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Risks and benefits related to alimentary exposure to xenoestrogens

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Abstract

Xenoestrogens are widely diffused in the environment and in food, thus a large portions of human population is worldwide exposed to them. Among alimentary xenoestrogens, phytoestrogens (PhyEs) are increasingly being consumed because of their potential health benefits, although there are also important risks associated to their ingestion. Furthermore, other xenoestrogens that may be present in food are represented by other chemicals possessing estrogenic activities, that are commonly defined as endocrine disrupting chemicals (EDCs). EDCs pose a serious health concern since they may cause a wide range of health problems, starting from pre-birth till adult lifelong exposure. We herein provide an overview of the main classes of xenoestrogens, which are classified on the basis of their origin, their structures and their occurrence in the food chain. Furthermore, their either beneficial or toxic effects on human health are discussed in this review.

1. Introduction

Xenoestrogens are estrogen mimicking compounds which are not produced by our body. These compounds are structurally or functionally related to human sex hormone 17 β -estradiol (E₂) and bind the estrogen receptors (ERs) with various degrees of affinity and selectivity. Due to their interaction with the ERs, xenoestrogens cause several effects on our organism, which sometimes may be beneficial for our health, whereas in most cases these effects are detrimental. Our exposure to xenoestrogens is mostly related to food ingestion, because these compounds may be present in the aliments, as well as in packaging materials or food contaminants (Figure 1).

Xenoestrogens may be of either synthetic or natural origin (Figure 2). The most abundant class of natural xenoestrogens is represented by *phytoestrogens* (PhyEs). PhyEs are plant-derived compounds often exerting a wide range of biological activities, including estrogenic activity, which are found in a variety of foods, most notably soy. Among natural xenoestrogens there are also *mycoestrogens*, which are substances produced by fungi. Synthetic xenoestrogens are instead molecules produced by chemical synthesis, which are widely used in industrial products, comprising also pharmaceutical estrogens. These

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synthetic compounds can interfere with the endocrine system and, therefore, cause several health problems. In fact, they are classified as endocrine disrupting chemicals (EDCs). EDCs are mostly man-made compounds, found in various materials such as pesticides, metals, additives or contaminants in food and personal care products. EDCs are defined as compounds that *"interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the development, behavior, fertility and maintenance of homeostasis"* (Crisp et al., 1988).

According to the World Health Organization (WHO), EDCs are suspected to be associated with altered reproductive function in males and females, increased incidence of breast cancer, abnormal growth patterns and neurodevelopmental delays in children, as well as changes in immune function (<http://www.who.int/ceh/risks/cehemerging2/en>). Human exposure to EDCs can occur via ingestion of food, dust and water, inhalation of gases and particles in the air and through the skin. EDCs can also be transferred from pregnant women to developing fetus or to children through the placenta or breast milk, respectively. It is important to note that also PhyEs may act as EDCs.

Considering that man-made chemicals, comprising estrogenic compounds, have become a part of everyday life, in 2012 the WHO developed the document *"State of the Science of Endocrine Disrupting Chemicals-2012"*, in collaboration with the United Nations Environment Programme (UNEP), in which the key points of this important field are summarized (WHO/UNEP, 2013). It is now widely known that most humans are continually exposed to these potentially dangerous substances. This is proven by the increasing incidence of many endocrine related disorders, comprising genital malformation, neurobehavioral disorders and the increased global rates of endocrine-related cancers.

This review reports on the most recent information about food-related xenoestrogens, with a particular focus on: 1) the potential benefits/risks related to PhyEs intake; 2) the risks linked to exposure to estrogenic EDCs (Tables 1 and 2).

2. Natural xenoestrogens

2.1 Phytoestrogens (PhyEs): general features

Phytoestrogens (PhyEs) are natural compounds structurally and/or functionally correlated with E₂. Interest in the potential role of PhyEs in preventing or treating diseases is demonstrated by the increasing number of papers that investigate the amounts of various PhyEs in food and plants. Most PhyEs are estrogen receptor ligands with a preference for the beta subtype (see, for example, Genistein $\beta/\alpha = 20$, Daidzein $\beta/\alpha = 7$, *S*-Equol $\beta/\alpha = 32$, Coumestrol $\beta/\alpha = 7$, Naringenin $\beta/\alpha = 11$, Apigenin $\beta/\alpha = 20$) (Minutolo et al., 2011; Paterni et al., 2014). Considering their chemical structures, PhyEs can be divided into different classes: lignans (Figure 3), flavonoids (flavones, flavonols, flavanones, isoflavones, isoflavandiols, homoisoflavones) and chalcones (Figure 4) (Sirotkin and Harrat, 2014). However the structures of PhyEs span a wide range of chemical classes and, therefore, some of them cannot be ascribed to any of the previously mentioned classes (Figure 5).

Lignans are polyphenolic components of plant cell walls and are found in berries, seeds, grains, nuts, fruits and cruciferous vegetables. They derive from phenylalanine via dimerization of substituted cinnamic alcohols. Secoisolaricinesol, matairesinol, lariciresinol and pinoresinol are four examples of lignans (Figure 3). Once ingested, they are metabolized by intestinal bacteria to enterolignans, such as enterodiol and enterolactone (Figure 3), which exert an estrogenic activity, albeit their effect is considerably weaker than that of estradiol (Rowland et al., 2003).

Flavonoids, which represent the main class of PhyEs, can be found in berries, wine, grains, nuts, soybean, legumes, *etc* (Figure 4). Their content in selected foods are reported in several accessible databases (United States Department of Agriculture, 2008; United States Department of Agriculture, 2011). Flavonoids are often conjugated with glucose or other carbohydrate moieties in their inactive form, whereas their bioactive form is represented by the un-conjugated compound (aglycone). Chalcones, which are flavonoid-related compounds lacking the heterocyclic C ring of flavonoids, can also be found in several edible plants and fruits (Figure 4). One of the most important source of estrogenic flavonoids is soy, containing relevant amounts of isoflavones genistein and daidzein, and the great interest for this nutrient is demonstrated by the increased number of soy-based products. Plants have always constituted an important source of flavonoids exerting estrogenic activity, as demonstrated by the high isoflavonoids content of *Pueraria Mirifica* leaves, in particular of puerarin, daidzin, genistin, daidzein, and genistein (Jungsukcharoen et al., 2014). Flavonoids obtained by the ethanolic extract of *Liriope platyphylla* aerial parts comprised about 17 already known PhyEs. All these compounds were evaluated for their estrogenic activity using a reporter-gene assay system, and two flavones, 3-*O*-methylquercetin and 6-*C*-methylquercetin-3-methyl ether, resulted the compounds with the most potent dose-dependent estrogenic activity. Moreover, these two compounds, together with another flavone, kaempferol, showed a high preferential affinity for the ER β subtype in binding assays. Furthermore, two homoisoflavones, 3-(4'-hydroxybenzyl)-5,7-dihydroxy-6-methylchroman-4-one and 3-(2',4'-dihydroxy-benzyl)-5,7-dihydroxy-6-methylchroman-4-one (Figure 4), in which the hydroxyphenyl group in position 2 of isoflavones is replaced by an hydroxybenzyl group in position 3 of the chromanone scaffold, displayed preferential binding affinities for ER β (Tsai et al., 2015). *Butea superba Roxb.*, bearing to the Leguminosae family, is commonly found in deciduous Thai forest and it is used by Thai indigenous for promoting male potency, becoming a traditional medicine used to promote male vigor. A recent study evaluated the behavior of six previously isolated components of this plant and, in addition, tested 23 different tuberous ethanolic samples, which were collected from 23 different provinces in Thailand, for their estrogenic and antiestrogenic activity. Among the six single components tested, 7-hydroxy-6,4'-dimethoxyisoflavone resulted the most potent estrogenic component, with a relative potency of 15% on ER α and of 5% on ER β . Then, the screening of the 23 tuberous ethanolic samples of *Butea superba Roxb.* revealed that practically all of them displayed a certain estrogenic activity, with a slight preference for the beta receptor subtype (Cherdshewasart et al., 2010).

Recently, some PhyEs extracted from mango fruit, such as mangiferin and quercetin, were found to selectively activate ER α in breast cancer MCF-7 cells, whereas norathyriol, which is a metabolite of mangiferin, activates also ER β (Wilkinson et al., 2015). Oleocanthal, a

bioactive compound found in olive oil, showed to bind to both estrogen receptors, inducing either agonistic or antagonistic effects depending on the cell line. This differential modulatory action could in part explain its wide range of pharmacological activities, such as anti-inflammatory, antiproliferative, and neuroprotective properties (Keiler et al., 2015).

Plants also produce second metabolites starting from some of the above mentioned PhyEs. One of the main metabolic reaction in plants is prenylation, which produces second metabolites of genistein, such as 8-prenylgenistein (8PG) and 6-(1,1-dimethylallyl)genistein (6DMAG), and of naringenin, such as 8-prenylnaringenin (8PN) and 6-(1,1-dimethylallyl)naringenin (6DMAN). The activity of these compounds was evaluated in three functionally different estrogen receptor assays (YEAST assay, MVLN luciferase assay and Alkaline phosphatase activity of Ishikawa cells). Naringenin metabolites 6DMAN and 8PN showed an enhanced estrogenic activity compared to that of naringenin, whereas genistein derivatives 6DMAG and 8PG generally displayed a weaker estrogenic potency than that of genistein (Kretzschmar et al., 2010). In another study, kwakhurin, another prenylated PhyEs isolated from the tuberous root of *Pueraria Mirifica*, showed a moderated estrogenic activity, comparable to that of daidzein (Chansakaow et al., 2000). However, is important to note that the introduction of a prenyl bulky group in the structure of these PhyEs metabolites may also change their functional properties in terms of agonistic/antagonistic activities. For example glabridin, an isoflavandiol found in the root extract of licorice (*Glycyrrhiza glabra*) shows a phytoSERM profile, since it behaves as an antagonist or agonist, depending on the cell lines utilized in the functional assays (Simons et al., 2012).

Genomic analyses revealed that most PhyEs exhibit a wide variety of patterns of gene regulation, which may be either similar or distinct from each other and from that of E₂. For example, the expression patterns of genistein and *S*-equol clustered together quite closely and were distinctly different from that of liquiritigenin, whose profile is the most different from that of E₂ (Gong et al., 2014).

The content of flavonoids PhyEs in 16 different types of bean, which are commonly present in the daily diet of several countries, was analysed. High levels of genistein, daidzein and quercetin were found at different concentrations depending on the species (de Lima et al, 2014). Some common culinary herbs constitute excellent sources of flavonoids, such as apigenin (in parsley and mint) or quercetin (in lovage and dill) (Justesen et al., 2001). In spite of the fact that natural rice generally produces low levels of PhyEs, new studies led to the production a transgenic rice expressing high levels of flavonoids (in particular genistein, naringenin kaempferol and apigenin), thanks to the introduction of their biosynthetic genes (Ogo et al, 2013).

Many components of traditional Chinese medicine (TCM) are based on their estrogenic activities. In fact plants that are commonly used in TCM contain a wide variety of PhyEs. In particular, the TCM botanical formulation MF101 contains bakuchiol, a meroterpene phenol extracted from the seeds of *Psoralea corylifolia*, naringin and its active metabolite naringenin, two compounds extracted from *Rhizoma drynariae* (Gu Sui Bu), and flavanone liquiritigenin, the most active estrogenic compound from licorice root (*Glycyrrhiza uralensis*) (Li et al., 2015). In addition, a recent study demonstrated the estrogenic activity of

some classical components of TCM, which proved to sustain bone growth and maturation without affecting other estrogen-dependent tissues (Tiosano et al., 2014). Finally, a terpenoid PhyEs, ferutinin, which was first extracted from *Ferula hermonis* root (Abourashed et al., 2001) was found to possess beneficial estrogenic effects on bone loss (Palumbo et al., 2012).

It is worth nothing that increasing efforts have been done in recent years in order to improve the efficiency of the methods used to detect PhyEs in food and plants (Wang et al., 2014; Li et al., 2013). Furthermore the amount of PhyEs is significantly affected by the manufacturing processes. For example, TPC (total phenolic content) and TFC (total flavonoids content) increased after fermentation of the plant-derived materials, and, for example, this is a popular processing method utilized to improve the texture and nutritional properties of soybean products. Even though fermentation could cause the breakdown of some healthful substances during heat treatment, soaking, and ripening, it is still a cost-effective method that can produce higher amounts of antioxidant and nutritious substances, such as the aglycone-forms of isoflavones (Xu et al., 2015).

2.2 Therapeutic applications of PhyEs as nutraceuticals

Currently, there is a great debate about the use of PhyEs as useful preventive or therapeutic compounds in several diseases, such as menopausal symptoms, osteoporosis, cardiovascular pathologies, and different types of cancer, as shown by the increasing number of studies and clinical trials concerning their uses, although contrasting results have so far been obtained. Moreover, it is important to mention that over-consumption of PhyEs and their derivatives might produce endocrine-related side effects, especially on the uterus (Barals et al., 2014).

It should be noticed that, while several papers describe the potential benefits of PhyEs, there is a general lack of information about their side effects (Patisaul and Jefferson, 2010). In particular, the genotoxicity of several PhyEs needs to be carefully considered. Practically, all PhyEs (or their metabolites) exhibit pro-apoptotic effects in some cell systems, but this aspect is far from being well understood. Furthermore, the variable concentrations of extracts can provoke different responses in assays. In fact, food extracts are often found to be devoid of genotoxic effects in *in vitro* assays, despite the clearly established genotoxic activity of their isolated pure phytoestrogenic compounds (Stopper et al., 2005). Nevertheless, the beneficial actions of alimentary PhyEs generally outrun their risks, and the next section illustrates their various potential therapeutic applications.

2.2.1 Beneficial effects on the Central Nervous System (CNS)—Neuroprotective role of PhyEs mediated by ER β activation was investigated in several studies. Daidzein proved to be neuroprotective by inhibiting the pro-apoptotic and neurotoxic effects caused by glutamate treatment in hippocampal cells. This effect seems to be dependent on ER β activation, since it was reversed when cells were pre-treated with a selective ER β antagonist, while the administration of a selective ER α antagonist did not influence the anti-apoptotic activity of daidzein. The membrane associated estrogen receptor GPR30 is also involved in the neuroprotective action of daidzein (Kajta et al., 2013). Another positive role of ER β in neuroprotection was highlighted in a study where genistein was evaluated in a model of global cerebral ischemia in gerbilis. Administration of genistein proved to be

neuroprotective, to reverse ischemia-induced memory impairment, to decrease malondialdehyde overproduction in the brain and to fully promote the survival of pyramidal cells in the CA1 hippocampal subfield. Interestingly, these effects are fully prevented by the administration of an ER β antagonist 30 minutes before carotid occlusion (Donzelli et al., 2010). Furthermore, genistein and daidzein proved to be neuroprotective in stroke-like injury *in vitro* in an ER-dependent manner (Schereihofer et al., 2009). Dietary soy and soy isoflavones were neuroprotective in experimental cerebral ischemia. Ovariectomised Sprague-Dawley mice were divided into two groups, one fed with a soy-free diet and another one with a diet containing high levels of soy PhyEs for 5 weeks. Soy intake was associated with a reduced inflammatory response in the cerebral cortex after transient middle cerebral artery occlusion (Shambayati et al., 2014). Among PhyEs, pterostilbene (PTER), a dimethylated analogue of resveratrol found in grapes and berries, exhibits a neuroprotective role in H₂O₂-treated SY5Y cells, mainly through ER α stimulation, which presumably involves a positive regulation of anti-apoptosis Bcl-2 expression and the activation of the MAPK/ERK and PI3K/AKT signaling pathways (Song et al., 2015).

Antinociceptive activity of PhyEs liquiritigenin was assessed in a rat model of persistent neuropathic pain. Intraperitoneal administration of liquiritigenin alleviated in a dose-dependent manner mechanical, thermal and cold hyperalgesia. Moreover, antinociceptive tolerance was not observed after daily administration (Chen et al., 2014).

PhyEs are useful also in the treatment of depression, as demonstrated by a study comprising 40 women. These patients were divided into 4 groups and treated respectively with fluoxetine (10 mg), soybean (100 mg), sertraline (50 mg), and sertraline (50 mg) plus soybean (100 mg). Soybean showed an antidepressant effect *per se*, and the association of soybean and antidepressants proved to be synergistic (Estrella et al., 2014).

Great interest is currently focused on the use of PhyEs in the prevention and treatment of Alzheimer's disease (AD), which is characterized by a neuronal dysfunction and by the presence of amyloid plaques in the brain. Many evidences highlight that the intake of PhyEs may prevent the AD. Moreover the increased frequency of the disease in post-menopausal women suggests a role for estrogens in development of AD. ERs regulate the expression of insulin-degrading enzyme (IDE), which plays a significant role in the catalysis of the beta amyloid protein. Among ERs, ER β seems to have the most important role. In fact, hippocampal neurons treated with an ER β agonist showed an increase in the IDE expression, which was completely abolished by the treatment with an ERs antagonist, whereas treatment with an ER α agonist did not produce any effect (Zhao et al., 2011). Intrahippocampal A β (1–40)-injected rats exhibited a lower spontaneous alternation score in the Y-maze spontaneous alternation test, an impaired retention and recall capability in the passive avoidance test, and fewer correct choices and more errors in the RAM task. Genistein significantly improved most of these parameters. However, when co-administered with fulvestrant, a potent ERs unselective antagonist, these beneficial results were reversed, thus demonstrating the involvement of the estrogenic pathway in the cognitive enhancement action of genistein (Bagheri et al., 2011). A phyto- β -SERM formulation composed of equal parts of soy-derived PhyEs (genistein, daidzein, and equol), displaying a 83-fold binding selectivity for ER β over ER α , was found to ameliorate health, prolonged survival, improved spatial recognition

memory, and attenuated amyloid- β deposition and plaque formation in the brain in a female triple transgenic mouse model of AD (Zhao et al., 2013). Scutellarin, the major flavone present in *Herba Erigerontis*, a Chinese medicine derived from *Erigeron breviscapus* (Zhu et al., 2009), *Zingiber officinalis* and *Amomum subulatum Roxb.* extracts (Kumal et al., 2015) proved to be active against AD symptoms. Genistein displayed a significant efficacy also against Parkinson disease (PD) (Baluchnejadmojarad et al., 2009). Another PhyEs showing efficacy against PD is puerarin, the major bioactive isoflavone isolated from the root of the *Pueraria lobata* (Willd.) Ohwi, which is well known as Gegen (Chinese name) in TCM. Puerarin has multiple pharmacological activities, but its protective effect against PD seemed to be due to an antagonistic effect on estrogen-response element (ERE)-reporter transcription via binding to ER β (Zhou et al., 2014). Some PhyEs showed efficacy also in reducing the symptoms of multiple sclerosis. Experimental allergic encephalomyelitis (EAE) is an autoimmune disease validated as an animal model of multiple sclerosis, genistein reduced EAE severity in mice only if administration started in the early phases of the disease (Jahromi et al., 2014). Despite these positive results, observational studies and randomised controlled trials in humans resulted in inconclusive findings about the effects of PhyEs on the cognitive functions of elderly people, and further studies are required (Soni et al., 2014).

2.2.2 Breast Cancer—One of the most important issues concerning the impact of PhyEs in human health is their ability to either increase or reduce the risk of developing breast cancer. The results so far obtained from preclinical studies are still controversial. Daidzein stimulates the growth of breast cancer cells and potentiates estrogen-induced cell proliferation in the uterus (Gaete et al., 2011). However, high concentrations of genistein inhibits the growth of breast cancer cells regardless of their ER status. On the other hand, low concentrations of genistein stimulate ER-positive breast tumors and abrogate tamoxifen-mediated growth inhibition in ER-positive breast cancer. Recent studies also demonstrated non-estrogenic anticancer effect of isoflavones (e.g., reactivation of epigenetically silenced tumor suppressor genes) (Kwon, 2014).

Chalcone isoliquiritigenin, a component of licorice extracts, behaves as an ER agonist in MCF7 cells, although its behavior was controversial and seemed to be dependent on the doses and on the exposure times. For example, high doses ($> 10 \mu\text{M}$) induce a dramatic drop in cell numbers, whereas long term exposure to low doses ($< 1 \mu\text{M}$) promotes cells growth through ER α activation (Maggiolini et al., 2002).

Some studies suggested a protective role of PhyEs against the development of breast cancer when their ingestion started prepubertally and it was associated with their ability to alter the morphology of the mammary gland during pubertal breast growth. PhyEs exposure during adolescence modulated the adult mammary gland sensitivity to E_2 and lifelong exposure resulted in dose-dependent differential effects on proliferation, gene expression, and DNA methylation in rat mammary glands. Further studies will be necessary to clarify their effective role, considering that response varies from different race and ethnicity (Blei et al., 2015). The preventive role of PhyEs if assumed during adolescence was also supported by the result of a study showing that intake of PhyEs during adolescence among Ontario women was associated with a reduced risk of developing breast cancer (Anderson et al., 2013). Intake of lignans was also associated with a reduced risk of developing breast cancer

(Abarzua et al., 2012), moreover enterodiol and enterolactone, alone or in combination with tamoxifen, seemed to reduce human breast cancer cell adhesion, invasion and migration *in vitro* (Chen and Thompson, 2003). However, the estrogenic behavior of enterolignans is not fully clear. It was hypothesized that they may act as antiestrogens on estrogen receptor-positive breast cancer and, therefore, be beneficial in breast cancer prevention strategies (Bergman et al., 2007).

β -Thujaplicin, one of the major constituents in *Chamaecyparis obtusa*, exerts various health beneficial effects. A recent study demonstrated that it significantly suppresses the proliferation of MCF7 and T47D luminal subtype breast cancer cells by arresting the cell cycle transition from the G1 to the S phase. Interestingly, β -thujaplicin down-regulated ER α expression, which led to cell growth inhibition. These results suggest that β -thujaplicin might be considered as a potent agent that regulates the hormone sensitive mammary tumorigenesis (Ko et al., 2015).

Glyceollins are a family of soy-derived isoflavonoid phytoalexins, whose production is increased in soybeans in response to various stress signals, such as fungal infection. The three major components of glyceollins identified in soybeans were Glyceollin I, Glyceollin II and Glyceollin III. Initially this glyceollins mixture was evaluated for its anticancer activity in a xenograft model of MCF-7 and BG-1 tumor formation in immunocompromised female ovariectomized nu/nu mice, showing an important antiestrogenic activity *in vivo* with a significantly suppressed estrogen-stimulated tumor growth of MCF-7 and BG-1 cells in ovariectomized female nude mice, and no agonistic effect in the uterus (Salvo et al., 2006). Then, these three components were purified and investigated separately: the active component of this mixture resulted to be glyceollin I, with an IC₅₀ value of 1.68 μ M against ER α , whereas the IC₅₀ values of glyceollins II and III were 6.57 and >10 μ M, respectively. Thus, this study demonstrated that glyceollin I acts as a potent ERs antagonist (Zimmerman et al., 2006). Moreover, further studies attributed the antiestrogenic activity of glyceollin I to the natural (–)-glyceollin I enantiomer, which was compared to those of the racemate and of the unnatural (+) enantiomer (Payton-Stewart et al., 2010). Furthermore, Glyceollin I proved to reduce E₂-stimulated proliferation of MCF7 cells and E₂-stimulated breast and ovarian cancer *in vitro*, and *in vivo* reduced E₂-stimulated breast and ovarian cancer and E₂-induced uterus growth, in an ERs dependent manner (Salvo et al., 2012). Although glyceollins seem to act as ER antagonists, in another recent study from a different research group, glyceollin I, II and III were tested as a mixture and they were found to behave as agonists with a preferential stimulation of ER β (Kim et al., 2010). Glyceollins seem to be active also in central nervous system where they display neuroprotective effects (Bamji et al., 2015).

Finally, it is important to consider that PhyEs can exert their anticancer activity also by interfering with targets that are different from the ERs; for example, genistein and calycosin, inhibit the growth of MCF7 cells through their regulation of Akt signaling pathways (Chen et al., 2015; Chen et al., 2014).

Overall, despite the large number of studies reported during the past few years in this area, both *in vitro* and *in vivo* studies are still controversial, and postmenopausal women with

high risk of developing breast cancer should avoid PhyEs intake, due to their possible capacity to stimulate proliferation in sensible tissue (Helle et al., 2014).

2.2.3 Endometriosis and endometrial cancer—Endometriosis is a hormone-related disease in which ERs are involved. PhyEs quercetin was used in an endometriosis rat model and it proved to modify the levels of ERs and progesterone receptor (PR) in hypothalamus, pituitary and endometrium, thus inhibiting estrogen and progesterone binding to their receptors. Quercetin regulates ERs and PR both in the reproductive system and in the CNS, leading to a decrease of serum estradiol. This caused the deficiency of hormone supplement in ectopic endometrium and reduced the height of endometrial epithelial layer and the number of ectopic endometrial glands, eventually leading to the atrophy of ectopic endometrial epithelial (Cao et al., 2014). A protective role of PhyEs in endometrial cancer is supported by the results of a clinical trial, where a multiethnic cohort study evaluated endometrial cancer risk in postmenopausal women after soy intake. This study showed that the risk of developing endometrial cancers was decreased in postmenopausal women with the higher intake of soy (in particular daidzein and genistein) (Ollberding et al., 2012).

2.2.4 Prostate cancer—PhyEs intake seems to be correlated also with a reduced risk of prostate cancer (PCa) in Asian populations. Genistein, daidzein and equol, an isoflavandiol metabolized from daidzein by bacterial flora in the intestines and prevalently found as *S*-enantiomer in humans, inhibit prostatic carcinogenesis in some animal models. ER α expression was upregulated in the epithelial cells in high-grade prostatic intraepithelial neoplasia (HGPIN), and most likely mediated the effects of estradiol in promoting prostate carcinogenesis as demonstrated in animal models. This role of ER α was further supported by the ability of the ER α antagonist toremifene to reduce the incidence of PCa in men with HGPIN. Inhibition of PCa epithelial cell growth is one of the most recognized protective roles of soy isoflavones in PCa. Moreover, genistein reduced the expression of ER α in two animal models. Furthermore, most PhyEs are ER β -selective ligands and this could be useful in the chemoprevention of prostate cancer, where ER β seems to play an anti-proliferative and proapoptotic role. In spite of these evidences, it is also important to note that other mechanisms, including antioxidant defense, DNA repair, inhibition of angiogenesis and metastasis, potentiation of radio- and chemotherapeutic agents, might contribute to the soy-mediated cancer prevention (Mahmoud et al., 2014).

A protective role of ER β against prostate cancer was also associated to ingestion of apigenin, a dietary flavonoid with proteasome-inhibitory activity. Apigenin induced apoptosis in prostate cancer cells (PC3), without affecting the mitochondrial membrane potential of the cells, showing specifically chymotrypsin-like activity of proteasome with no activity on trypsin and caspase-like activity. This was reflected by the low toxicity against normal prostate cancer cells (RWPE-1). This activity influenced the expression of both ERs in PC3 cells. In fact, ER β is usually downregulated in prostate cancer. Apigenin increased in a dose-dependent manner the expression of ER β and downregulated the expression of ER α . Apigenin displayed a very interesting pharmacological profile and can now be considered as a lead compound for targeting prostate cancer (Singh et al., 2014). Rat with testosterone-induced prostatic hyperplasia were treated with *Pueraria mirifica* (PM) extract, which

contains daidzenin and genistein, and a reduction of the increase in the prostate/body weight ratio was found after treatment, showing a significant inhibition of benign prostatic hyperplasia (Masrudin and Mohamad, 2014). These two compounds were found also to be efficient in reversing DNA methylation in prostate cancer cell lines, such as PC3, DU145 and LNCaP. Interestingly, genistein and daidzein induced a demethylation of all the promoter regions studied, with the exception of those that were unmethylated in control cells, and this action was found to be probably mediated by ER β (Adjakly et al., 2012). Recently, beverage Haelan 951, containing genistein and daidzein, displayed some promising effects on the viability, growth and apoptosis of different human pancreatic cancer cell lines (Rothe et al., 2015).

2.2.5 Colorectal cancer—A blend of ER β agonists and lignin (Eviendep[®], CM&D Pharma Limited, United Kingdom) was used in alimentary supplementation in familial adenomatous polyposis (FAP) patients with ileal pouch-anal anastomosis (IPAA) for three months (5 mg each day at breakfast and dinner). FAP is a disease with autosomal dominant inheritance, patients are exposed to a high risk of developing duodenal adenomas. This study demonstrated that supplementation with Eviendep[®] for a short period (90 d) resulted effective in reducing polyps number by 32% and size by 51%. Moreover, different PhyEs contained in Eviendep[®] are in a lower dose than the effective dose needed for a single component to obtain the same effect, showing a synergistic and/or potentiating effect that is desirable for a long-term exposure (Calabrese et al., 2013). This result supports the protective role of ER β in colorectal carcinogenesis. Genistein also showed a protective role against colorectal cancer *in vivo*. In fact, ovariectomized (OVX) female Wistar rats treated for three weeks with genistein showed a reduced proliferation in ileal and colonic mucosa cells, with an increased rate of apoptosis in the small intestine and colon. These effects were completely antagonized by ERs antagonist fulvestrant (Schleipen et al., 2011). In mice implanted with human colorectal cancer tumors, orally administered genistein did not inhibit tumor growth, but it did inhibit distant metastasis formation, and displayed no toxicity (Xiao et al., 2014). Apigenin and naringenin showed to be effective in the reduction of ER-mediated cell growth in non-malignant young adult mouse colonocytes (YAMC) and, interestingly, when administered in combination, they showed a strong enhanced activity with significantly lower concentration compared to the single administration (Yang et al., 2014). Sylmarin, a less common PhyEs extracted from milk thistle (*Silybum marianum*), showed protective properties against colorectal cancer. In fact, a reduction in the progression of colorectal cancer was observed in male mice fed with a sylmarin-enriched diet, together with an increase level of ER β expression in the intestinal mucosa (Barone et al., 2010).

2.2.6 Osteoporosis—Increasing evidences underline that estrogen receptors, and in particular ER α , might play a crucial role in bone homeostasis. This is supported by the fact that many postmenopausal women are affected by this pathology, in which marked bone resorption is observed (Nilsson et al., 2011). The main strategy used in the treatment of osteoporosis is estrogen replacement therapy (ERT) (Sexton, 2001), but in recent years patients turned their attention to PhyEs composition, due to the fact that a long-term therapy, such as ERT, may induce a series of side effects related to the stimulation of ER α (Harris et al., 2002). Bakuchiol is a meroterpene phenol extracted from the seeds of *Psoralea*

corylifolia, used to treat osteoporosis. This estrogenic component activates both ER subtypes, with a stronger binding affinity for ER α than for ER β (Xin et al., 2010). Also medicarpin, a phytoalexin found in dietary legumes and structurally related to isoflavones, demonstrated to stimulate osteoblast differentiation and mineralization, by increasing ER β expression in osteoblast. Medicarpin acts as an ER agonist in the bone, but, differently from ERT, it does not promote uterus growth. Administration of medicarpin to female Sprague–Dawley rats for 30 days resulted in an increased formation of osteoprogenitor cells in the bone marrow and osteoid formation (mineralization surface, mineral apposition/bone formation rates). Moreover, thanks to its excellent bioavailability, it may be considered as a very interesting option in osteoporosis treatment (Bhargavan et al., 2012). Another PhyEs that proved to inhibit bone loss in ovariectomized mice and rats is equol. Interestingly, all the positive effects of equol were abolished by an estrogen receptor antagonist (ICI182780), showing the implication of ERs in its effects (Wang et al., 2014). Genistein also proved to be potentially useful in the treatment and prevention of osteoporosis, since it partially reversed the detrimental effect of intermittent hypoxia on bone mass and bone strength *in vivo* (Song et al., 2014). Oral administration of ferutinin, a plant-derived ester of a sesquiterpenic alcohol, which acts as an ER α agonist (IC₅₀ = 33.1 nM) and an agonist/antagonist for ER β (IC₅₀ = 180.5 nM), was able to improve bone regeneration of critical-size bone defects *in vivo* (Zavatti et al., 2015). Finally, a recent study revealed that in southern Chinese postmenopausal women the PhyEs dietary intake influences the bone mineral density, depending on the different ER α gene polymorphisms (Luo et al., 2015).

2.2.7 Menopause symptoms—There is a great debate about the use of PhyEs in menopause. In fact, up to now only few studies were carried out in order to evaluate the benefits and the potential side effects of PhyEs in postmenopausal women. For example, PhyEs were evaluated for the treatment of vasomotor symptom (VMS). A recent study evaluated the association of self-reported vasomotor symptom frequency with race/ethnicity among a diverse midlife US population and explored menopause symptom differences by dietary soy isoflavone (genistein + daidzein) consumption. This study confirmed that VMS expression varied by race/ethnicity. In US population it is difficult to evaluate whether these differences could be related to dietary soy intake, due to the extremely low soy intake. Interestingly, headache and pain were more common in American Indian women rather than in Asian Indian women, so VMS may also be related to the different perception of pain depending on different environments (Reed et al., 2013). Among PhyES, *S*-Equol was found to be effective in treating symptoms related to menopause such as vasomotor symptoms and osteoporosis (Jackson et al., 2011). *S*-Equol was used in a randomised, double-blind, placebo-controlled trial in Japanese women aged between 40 and 59 years. Significant improvements were observed in mood-related symptoms in equol-treated women (Ishiwata et al., 2009).

A nice review by Bedell *et al.* analysed the pros and cons of the use of PhyEs in menopause. The key point was that PhyEs were quite a new therapy in the treatment of menopausal symptoms and sometimes different studies produced contrasting results. The main evidence was that all the studies so far analyzed evidenced that PhyEs intake was devoid of serious

adverse effects, although the real beneficial effects were far from be well-established (Bedell et al., 2014).

2.2.8 Cardiovascular diseases—Strong scientific evidence suggests that estrogens might play an important role in cardioprotection and cardiovascular diseases. The mechanisms involved in the cardioprotective role of estrogens are currently under investigation, and there is strong evidence supporting the involvement of both ER α and ER β (Murphy, 2011). PhyEs have been considered for many years as important food components that are useful in preventing cardiovascular diseases, with favorable clinically effects on the low-density lipoprotein (LDL), which is considered to be one of the main responsible factors for the cardiovascular risk (Wroblewski et al., 2010). The analysis of several cohorts studies, which evaluated the association between flavonoids intake and incidence or mortality from cardiovascular disease, revealed that small amounts of flavonoid-based PhyEs may lower the risk of coronary heart disease mortality (Petersin et al., 2012). The association between urinary PhyEs levels and cardiovascular mortality risk was also evaluated, and it was found that enterolignan urinary concentrations were associated with a reduced risk of death from cardiovascular disease, whereas an opposite association was found for urinary concentration of total isoflavones (Reger et al., 2015). These results are consistent with previously published results, which confirmed that enterolignan intake was correlated with elevated high-density lipoprotein (HDL) levels and reduced triglyceride concentrations in US adults (Penelalco et al., 2012). However, it is important to note that that PhyEs metabolism could change among different race and ethnicity, hence these results should be interpreted with caution. The American Heart Association (AHA) does not recommend the use of isoflavone PhyEs supplements in food or pills for the prevention of cardiovascular diseases, since direct cardiovascular health benefits of PhyEs seems to be only marginal, whereas some possible undesired side effects may take place (Sacks et al., 2006).

2.2.9 Other diseases—Daidzein and genistein exerted a variety of effects on catecholamine signaling, including catecholamine synthesis, secretion, and uptake in the adrenal medulla. These findings may provide new insight into the pharmacological potentials of plant flavonoids on the catecholamine system. In particular, daidzein stimulated catecholamine synthesis through plasma membrane estrogen receptors in cultured bovine adrenal medullary cells, which were used as a model of central and peripheral sympathetic neurons (Yanagihara et al., 2014). Genistein proved to be effective against pulmonary hypertension (PH). PH was induced in male rats by using monocrotaline. In this model, genistein-based therapy resulted in significant improvements in lung and heart functions, moreover it reversed PH-induced pulmonary vascular remodeling *in vivo* and inhibited human pulmonary artery smooth muscle cell proliferation *in vitro* through ER β (Matori et al., 2012). Interestingly PhyEs intake can also alter the metabolic profile as demonstrated in rainbow trouts (*Oncorhynchus mykiss*), where genistein and daidzein seem to produce estrogenic effects in liver and to affect growth performance and nutrient partitioning (Cleveland and Manor, 2015).

2.2.10 Interactions with other drugs—Use of soy supplements is increasing among patients, due to their perception that soy PhyEs may have positive effects on their health. It

is important to mention that PhyEs can interfere with other drugs and, therefore, alter their therapeutic efficacy. A recent paper reports that PhyEs dramatically increased the cardiotoxicity in male mice receiving at the same time a chemotherapeutic tyrosine kinase inhibitor, such as Sunitinib. This combination produced an augmented lethality *in vivo* and an increased toxicity in isolated cardiomyocytes, when compared to the administration of Sunitinib alone (Harvey and Lainwand, 2015). Genistein intake was correlated with an enhanced multidrug chemoresistance in hepatocellular carcinoma (Rigalli et al., 2015). Pharmacokinetic interactions of genistein and imatinib were evaluated in rats and genistein seems to decrease imatinib plasma levels probably through effects on cytochrome CYP3A4; however the clinical significance of the pharmacokinetic interaction between imatinib and genistein still needs to be confirmed through further studies (Wang et al., 2015). Therefore, considering the increasing interest and consumption of PhyEs, further studies about PhyEs-drugs interactions are urgently needed, since it is now proved that PhyEs intake can alter the efficacy and the safety of several drugs.

2.3 Mycoestrogens: zearalenone

Food can be contaminated by naturally-occurring mycoestrogens, which are estrogens produced by fungi. One of the most widely diffused mycotoxin is zearalenone (Figure 6), a resorcylic acid lactone produced by *Fusarium* species, in particular *Fusarium graminearum* and *Fusarium culmorum*, which is frequently found as contaminant in corn, oats, wheat, and rice. Zearalenone is a potent ERs agonist with an IC₅₀ in the nanomolar range (ER α -RBA = 4.3%, ER β -RBA = 6.0%). Thus, zearalenone enters the food chain and represents a serious risk for both animals and humans (Takemura et al., 2007). Several adverse effects were associated to zearalenone exposure in animals. For example, cases of ovarian atrophy, prolonged estrus, persistent corpora lutea, false pregnancy, decreased fertility, stillbirth, implantation failure and delivery of weak piglets were observed in sexually mature female pigs (Malekinejad et al., 2005). Moreover, zearalenone was found to negatively affect the reproductive system of males, mostly by decreasing sperm counts and viability (Filannino et al., 2011). However, zearalenone is rapidly metabolized, in particular its glucuronidation represents an important and fast reaction of detoxification (Frizzel et al., 2015).

2.4 Drugs of abuse: Δ^9 -tetrahydrocannabinol

Several compounds, both of natural and synthetic origin, were found to bind the ERs as off-targets, thus representing an important problem due to the possible side effects related to their probable behavior as endocrine disruptors. An example is represented by Δ^9 -tetrahydrocannabinol (Δ^9 -THC, Figure 6), which is a biologically active component found in Marijuana, a widespread recreational drug of abuse and a recently recognized efficient therapeutic agent in support to cancer patients. Δ^9 -THC exhibited a variety of pharmacological and toxicological effects, such as analgesia, hypotension, reduction of inflammation and anticancer effects. However Δ^9 -THC is also well known for its psychotropic effects. Recently Δ^9 -THC was recognized to produce endocrine disrupting effects, in particular on reproductive behavior, by altering the ER α /ER β ratio in cells, via an up-regulation of ER β (Takeda, 2014). These evidences are important and, if confirmed, Δ^9 -THC should be considered as an established estrogenic EDC.

3. Synthetic xenoestrogens: Endocrine Disrupting Chemicals (EDCs)

The human organism is exposed to several substances, especially from the environment, which could cause severe adverse effects and pathologies, by acting as endocrine disrupting compounds. Among these substances one of the major class is represented by synthetic xenoestrogen (Figure 7). These compounds are able to bind to the ERs by means of various types of protein-ligand interactions, which affect their different affinity and selectivity. A recent correlative analysis study revealed that these chemicals, displaying binding affinities ranging from subnanomolar to micromolar values, act in a subtype-dependent manner as full agonists or partial agonists/antagonists, by using different combinations of the activation functions 1 and 2 of ER α and ER β (Delfosse et al., 2015).

Most of the synthetic xenoestrogens that may be found in the environment and, therefore, in food, are structurally related to natural estrogens and possess estrogenic activities. Among them there are, for example, synthetic hormones (such as ethynylestradiol EE₂, present in birth control pills), compounds commonly used in personal care products due to their antibacterial properties (such as parabens), and pesticides. One of the most dangerous class is represented by bisphenols, synthetic compounds that are used in the production of certain plastics and resins (Delfosse et al., 2015). Several bisphenols were found to be estrogenic EDCs by binding to both receptor subtypes (Stossi et al., 2014). One of the most widely diffused and dangerous synthetic xenoestrogen is bisphenol A (BPA), which is widely produced and largely diffused in the environment and in foodstuff, such as plastic bottles and thermal paper. The increasing interest in studying BPA actions is due to the fact that BPA exposure may be associated to the development of several types of hormone-related cancers (Gao et al., 2015) and to the alteration of the neuroendocrine system, which could affect brain development and produce physiological/behavioral effects (Rebuli et al., 2014). To avoid these problems, nowadays BPA has been replaced by other bisphenols, such as bisphenol S (BPS). However, also this derivative shows some cardiotoxicity in female rat hearts, just like BPA (Gao et al., 2015). In addition, BPA metabolites formation should be seriously taken into due consideration. In fact, BPA is rapidly converted *in vivo* to BPA-glucuronide (BPA-G), which constitutes its predominant metabolite. BPA-G has long been believed to be biologically inactive, because it lacks estrogenic activity. Nevertheless, it was recently shown that BPA-G induces adipogenesis, and this effect was not observed in the presence of ERs-antagonist fulvestrant, thus suggesting that BPA-G-generated adipogenesis follows an estrogenic pathway (Boucher et al., 2015). Halogenated bisphenols A (H-BPAs), such as tetrachlorobisphenol A (TCBPA), which are widely used in industrial production of several materials, were found to be present in various environmental matrices and detected in human serum and breast milk. Furthermore, they showed to be more potent toxicants than BPA itself (Song et al., 2014). Synthetic xenoestrogens are generally pervasive and widely dispersed in the environment and may bio-accumulate. In fact, these chemicals typically end up in either stormwater or wastewater, with a potentially serious impact on aquatic life and wildlife. This is a very important problem related to food contamination, including also fruits and vegetables, since vegetable fields are principally irrigated by reclaimed water, which often contains considerable amounts of these EDCs (Sidhu et al., 2015). Fruits and vegetable represent also one of the main human exposure sources to organochlorine

pesticides, dangerous compounds related with increased risk of developing several hormonally-related cancers (Lerro et al., 2015). The increasing interest in the determination of these chemicals is due to consolidated evidences underlining their role in the pathogenesis of several diseases such as cancer, obesity (Yang et al., 2015), diabetes (Chevalier and Fenichel, 2015) and reproductive pathologies (Kumar and Holt, 2015). EDCs exposure is particularly dangerous during childhood. In fact it was estimated that EDCs exposures in the EU substantially contributed to the development of obesity and diabetes, with a moderate probability of €18 billion costs per year. These results further emphasize the need to control EDCs exposures and diffusion in the environment (Legler et al., 2015). Moreover, nearly €15 billion annual costs in the EU were associated with male reproductive disorders and diseases due to EDCs exposure. These estimates represented only a few EDCs for which there were sufficient epidemiological studies and those with the highest probability of causation (Hauser et al., 2015). However, one of the major costs/year was attributed to neurobehavioral deficits and disease derived from EDCs exposure, with a high probability of >€150 billion costs/year (Bellanger et al., 2015).

Several diseases, such as those affecting female and male reproductive systems, neurodevelopment, metabolic disorders and thyroid, were confirmed to be correlated to EDCs exposure by the WHO in 2012 (WHO/UNEP, 2013). Moreover, it nowadays evident that human fertility rates are declining all over the world, especially in industrialized countries. It is worthwhile mentioning that exposures to these substances during pregnancy may be really dangerous for the health of the fetus and produce negative effects during the growth of the child (WHO/UNEP, 2013). In addition, it is important to note that EDCs do not interact only with ERs, but also with a large panel of other nuclear receptors comprising the androgen receptor, the estrogen-related receptors and the retinoid X receptors (Grimaldi et al., 2015), therefore some of their effects on human health might not be necessarily due to the activation of estrogenic pathways.

Hormones were also found to be added illegally in some categories of food. For example, in recent years several emerging healthcare anti-aging products indicated to regulate blood pressure and blood glucose, contain substances, such as estradiol and 17 α -ethinylestradiol, that are illegally used to improve the potency of these products (He et al., 2014).

Finally, 2,3,7,8-tetrachloro-*p*-dioxin (TCDD) is one of the most relevant member of the general class of dioxins, which are persistent environmental contaminants. TCDD is produced as a side-product during chemical synthesis, especially of some herbicides, or as a byproduct of combustion of some organic compounds. TCDD is able to produce estrogenic effects in various tissues, since it binds to the aryl hydrocarbon receptor (AhR), which then interacts with the ERs and elicits an AhR-mediated estrogenic action (Boverhof et al. 2006).

An important aspect related to monitoring EDCs exposure levels in humans is the reliability of the analysis of samples and the identification and quantification of EDCs. In fact samples are often constituted by complicated matrices, where initially the compound of interest must be extracted from, then isolated, identified and quantified. Several analytical methods are nowadays available to detect estrogenic EDCs, depending on the nature of the sample to analyze (milk, meat, miscellaneous matrices, fish, packaging materials, etc) in a cost-

effective way, and increasing efforts in finding more sensible and accurate analytical methods are currently underway (Adamusova et al., 2014; Capriotti et al., 2013; Wang et al., 2008; Kudlaka et al., 2015; Rotroff et al. 2014).

3.1 EDCs in foodstuff

EDCs are widely diffused in food, as shown by the high number of studies on different food samples which confirm their presence in them. For example, BPA was detected in all vegetable and fruit samples including pumpkin, sweet potato, citrus, and apple from local markets (Lu et al., 2013). Fruits and vegetables can be exposed to synthetic xenoestrogens during the irrigations process, in which plants are irrigated with wastewater effluents and freshwater and treated with several types of biosolids. All these factors influence their content of estrogenic compounds. Biosolids had a minor effect on hormones content, whereas irrigation water, which contained significant amounts of hormones, had the most substantial effect for example on the EDCs content in lettuce (Shargil et al., 2015). In a separate study samples of food and milk infant formula were found to possess estrogenic activity, showing that estrogenic compounds were omnipresent in foodstuff and were not limited to soy-based food (Behr et al., 2011). Xenoestrogenic compounds may also be found among food preservatives. For example, butylated hydroxyanisole (BHA), an antioxidant consisting of a mixture of two regioisomeric organic compounds, 2-*tert*-butyl-4-hydroxyanisole and 3-*tert*-butyl-4-hydroxyanisole, is used as a food additive (E320). Contrasting results have so far been reported, since a study described BHA as an ERs agonist (Ter Veld et al., 2006), whereas another one considered it as an anti-estrogenic compound, which was able to decrease uterine weight in immature female rats (Kang et al., 2006).

Synthetic xenoestrogens are also present in food packages and can pass from package to food. A recent study analyzed food contact material samples for their (anti)-estrogenic and (anti)-androgenic activity. Estrogenic activity was detected in 7 of 10 of bottle water samples and in 44% of food packaging samples (Mertl et al., 2014).

BPA is widely present in thermal paper receipts. Nevertheless, a study analyzing BPA urine content in volunteers who normally handle BPA-containing thermal paper receipts (either professionally or as consumers) seems to indicate that this type of exposure has a limited effect on systemic BPA levels (Porras et al., 2014). In addition to BPA, also terephthalic acid (TPA), a major chemical precursor of polyethylene terephthalate (PET) containers that are used for food storage and beverages, was found to increase the ER α :ER β ratio in human breast cells, suggesting an estrogenic effect. Moreover, in addition to its carcinogenic potential, TPA also promoted resistance to tamoxifen induced apoptosis (Luciani-Torres et al., 2015). These chemicals were found also in animal foodstuff, with most samples showing significant estrogenic activities and high BPA contents (Wang et al., 2014).

3.2 Synthetic xenoestrogens and personal-care products

Xenoestrogenic EDCs are broadly diffused in personal care products which are daily used by people. A class of compounds of interest, due to their possible estrogenic activity, comprises parabens, which are alkyl esters of *p*-hydroxybenzoic acid. Parabens are

extensively used in cosmetics, pharmaceuticals, personal care products and also in food products due to their antimicrobial activity. In addition to food ingestion, exposure to parabens may occur through skin, lips, eyes, oral mucosa, nails and hair. Due to their efficient antibacterial and fungicidal properties, stability at different pH values and temperatures and low cost, there is a widespread chronic human exposure to parabens. Therefore, these compounds have been considered as endocrine disruptors to be controlled for their possible adverse effects. Parabens are considered as weak estrogenic agents and their estrogenic activity is considerably lower than that of 17 β -estradiol, but it is not negligible, as demonstrated by several studies which reported their estrogenic activity in cells (Karpuzoglu et al., 2013). Rats and rabbits exposed to parabens (such as methyl, ethyl or butyl parabens) showed that these chemicals were taken up in considerable amounts, but then they were rapidly hydrolyzed and excreted. Nevertheless, these *in vivo* experiments underlined that daily sperm production and serum testosterone levels were negatively affected by parabens, which also produced uterotrophic effects in ovariectomised rats. Almost all the currently known parabens resulted positive in estrogenic assays. Estrogenic potency of these derivatives increases with the alkyl chain length. Moreover, long chain parabens also seem to be more toxic. It is important to note that parabens have also been used in baby and children products, thus representing a serious risk for their health and development (Bobjer et al., 2010). ER α expression was found to be increased in MCF7 cancer cells that had been exposed to parabens, thus confirming that these compounds actively contribute to breast cancer progression. Interestingly, parabens action was prevented by ERs blocker ICI182780 in MCF7 cells but not in non-cancerous breast cells, suggesting a different mechanism of action for these two cell lines (Wrobel and Gregoraszczuk, 2014).

Among personal care products, some estrogenic compounds are used as UV filters in cosmetics, topical sunscreens in lotions, and hair sprays to protect skin and hair from UV irradiation. For example, 4-methylbenzylidene camphor (4-MBC) is a widely used UV absorbing substance used in sunscreen products. It was demonstrated that 4-MBC binds to ERs, although its affinity is not extremely high (Klann et al., 2005). Nevertheless, 4-MBC is potentially dangerous for two reasons: 1) its estrogenic activity can directly be harmful to humans who abundantly use products where it is contained; 2) its dispersion in water and its consequent bioaccumulation in aquatic species poses a serious environmental concern. In fact, a high bioaccumulation of UV filters was demonstrated in seawater samples from beaches in Gran Canaria Island (Rodriguez Sanchez et al., 2015), and high levels of 4-MBT were found in fish from Iberian river basins (Gago-Ferrero et al., 2015). Another widely diffused UV filter is benzophenone 2 (BP-2). Here again, high levels of this compound were found in aquatic species. It is important to note that BP-2 exposure in fish produced estrogenic effects through ER α on vitellogenin induction, secondary sex characteristics, gonadal development and reproduction (Weisbrod et al., 2007).

3.3 EDCs in the environment and effects on wildlife and aquatic species

Considering the wide range of diffusion of estrogenic EDCs in the environment in the past few decades, it is not surprising that in recent years many researchers turned their attention to the study of the effects of these compounds in animal models. Aquatic habitat is highly contaminated by EDCs. These chemicals were detected in almost all aquatic sources tested

and, most importantly, in many cases their contents were above bioactive concentrations. The effect of BPA exposure in aquatic species consisted in activation of the ERs, increase of brain aromatase activity, disruption of gametogenesis in both males and females, altered development (neuronal, cardiac, germ cells, and sexual differentiation) and changes in sex ratios after embryonic exposure (Bhandari et al., 2014). It should be noted that the effects of exposure to these chemicals may vary from species to species (Segner et al., 2013), and this could be partially explained by considering the differences in the receptor ligand binding domains and, consequently, in the different interaction of xenoestrogens with the ERs of each species (Miyagawa et al., 2014).

A recent study reported the presence of several bisphenol (BP) derivatives detected in different samples of sewage sludge collected from wastewater treatment plants in China. Estrogenic activity was detected by using a bioluminescence yeast estrogen screen (BLYES) assay and all the collected samples showed significant estrogenic activities. When the same assays were repeated in the presence of ICI182780, a potent ERs antagonist, a marked reduction in the bioluminescence was observed, indicating that BPs induced bioluminescence by activating the ERs. This study underlined that BPs are widely diffused in China representing an emerging problem about the presence of estrogenic contaminants that are potentially dangerous for human health (Ruan et al., 2015).

Pharmaceutical estrogens, such as ethynylestradiol (EE₂), which is used in contraceptive formulation, currently represents an emerging environmental problem (Khan et al., 2014). The affinity of EE₂ for the human ERs is considerably higher than that of estradiol. Moreover, due to its nonpolar and hydrophobic character, it is resistant to biodegradation and it is nowadays widely diffused in the environment. The effects observed in exposed organisms were determined by the analysis of male and female fish plasma vitellogenin, an estrogen-inducible yolk precursor protein which is normally produced only in mature female fish. The results indicated progressively and time-dependent increased amounts of this protein, accelerated proportions of intersex fish, decreased eggs and sperm production, reduced gamete quality, completed feminization of male fish, reduced fertility and fecundity and also behavior changes. Although aquatic species in early life seemed to be more sensible to EE₂ exposure, EE₂ also proved to be extremely toxic to adult aquatic organism. Furthermore, vertebrates, including mammals, proved to be sensible to EE₂ exposure, in particular during their postnatal development (Aris et al., 2014).

Dioxins, in particular TCDD, are persistent environmental contaminants with EDCs properties, which significantly affect wildlife. In addition to their direct interference with the endocrine system, which are mostly related to reproduction and pregnancy, they cause a wide variety of other toxic effects, such as carcinogenicity, hepatotoxicity, and immunosuppression (Radenkova-Saeva J. 2009). These effects are particularly dangerous because these compounds are very resistant to metabolism and biodegradation.

It should be noticed that aquatic species, such as fish, amphibians, aquatic reptiles and mammals, are most affected by EDCs exposures and their population is declining in contaminated areas. This phenomenon may be associated to the negative effects of EDC on fertility. However similar effects have also been observed in terrestrial species. This has a

profound impact on humans, since we are at the top of the food chain and our eating habits may expose us to risky levels of EDCs.

3.4 Effects of EDCs on human health

Disruption of ER signaling by EDCs has been demonstrated to produce adverse effects on human health and, in particular, on fertility, pregnancy and fetus development. Hyperplasia of endometrial glands, dystocia, prolapse of the uterus and infertility were observed in sheep and in other ruminants species exposed to forages containing estrogenic contaminants (Bazer et al., 2014). One of the main class of compounds affecting pregnancy is represented by organochlorine pesticides. The effect of exposure to methoxychlor (MXC), a weak synthetic estrogen used as a pesticide with estrogenic, anti-estrogenic and anti-androgenic activities, was evaluated in male fetal and neonatal rats. In this study, MCX exposure during embryonic and postnatal development reduced body weight and bone size; moreover cortical porosity resulted negatively affected compared to control. MXC might act as an ER β antagonist, thus inhibiting the proper mineralization of the developing skeleton, however significant differences may be observed in different species (Fagnant et al., 2014). In addition, it should be considered that the major metabolite of MXC, hydroxyphenyltrichloroethane (HPTE), is even more potent than MCX as an EDC (Uzumcu et al., 2006).

Another dangerous substance widely used as pesticide in last decades is dichlorodiphenyltrichloroethane (DDT), it was showed that stimulation of membrane estrogen receptor seemed to play an important role in the propagation of DDT-induced apoptosis during the early stages of neural development (Kajta et al., 2014). Among other chlorinated pesticides, dichlorodiphenyldichloroethylene (DDE) proved to negatively affect pregnancy. In fact the presence of DDE and other organochlorine pesticides in maternal blood and placental tissue represents a very dangerous prenatal exposure hazard for fetuses, due to chronic bioaccumulation and poor elimination, with possible deleterious effect on pregnancy and fetus health (Tyagu et al., 2015). Chlordecone, an organochlorine insecticide which has been widely used in the French West Indies until 1993, resulted in a long-term soil and water contamination. Chlordecone exposure through contaminated food during critical periods of development (gestation and early infancy) was found to negatively affect infant growth (Coste et al., 2015).

Another dangerous class of pesticides are the polychlorinated biphenyls (PCBs), industrial chemicals historically used as pesticides, coolants or heat transfer agents in electrical transformers, which showed estrogenic or anti-estrogenic activities (Zhang et al., 2014). Due to their elevated toxicity, PCBs use was banned in 1979. However, due to their widespread use, these compounds are still present in several food supplies (fish, dairy, hamburger, and poultry being the most contaminated) and in our bodies. In particular, PCBs exposure could cause long-term health problems, such as neurological and hormonal diseases, especially for those who were exposed *in utero* (Crinnion, 2011).

4-*tert*-Octylphenol, another EDCs extensively used in industry and widely diffused in the environment, displayed adverse effects on fat metabolism in pregnant rats, by inhibiting fat deposition via an interference with the regulation of lipogenic genes in the liver and adipose

tissue. This alteration might affect the nutrition balance during pregnancy and can cause metabolism-related diseases, however the exact role of the ERs in these alterations was not investigated in more details (Kim et al., 2015).

BPA fetal exposure was studied in mice and it seemed to advance puberty onset, disturb estrous cyclicity, increase body weight gain, and cause fertility problems, which became more severe with age. Therefore, it is possible that BPA prenatal exposure in humans may affect the development and function of the uterus, which lead to early and late pregnancy losses (Wang et al., 2014). In addition, BPA exposure during early pregnancy affects placenta morphology and angiogenesis in mice. Embryonic structures (head, forelimb) also showed some alterations, potentially related to unbalanced embryonic nutrition and/or to modulation of genes involved in embryo development. These findings support the fact that placenta is directly involved in the effects of BPA, even at environmentally relevant dose levels (Tait et al., 2015). Moreover, the first emerging studies evaluating the effects of BPA exposure in several generations of mice underlined that some reproductive dysfunctions in female mice can be transgenerational in nature (Ziv-Gal et al., 2015).

Fetal exposure to BPA was evaluated by analyzing the correlation between placental BPA concentration, infant birth weight and other maternal and infant parameters in the southeastern USA. All placenta samples contained quantifiable amounts of BPA and fetal growth was found to be affected by this EDC. This evidence was found to be particularly alarming, since BPA detoxification is lower in fetus liver than in that of adults (Troisi et al., 2014). It should be considered that the effects of BPA exposure during pregnancy and early life may also appear only in adulthood. Perinatal exposure to BPA and to other EDCs can influence the behavior in adulthood, often leading to parental and social behavior problems. For example, rodents exposed to synthetic xenoestrogens (BPA and phthalates) during perinatal period showed compromised social behavior (Rosenfeld, 2015). Additional studies evaluated the correlation between prenatal BPA exposure and the behavior of children in school age. The negative effects linked to this exposure seem to be gender-dependent, with boys being more affected than girls. In particular, children exposed to BPA during pregnancy showed altered behavior with depression problems, somatic complications and oppositional/defiant behavior at age 6–10 (Evans, 2014). More recently, BPA exposure in early life was correlated with an altered susceptibility to tumor formation in particular sites, such as prostate and breast. This could be due to an epigenetic reprogramming of these tissues depending on the activation of a non genomic response by BPA and other EDCs (Trevino et al., 2015). BPA exposure during fetal life is currently being considered as a time bomb for prostate cancer. In fact, during embryonal development, prostate stem cells mainly have an epithelial structure and some of them persist during adulthood. It was observed that when these cells were exposed to estrogen-like endocrine disruptors, they become more prone to abnormal growth, leading to cancer (Lobaccaro and Trousson, 2014). BPA exposure was also evaluated in prepubertal and adult rats, alone or in combination with PhyEs genistein. Rats assumed BPA, genistein or a combination of both through lactation. Then cells apoptosis, proliferation and protein expression were investigated, with a particular focus on mammary gland modifications. BPA exposure increased cell proliferation in mammary gland of adult PND50 rats, a process associated with an increased risk of chemically-induced cancer development. On the other hand, genistein exposure stimulated cell

proliferation in prepubertal rats, a process that correlates with mammary gland maturation and chemoprevention. Interestingly, the combination of both of them produces the same effect as that of genistein alone, which induces mammary gland maturation, thus suggesting mammary chemoprevention (Wang et al., 2014).

In addition to bisphenols, another chemical class of substances that are used as plasticizers and frequently found in several food products is represented by phthalate esters, which can exert adverse effects on human reproduction. Among them, dibutyl phthalate (DBP) is one of the most commonly diffused. DBP perinatal exposure significantly increases estradiol and decreased testosterone serum levels in immature offspring rats. It also up-regulates the aromatase level and down-regulated the expression of ER β , which may cause neurotoxicity in immature offspring (Li et al., 2014). However, the interaction of DBP with the ERs is not completely understood yet (Rouiller-Fabre et al., 2015). In utero exposure to another plasticizer, butyl benzyl phthalate, induced a delayed pubertal onset and modified the morphology of the mammary gland. In addition, modifications in gene expressions that are associated with an increased susceptibility to carcinogenesis were observed (Moral et al., 2011). Interestingly, the metabolites levels of another phthalate, di-(2-ethylhexyl)phthalate, in urine proved to be related with obesity and insulin resistance in humans (Smerieri et al., 2015).

However, EDCs may also cause other types of pathologies, which are not strictly related to reproduction, such as hepatotoxicity, immunosuppression, type 2 diabetes, and cancer (Soto et al. 2010).

4. Conclusion

The wide diffusion of xenoestrogens in the environment and the high probability of exposure to them, especially in the food chain, make this class of compounds a urgent concern to be taken care of. PhyEs intake has rapidly increased in recent years, due to the growing number of marketed soy-based products, and supported by several evidences that underline the important role of PhyEs enriched food in health prevention. People generally prefer natural products to classical therapeutic treatments, perceiving PhyEs as safer and deprived of significant side effects, which are instead typical of standard therapies. Nevertheless, this general conviction misjudges the problems that may be encountered with PhyEs intake, since there are contrasting data about these products and, in particular, no clear results deriving from clinical trials are currently available. Moreover, the correlation of PhyEs efficacy with the race and ethnicity (Asian vs European) contributes to the questionable use of PhyEs. PhyEs may actually represent an important class of alternative therapeutic agents in several pathologies, however further information and studies are necessary to have a better understanding of the real benefits compared to the possible problems related to their use.

In general, EDCs' influence in biological systems represents a global problem and interdisciplinary studies are increasing in order to evaluate the environmental fate, endocrine potential, metabolic pathways and toxic effects related to EDCs exposure. Human exposure to EDCs is inevitable and people are daily exposed to these chemicals through both the consumption of contaminated food and the use of industrial products containing them, most

often in chronic low doses. The long-term exposure may adversely affect the endocrine system, leading to a negative impact on health and, unfortunately, this is far to be exactly established. Many sources of EDCs are still not known, because of insufficient reporting and information on chemicals in products, materials and goods and this lack of information worsens the present situation. EDCs have been widely found in materials used by infants and children, such as baby bottles, as well as in food and breast milk. This is a major problem since young people generally have higher exposure to chemicals due to their higher metabolic rates, higher amounts of ingested food, drink and air per body weight, when compared to those in adults, as well as higher hand-to-mouth and object-to-mouth activities. Moreover, it has been shown that exposure to EDCs in pre-birth or early life may sometimes manifest only later in life or even in future generations, making risk evaluations very difficult. Therefore, more scientific evidence is badly needed to identify the effects of EDCs in humans.

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Figure 1.
Human exposure to alimentary sources of xenoestrogens.

Figure 2.
Classification of xenoestrogens.

Figure 3.
Chemical structures of lignans and their metabolites enterolignans.

Phytoestrogens: Flavonoids and Chalcones

Figure 4.
Chemical structures of flavonoids and chalcones.

Phytoestrogens with different chemical structures

Figure 5.
PhyEs with different chemical structures.

Mycoestrogens

Zearalenone

Drug of abuse

Δ^9 -Tetrahydrocannabinol
(Δ^9 -THC)

Figure 6.
Chemical structures of other natural xenoestrogens.

Figure 7.
Chemical structures of synthetic xenoestrogens.

Table 1

Natural xenoestrogens: Biological activities and sources.

Natural Xenoestrogens	Compounds	Activities ¹	Sources ²
Lignans ³	Lariciresinol	Cardioprotective (clinical trial) Reduced risk breast cancer (<i>in vitro</i>)	berries, seeds, grain, nuts, fruits and cruciferous vegetables
	Matairesinol		
	Pinoresinol		
	Secoisolariciresinol		
Phytoestrogens	3-(2',4'-Dihydroxybenzyl)-5,7-dihydroxy-6-methylchroman-4-one	<i>In vitro</i> estrogenic activity (ER β)	<i>various</i> ⁴
	3-(4'-Dihydroxybenzyl)-5,7-dihydroxy-6-methylchroman-4-one	<i>In vitro</i> estrogenic activity (ER β)	<i>various</i> ⁴
	3- <i>O</i> -Methylquercetin	<i>In vitro</i> estrogenic activity (ER β)	<i>Liriope platyphylla</i> aerial part
	6-(1,1-Dimethylallyl)genistein	<i>In vitro</i> estrogenic activity	Derived from genistein metabolism in plants
	6-(1,1-Dimethylallyl)naringenin	<i>In vitro</i> estrogenic activity	Derived from naringenin metabolism in plants
	6- <i>C</i> -Methylquercetin-3-methyl ether	<i>In vitro</i> estrogenic activity (ER β)	<i>Liriope platyphylla</i> aerial part
	7-Hydroxy-6,4'-dimethoxyisoflavone	<i>In vitro</i> estrogenic activity	<i>Butea superba</i> Roxb.
	8-Prenylgenistein	<i>In vitro</i> estrogenic activity	Derived from genistein metabolism in plants
	8-Prenylnaringenin	<i>In vitro</i> estrogenic activity	Derived from naringenin metabolism in plants
	Apigenin	Protective role in prostate cancer cells (<i>in vitro</i>) Protective role in colorectal cancer cells (<i>in vitro</i>)	Parsley and mint
	Calycosin	Inhibition proliferation MCF7 cells (Akt) (<i>in vitro</i>)	<i>various</i> ⁴
	Daidzein	Neuroprotective (<i>in vitro</i>) Protective role in prostate cancer cells (<i>in vivo</i>)	Soy

Natural Xenoestrogens	Compounds	Activities ¹	Sources ²
	Daidzin	<i>In vitro</i> estrogenic activity	<i>Pueraria Mirifica</i> leaves
	Genistein	Neuroprotective (<i>in vivo</i>) Protective in AD (<i>in vivo</i>) Protective in PD (<i>in vivo</i>) Reduce symptoms of multiple sclerosis (<i>in vivo</i>) Protective role in colorectal cancer (<i>in vivo</i>) Protective role in prostate cancer (<i>in vivo</i>) Osteoporosis (<i>in vivo</i>) Increased breast cancer risk (<i>in vitro</i>)	Soy
	Genistin	<i>In vitro</i> estrogenic activity	<i>Pueraria Mirifica</i> leaves
	Glabridin	<i>In vitro</i> estrogenic/antiestrogenic activity	<i>Glycyrrhiza glabra</i> root
	Kaempferol	<i>In vitro</i> estrogenic activity (ER β)	
	Kwakhurin	<i>In vitro</i> estrogenic activity	<i>Pueraria Mirifica</i> tuberous root
	Liquiritigenin	Antinociceptive activity (<i>in vivo</i>)	<i>Glycyrrhiza uralensis</i> root
	Naringenin	Protective role in colorectal cancer (<i>in vitro</i>) Protective in AD (<i>in vivo</i>)	<i>Rhizoma drynariae</i>
	Naringin	<i>In vitro</i> estrogenic activity	<i>Rhizoma drynariae</i>
	Puerarin	Protective in PD (<i>in vitro</i>)	<i>Pueraria Mirifica</i> leaves
	Quercetin	Activate ER α in MCF7 cells (<i>in vitro</i>) Protective role in endometrial cancer (<i>in vivo</i>)	Mango fruit, lovage and dill
	Scutellarin	Protective in AD (<i>in vivo</i>)	Soy, <i>Erigeron bevicarpus</i> , <i>Zingiber officinalis</i> and <i>Annonum subulatum rox</i>
	S-Equol ⁵	Protective role in prostate cancer (<i>in vivo</i>) Osteoporosis (<i>in vivo</i>)	Milk thistle

Natural Xenoestrogens	Compounds	Activities ¹	Sources ²
Chalcones	Sylimarin	Menopausal symptoms (clinical trial)	<i>various</i> ⁴
	Isoliquiritigenin	Increased breast cancer risk (<i>in vitro</i>)	<i>Glycyrrhiza glabra</i>
	Bakuchiol	<i>In vitro</i> estrogenic activity	<i>Psoralea corylifolia</i> seeds
	β -Thujaplicin	Reduced breast cancer risk (<i>in vitro</i>)	<i>Chamaecyparis octusa</i>
	Coumestrol	<i>In vitro</i> estrogenic activity (ER β)	<i>various</i> ⁴
	Ferutinin	Osteoporosis (<i>in vivo</i>)	<i>Ferula hermonsis</i> root
	Glyceollin I	Neuroprotective (<i>in vivo</i>) Reduced breast and ovarian cancer (<i>in vivo</i>) ϕ	Soybeans (cultured with fungi)
	Glyceollin II	Neuroprotective (<i>in vivo</i>) Reduced breast cancer risk (<i>in vivo</i>) ϕ	
	Glyceollin III	Neuroprotective (<i>in vivo</i>) Reduced breast cancer risk (<i>in vivo</i>) ϕ	
	Mangiferin	ER α activation in MCF7 (<i>in vitro</i>)	
	Medicarpin	Osteoporosis (<i>in vivo</i>)	Mango fruit
	Norathyniol	ER β activation in MCF7 cells (<i>in vitro</i>)	Mango fruit
	Oleocanthal	<i>In vitro</i> estrogenic/antiestrogenic activity	Olive oil
	Pterostilbene	Neuroprotective (<i>in vitro</i>)	Grapes and berries
Mycoestrogens	Zearalenone	False pregnancy (<i>in vivo</i>) Decreased fertility (<i>in vivo</i>) Negatively affects male reproductive system (<i>in vitro</i>)	Contaminant in corn, oats, wheat, rice (produced by <i>Fusarium</i> species)

Natural Xenostrogens	Compounds	Activities ¹	Sources ²
Drugs of abuse	⁹ -Tetrahydrocannabinol	Affects ER α /ER β ratio (<i>in vitro</i>) and reproductive behavior.	Marijuana

¹The activity is mediated by interaction with ERs.

²For details, see USDA database. The origin is reported when specified in the reference paper.

³Metabolized to active enterolignans (enterolactone and enterodiol).

⁴Generally found in: soybean, plants, berries, wine, seeds, grains, nuts and legumes.

⁵Metabolized from daidzein by bacterial flora in the intestine.

⁶Tested as a mixture of Glyceollin I, II and III.

Table 2

Synthetic xenoestrogens: Biological activities and sources.

Synthetic Xenoestrogens	Activities	Sources
4- <i>tert</i> -Octylphenol	Negatively affects pregnancy and development	Generally found in plastic and, consequently, as contaminants in foodstuff, fruits and vegetables.
Benzylbutylphthalate	Negatively affects pregnancy and development	
Bisphenol A (BPA)	Correlated with hormone related cancer Alteration neuroendocrine system Altered development observed in aquatic species Negatively affects pregnancy and development	
Bisphenol A glucuronide	Generates adipogenesis (<i>in vivo</i>)	
Bisphenol S	Cardiotoxicity	
Di-(2-ethylhexyl) phthalate	Negatively affects pregnancy and development	
Dibutyl phthalate	Negatively affects pregnancy and development	
Terephthalic acid	<i>In vitro</i> estrogenic effect	
Tetrachlorobisphenol A	More toxic than BPA, Potentially carcinogenic	
Ethinil estradiol	Reduced fertility and fecundity Behavior changes in aquatic species	Pharmaceuticals (found in aquatic environment)
Butylparaben	<i>In vitro</i> estrogenic activity Increased breast cancer risk	Personal care products [/]
Ethylparaben		
Methylparaben		
Butylated hydroxyanisole	<i>In vitro</i> estrogenic/antiestrogenic activity	Food preservatives
Benzophenone-2	<i>In vitro</i> estrogenic activity	UV Filters in cosmetic and topical sunscreens [/]
4-Methylbenzylidene Camphor	Highly diffused in aquatic environment	

Synthetic Xenoestrogens	Activities	Sources
Polychlorinated biphenyls	Neurological and hormonal diseases	Used as coolant, plasticizers and pesticides and found in several food supplies
Chlordecone	Associated with hormone related cancer Negatively affects pregnancy and development	Pesticides (fruits and vegetables)
Dichlorodiphenyldichloroethylene		
Dichlorodiphenyltrichloroethane		
Hydroxyphenyltrichloroethane		
Methoxychlor		
TCDD	Carcinogenicity, hepatotoxicity, immunotoxicity reproductive and developmental toxicity	Environmental contaminant

Direct contact to human and indirect exposure through aquatic environments.