at the same time, they increase the activity of human and rodent cytochrome CYP 1A2 and 2B (Wanwimolruk et al., 2009; Muto et al., 2001; Park et al., 2009; Jang et al., 2005; Mancuso and Barone, 2009). Catechins have a direct inhibitory effect on CYP 3A4, and for this reason they increase the bioavailability of the calcium channel blockers (verapamil and diltiazem) and raise the risk for complications (atrioventricular block) (Chung et al., 2009; Li and Choi, 2008); they also increase the plasma concentrations of midazolam, thus amplifying the risk of prolonged sedation (Muto et al., 2001). The inhibition by green tea of CYP3A4 could be extremely deleterious, particularly in the case of prolonged/chronic consumption of this beverage, because this isoform is responsible for the metabolism of most drugs. This is of particular interest for patients undergoing anticancer therapy, since there are confusing results regarding the beneficial effects of green tea use in reducing the incidence of several types of malignancies (esophageal, stomach, liver, colorectal, and breast cancers). Studies reveal that the component of green tea and black tea influence on one hand the metabolism of anti-cancer drugs and on the other hand that of the drugs used for treating cancer associated disorders. Moreover, green tea components have an up-regulatory effect on CYP 1A2 and therefore reduce the bioavailability of the antipsychotic drug clozapine (Jang et al., 2005). In addition, catechins have an inhibitory effect on the activity of sulfotransferases (isoforms 1A1 and 1A3), enzymes that are involved in the metabolism of drugs such as methyldopa or β2-adrenoceptor agonists, thus increasing their plasma concentrations and side effects (Nagai et al., 2009; Nishimuta et al., 2007; Mancuso and Barone, 2009).

Sulfotransferases are also responsible for the metabolism of catechins from tea, both green and black, and their inhibition contributes to the rise of the catechin concentration to levels that can interfere with the metabolism of other drugs (Mancuso and Barone, 2009).

Green tea derivatives can also inhibit the activity of bortezomib, which is an anticancer agent effective in multiple myeloma and mantle cell lymphoma. Epigallocatechin-3-gallate (EGCG) has been shown to augment the toxicity of cyclophosphamide and doxorubicin, probably because it increases the activity of CYP2B and NADPH-Cyt-P-450 reductase (Park et al., 2009; Dudka et al., 2005).

Furthermore, the mango (*M. indica*) stem bark extract interferes with the activity of several metabolizing enzymes: it changes oxidations catalyzed by CYP1A2 and 2B1, it reduces CYP1A2 activity and it inhibits CYP1A1/2 activity on rat hepatocytes and human microsomes (due to mangiferin, one of the major components in the extract), thus leading to interactions with conventional drugs. Treatment of human cultured hepatocytes for 48 h with sub-cytotoxic concentrations of the extract induced a 50% inhibition for CYP1A2, 2A6, 2C9, 2D6 and 3A4 (Rodeiro et al., 2008a,b; Zhou et al., 2007; Ulbricht et al., 2008; Chieli et al., 2009).

Flavonoids have been shown to be substrates for UGTs and, in this respect, when taken in combination with certain drugs, may inhibit their glucuronidation as a result of competitive inhibition leading to overdose increased toxicity. For example, naringenin or quercetin (200 mg/kg) (which are glucuronidated) markedly increased the *in vivo* anesthetic duration and hepatotoxicity of propofol (anesthetic) in mice as a result of inhibiting propofol glucuronidation (Galati and O'Brien, 2004).

The *M. indica* stem bark extract reduced UGT1A9 activity (about 60%) and had a greater effect on UGT1A1 and 2B7 than on UGT1A9 (about 55% *vs.* 35% reduction, respectively). Moreover, mango stem bark extract polyphenolics inhibit the activity of esterases. This provides a possible mechanism explaining the potential interaction of the mango extract with ester prodrugs like lovastatin and enalapril (Chieli et al., 2009; Rodeiro et al., 2013).

Recent literature data supports the argument that polyphenols can inhibit pancreatic α-amylase or α-glucosidases and this is an important mechanism involved in their hypoglycemic effect. This resulted in the dietary management strategy for glycemic control in Japanese patients with type 2 diabetes mellitus ("*eating vegetables before carbohydrate*"), indicating that dietary

carbohydrates consumed after vegetables are digested slowly and require less insulin for subsequent metabolic disposal (Xiao and Hogger, 2014; Tiwari, 2014; Imai et al., 2013).

4.2. Resveratrol

In addition to catechins the stilbene resveratrol is a natural product that has demonstrated potential interactions with P450 enzymes and consequently the metabolism of drugs. Resveratrol-rich vegetal products act not only on membrane transporters but also on metabolizing enzymes; Chi et al. (2012) proved that *Polygonum cuspidatum* (important source of resveratrol), inhibits the activities of CYP3A, involved in the metabolism of carbamazepine, thus increasing systemic exposure to the drug. Several *in vitro* studies proved that resveratrol inhibited CYP1A1, CYP1B1, CYP3A4, CYP2E1 and CYP1A2 enzyme activities, suppressed the expression of CYP1A1 and inhibited benzo[a]pyrene-induced DNA adduct formation, while at the same time inducing phase II detoxification enzyme expression (Yueh et al., 2005; Revel et al., 2003; Chen et al., 2004; Piver et al., 2001; Chang and Yeung, 2001; Sainz et al., 2003; Szaefer et al., 2004). The latter constitutes strong evidence with regard to resveratrol chemopreventative action, *i.e.*, induction of phase II drug metabolizing enzymes can in theory detoxify the deleterious and mutagenic effects of carcinogens intracellularly (Ciolino and Yeh, 1999). Chow et al. (2010) proved in a clinical study involving healthy volunteers, that 1 g resveratrol daily administered for 4 weeks induced a 16% decrease in the caffeine/paraxanthine metabolic ratio, suggesting an induction of CYP1A2 activity (enzyme that is involved in the activation of procarcinogens). It further inhibited the activities of CYP3A4, CYP2D6, and CYP2C9, (33%, 70%, and 171%, respectively) with consequent effect on general metabolism of drugs. Resveratrol has been shown to induce UGT, GST, and quinone reductase activities in *in vitro* and *in vivo* systems. Thus resveratrol could be a major source of pharmacokinetic drug interactions.

Miao et al. (2014) showed that resveratrol- 3-*O*-glucoside from grape skin extract is also an effective non-competitive inhibitor of human pancreatic α-amylase, interacting with the aminoacid residues from the active site of the enzyme. Since α-amylase is one of the main enzymes that hydrolyzes starch in the intestinal lumen and consequently increases the glucose level available for absorption, the grape skin extract might act as an antinutritional factor, in terms of its potential to inhibit the activities of carbohydrate-hydrolysing enzymes.

4.3. Curcuminoids

Curcumin is another natural compound with documented anticancer activity. Experimental studies have proved that curcumin inhibits 50% of CYP3A4 activity in rat liver thus reducing the CYP-mediated metabolism of tamoxifen to its active metabolite, 4-hydroxytamoxifen. The enhanced bioavailability of tamoxifen by curcumin may be mainly due to inhibition of the CYP3A4-mediated metabolism and to inhibition of the P-gp efflux transporter in the small intestine. Moreover, curcumin inhibited CYP1A1 and 1B1 induction by TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin), contributing to the prevention of malignant transformation in a similar fashion to that noted by resveratrol (Cho et al., 2012; Bamba et al., 2011; Choi et al., 2008).

4.4. Grapefruit juice

Bailey et al. (1998) indicated that grapefruit juice inhibits the drug pre-systemic metabolism mediated by CYP, particularly the isoform CYP3A4 in the bowel. Grapefruit juice acts on CYP3A4, (which metabolizes many of the commonly prescribed drugs) and drug transporter proteins (such as P-gp) at the intestinal level; it also inhibits hepatic P-gp, without affecting the activity of liver CYP3A4 (Uno and Yasui-Furukori, 2006). The inhibition of the liver enzymes CYP3A4 and CYP1A2 is mainly attributed to the flavonoids naringenin and apigenin being present in the juice. A similar pattern of inhibition is evident for citrus juice as citrus fruits are very rich source of hersperitin and naringenin that are inhibitors of CYP1A2 activity (Doodstdar et al., 2000). Moreover, the flavone constituent of citrus fruits nobiletin has been shown to be a substrate for CYP1A2 thus accounting for competitive inhibition for several known CYP1A2 drug-substrates (Koga et al., 2011). Some of the flavonoid compounds present in grapefruit (quercetin, naringenin), also inhibit transporter proteins of organic cations (OCT) and organic anion transporter (OAT) from the basal membrane of intestinal epithelium (Panchagnula et al., 2005). The inhibition of CYP3A4 seems to be irreversible, and may be induced after consuming 200–300 ml of juice, while the effect of increasing the bioavailability and toxicity of the drugs, may occur in the first 24 h after the intake. Moreover, grapefruit juice flavonoids have demonstrated esterase inhibitory activity and this concept provides an explanation of their plausible mechanism of interaction with ester prodrugs (Li et al., 2007).

The most important drugs mentioned in the literature that interact with grapefruit juice in terms of adverse events are calcium channel blockers (amlodipine, felodipine, manidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, pranidipine, etc.), angiotensin II receptor blockers (losartan), beta-blockers (talinolol, acebutolol), some antiarrhythmic drugs (amiodarone, quinidine, disopyramide and propafenone), anticancer agents (vinblastine), and some statins (atorvastatin) (Ofer et al., 2005; Bailey, 2010; Owira and Ojewole, 2010; Jáuregui-Garrido and Jáuregui-Lobera, 2012).

4.5. Other plant extacts

Devil's Claw (*Harpagophytum procumbens*) is used as an alternative to conventional anti-inflammatory drugs (NSAIDs) (Grant et al., 2007; Warnock et al., 2007; Romiti et al., 2009). Unger and Frank (2004) reported the results of an *in vitro* study showing inhibitory effects of Devil's Claw on six human CYP450 (CYP1A2, 2C8, 2C9, 2C19, 2D6 and 3A4). Georgiev et al. (2012) proved that Devil's claw extracts displayed significant cholinesterase inhibitory activity (even higher than that of pure galanthamine in the case of butyrylcholinesterase inhibition assay).

Chamomile (*Matricaria recutita* L., *Asteraceae*) extract used for the treatment of indigestion, cramps, and inflammation inhibits CYP450 enzymes (CYP1A2, CYP2C9, CYP2D6, and CYP3A4) with CYP1A2 being more prone to inhibition than the other isoforms (Mukherjee et al., 2011). Chamomile contains large portions of apigenin and luteolin that have been shown to inhibit CYP1A2 enzyme (Arroo et al., 2008).

Black cohosh (*Cimicifuga racemosa*) extract is used among Native Americans to treat different conditions, including diarrhea, sore throat, rheumatism but also menopausal disorders, acting as an anti-inflammatory, antipyretic, and analgesic remedy. Black cohosh extract displays inhibitory effects on CYP3A4, CYP2D6 and carboxyesterase that result in the inhibition of active tamoxifen and irinotecan metabolites generation (Li et al., 2011; Ye et al., 2014; Zhou et al., 2003; Gorman et al., 2013).

St. John's wort *(Hypericum perforatum)* and its active constituent (hyperforin) is a potent inducer of CYP3A4, CYP2C19 and CYP2C9, and can enhance the clearance of many drugs, including cyclosporine, innadivir, clopidogrel and docetaxel. This leads to decreased efficiency of the above mentioned drugs, while St John's wort has been shown to reduce the AUC and Cmax of digoxin. The use of St. John's wort preparations is not recommended in people

Table 3
Clinical outcomes of natural compunds in human studies.

Clinical outcome	Effect/mechanism of action	Dosage model	References
Positive clinical outcome in stage 1 hypertensive patients	Reduction of systolic, diastolic and mean arterial pressures by limiting the production of angiotensin II	730 mg quercetin/day, 4 weeks	Edwards et al. (2007)
Increased bioavailability of drugs used for CVD (*e.g.*: talinolol, verapamil, diltiazem, atorvastatin, etc.)	Interaction with substratesd of P-gp and/or CYP450	Single intake of grapefruit juice (250 ml)	Reddy et al. (2011), De Castro et al. (2008)
Decreased bioavailability of drugs used for CVD (*e.g.*: atenolol, celiprolol)	Increased CYP metabolism	Chronic use of *Ginkgo biloba*	Piao and Choi (2008)
	Reduction of intestinal absorbtion	Chronic use of orange juice (mainly due to hesperidin)	Jáuregui-Garrido and Jáuregui-Lobera (2012)
Increased toxicity of drugs (amiodarone, quinidine, disopyr-amide, propafenone, digoxin, felodipine, antineoplastic agents, midazolam, etc.)	Interaction with substrated of P-gp and/or CYP450	Chronic use of grapefruit juice, Siberian ginseng (*Eleutherococcus senticosus*), peppermint oil, green and black tea	Ohnishi et al. (2006), Goosen et al. (2004), Dresser et al. (2002b), Jáuregui-Garrido and Jáuregui-Lobera (2012), Golden et al. (2009), Shah et al. (2009)

who are taking immunosuppressants or cardiovascular drugs and should be closely monitored (Zhou et al., 2003; Ye et al., 2014; Goey et al., 2014; Rahimi and Abdollahi, 2012; Lau et al., 2011).

G. biloba extract is used both traditionally and therapeutically for disorders associated with a reduction of cerebral blood flow. Studies show that components of *G. biloba* (such as amentoflavone) are potent inhibitors of CYP2C9 and CYP3A4; this has a direct impact on the metabolism of drugs, especially those administered to elderly patients, including tolbutamide. It has been suggested that *G. biloba* as well as Ginseng should not be combined with anticoagulants, due to possible toxic interactions (Von Moltke et al., 2004).

Many traditional Chinese herbal medicines have been reported to modulate (inhibit or increase) the activity of CYP450 system and causing herb–drug interactions (Zhou et al., 2003). Woohwang-cheongsimwon (Chinese name Niuhuang Qinxin Wan), a traditional formulation medicine for the treatment of hypertension, arteriosclerosis, coma, and stroke in China and Korea, inhibits the activity of CYP2B6 *in vitro* (Kim et al., 2008; Ye et al., 2013).

Lotus leaves (from *Nelumbo nucifera*) are commonly used in China as a "tea drink", while this herbal product is also traditionally used by Chinese medicine for the treatment of sun stroke, for thirst, or to cure both diarrhea and fever. Recent research has demonstrated various pharmacological effects for lotus leaves, such as anti-hyperlipidemia, anti-obesity, anti-oxidant, anti-HIV, anti-microbial, and anti-hypoglycemic activities (Ye et al., 2014). The lotus leaf alcoholic extract, rich in aporphine alkaloids, was found to be a strong inhibitor of the CYP2D6 isoenzyme. This isozyme catalyzes approximately 30% of the clinically encountered drugs (antidepressive drugs – fluoxetine and amitriptyline, β-blocking agents – metoprolol and propranolol, antipsychotic drugs – chlorpromazine, perphenazine, and even tamoxifen) and its inhibition may result in potential adverse drug interactions leading to increased plasma levels of another drug administered concomitantly and resulting in drug-induced toxicity (Ye et al., 2014; Fukumoto et al., 2006; Li et al., 2011).

While the interactions of natural products and herbal constituents upon the metabolic capacity of drug metabolizing enzymes are apparent, the impact of genetic polymorphisms of the latter is a matter of increasing alert for patients and clinicians. It is widely accepted that certain gene variants of cytochrome P450CYP enzymes can yield functionally inactive or highly active enzymes. For example the CYP3A4*22 allele has been shown to metabolize the drug cyclosporine faster in human renal transplant patients (Lunde et al., 2014). It becomes evident that patients that encounter polymorphisms in the CYP3A4 gene may have a completely different response with that of their corresponding wild type subjects. In that case the effects of an herbal diet that contains CYP3A4 inhibitors or substrates will further alter the clinical picture with respect to CYP3A4-mediated drug metabolism. As a result, caution should be taken so as to safely validate the genetic profile of patients with respect to CYP variants and drug therapy or daily diet.

Studies on the interaction of medicines with food supplements are heterogenous, first because generally they are focussing on the medicine and less on the clinical outcome, secondly because the composition and dosage of the compounds are not mentioned, so there is difficult to appreciate if they were supplements or they were the consequence of a certain diet and, most important, the clinical outcome was not equivalently quantified. However, particularly interest was given to the cardiovascular consequences. Table 3 summarizes such findings in human studies.

5. Conclusions

The co-administration of natural products along with conventional medicines can induce a modified bioavailability and important changes of metabolic pathways, leading either to therapeutic inefficacy or increased risk of toxicity. Reports show that most of the patients using chronic prescription medications are also associating herbal supplements or vegetal rich diets without understanding the risks. This problem is also complementary with the fact that even physicians are not always aware of the risk of interactions.

It is generally accepted that natural compounds should be avoided as supplements for patients undergoing chemotherapy in order to avoid the risk of decreased availability. However, rarely the patient and/or physician are careful to avoid ingestion of beverages like green tea and grapefruit juice and soy-based food. Moreover, in case of cancer treatment, the patient should be hydrated and fresh juices or herbal tees are reccommended in addition to water, on the general assumption that they cannot harm.

The biphasic response of herbal/vegetable compound-drug interactions adds more complexity to the adverse toxicity effects

caused by drug administration to patients. Several products lead to an increase of the drug concentration when administered in short term regimen but may induce an increased metabolism and decreased effect after prolonged intake. It is the case of CVD diseases, in which the patient is reccommended a lipid-low diet, and also an increased amount of liquids, which is generally, supplemented with fruit juice and/or tea drinks.

The present review, far from being exhaustive, presents only a few findings regarding the interaction of medicines with natural products. Further systematic studies are necessary in order to unravel the risks of food/natural supplement—drug associations.

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