Review

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Abstract: The microbiota is now recognized as one of the major players in human health and disease, including cancer. As regards breast cancer (BC), a clear link between microbiota and oncogenesis is still to be confirmed. Yet, part of the bacterial gene mass inside the gut, constituting the so called "estrobolome", influences the sexual hormonal balance and, since the increased exposure to estrogens is associated with an increased risk, it may impact on the onset, progression, and treatment of hormonal dependent cancers, which account for more than 70% of all BCs. The hormonal dependent BCs are also affected by environmental and dietary endocrine disruptors and phytoestrogens which interact with microbiota in a bidirectional way: on one side disruptors can alter the composition and functions of the estrobolome, on the other the gut microbiota influences the metabolism of endocrine active food components. This review highlights the current evidence about the complex interplay between endocrine disruptors, phytoestrogens, microbiome, and BC, within the frames of a new "oncobiotic" perspective.

Keywords: microbiome; endocrine disruptors; estrobolome; personalized medicine; oncobiotic

1. Introduction

Breast cancer (BC) is currently one of the most prevalent cancers, with an estimated number of 2.3 million new cases worldwide [1] and represents the 5th cause of cancer-related deaths [2].

The BC incidence is expected to increase further, particularly in low- and medium-income countries, due to the westernization of lifestyles (e.g., delayed pregnancies, reduced breastfeeding, low age at menarche, lack of physical activity and poor diet), more accurate registration of cancer cases and improved cancer detection [3]. Current projections indicate that by 2030 the number of new cases diagnosed will reach 2.7 million annually [4].

The World Health Organization (WHO) distinguishes at least 18 different histological BC types among a wide spectrum of tumors featuring different morphologies, molecular characteristics, and clinical behaviors [5]. Independently from histological subtypes, invasive BC can be divided into molecular subtypes based on mRNA gene expression levels. In 2000, Perou et al. identified 4

molecular subtypes from microarray gene expression data: Luminal, HER2-enriched, Basal-like, and Normal Breast-like [6]**;** further studies allowed to divide the Luminal group into two subgroups (Luminal A and B) [7–11].

Luminal A tumors are characterized by the presence of estrogen-receptor (ER) and/or progesterone-receptor (PR) and absence of HER2. This subtype [12,13] is associated to a low expression of genes related to cell proliferation and shows a better prognosis, compared to Luminal B tumors, which are ER positive but may be PR negative and/or HER2 positive.

Overall, 80% and 65% of patients are diagnosed with BC positive for estrogen receptor (ER) and progesterone receptor (PR), respectively [9].

A new classification has recently been proposed for HER 2 tumors with a score of 1+ or 2+ without amplification by the ISH method (in situ hybridization); these are nicknamed HER 2 low breast cancer and account for more than half of all breast cancer cases.

On the basis of the latest studies it has been seen that this subcategory of tumors could benefit from new anti HER 2 drugs; however we are far from being able to define HER 2 low tumors as a separate clinical entity with its prognosis and specific features.[14]

Validation of techniques to identify HER2 heterogeneity in order to effectively treat tumors with non-uniform HER2 expression is needed. [15]

BC is a multifactorial disease, and several genetic and environmental aspects are recognized as risk factors for its onset and progression [16]. Among them, age, and modifiable factors such as obesity, type II diabetes, sedentary habits, alcohol, radiation, hormonal replacement therapy, and periodontal disease have direct implications on gut microbiota composition, so that recent studies have highlighted the association between microbial alterations and those risk factors for BC, through metabolic and immunitary pathways, hormonal balance, and cancer microenvironment [17–19].

As regards the sexual hormonal balance, estrogens, and endocrine active compounds play a role in shaping the gut microbiome, potentially impacting the clinical management of hormone-dependent cancers [20].

2. Endocrine disruptors, phytoestrogens and breast cancer

An Endocrine Disruptor (ED) is defined by the U.S. Environmental Protection Agency (EPA) as "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process" [21].

Both estrogens and EDs, binding to estrogen receptors, elicite downstream gene activation and trigger intracellular signaling cascades [22] in a variety of tissues, thus affecting reproductive health and hormonal dependent cancers risk [23–25].

Endocrine disruptors are a group of highly heterogeneous molecules, grossly divided into synthetic and natural compounds (phytoestrogens).

2.1. Synthetic Endocrine disruptors

The synthetic chemicals with endocrine activities have multiple uses, such as industrial solvents/lubricants (polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs) and dioxins), plastics (bisphenol A (BPA)), plasticizers (phthalates), pesticides (methoxychlor, chlorpyrifos, dichlorodiphenyltrichloroethane (DDT)), fungicides (vinclozolin), pharmaceutical agents (diethylstilbestrol (DES)) and heavy metals such as cadmium [25,26].

The most common pathways of exposure to EDs are by inhalation, food intake, transplacental and skin contact [25,27,28]. By these means, EDs enter the food chain and accumulate in animal tissues up to humans mainly in adipose tissue, since most of EDs are highly lipophilic [29–31].

The mechanisms of action of EDs include a variety of possible pathways involved in endocrine and reproductive systems: via nuclear receptors, nonnuclear steroid hormone receptors (e.g., membrane estrogen receptors (ERs)), nonsteroid receptors (e.g., neurotransmitter receptors such as serotonin, dopamine, norepinephrine), orphan receptors [e.g., aryl hydrocarbon receptor (AhR)], enzymatic pathways involved in steroid biosynthesis and/or metabolism[25].

Another mechanism is the aromatase up-regulation (eg. phenolic EDs) and increased estradiol biosynthesis, that is linked to ER-positive breast cancer cell proliferation in vitro [32].

Furthermore, an epigenetic action, such as DNA methylation and/or acetylation and histone modifications, may be involved in mechanisms related to endocrine disruption [33–35].

The exposure to EDs has been related to multiple diseases, such as diabetes, metabolic syndrome, obesity, cardiovascular and neurological disorders [29,37]. Some EDs such as bisphenol A (BPA), dichlorodiphenyltrichloroethane (DDT) and polychlorinated biphenyls (PCBs) are also associated with infertility and cancer [29–40].

According to the International Agency for Research on Cancer (IARC) classification, some of the EDs (BPA, DDT and PCBs) have key characteristics of human carcinogens, since they can alter cell proliferation, cell death or nutrient supply; are genotoxic; have immunosuppressive activity; induce epigenetic alterations, oxidative stress and chronic inflammation [39]. In addition, BPA by interacting with the estrogen receptor-α(ERα), induces cell proliferation and reduces apoptosis rate, affecting the prognosis of BC patients [40–42].

A growing number of studies have investigated the correlations between EDs and BC onset and progression [43]. Before the mammary gland development is completed, within the third trimester of the first pregnancy, breast tissue is particularly prone to carcinogenic effects and a prolonged exposure to low levels of EDs [44–46], can lead to an increased risk of carcinoma in upcoming years [47,48].

Some pesticides such as DDT, the dichloro-diphenyl-dichloroethylene (DDE), aldrin, and lindane have been associated with an increased risk of BC [49,50], either estrogen receptor-positive tumors (β-hexachlorocyclohexane and Pentachlorothioanisole) [51] or HER2-positive tumors (DDT) [52], in post-menopausal as well as in pre-menopausal women [53,54]. Among the heavy metals, cadmium was positively associated with BC [55,56].

Interestingly, women with an altered body composition and an excess of fat mass have shown a greater likelihood of BC after exposure to PCB [57], due to the lipophilic nature of these molecules.

Some EDs, such as BPS, are also involved in enhancing the progression and the metastatic spread of BC cells, by inducing tumor proliferation and epithelial-mesenchymal transition [58,59].

2.2. Phytoestrogens

Phytoestrogens are plant-derived polyphenolic non-steroidal compounds, exhibiting chemical structures and/or functions like those of 17β-estradiol (E2) [38,60,61], which enable them to bind to estrogen receptors [62,63]. For this reason, they are considered endocrine disruptors with potentially beneficial (a lowered risk of osteoporosis, heart disease and menopausal symptoms) and detrimental health effects.

In epidemiological studies, Asian populations who consume on average much more soy products than Western populations, have lower rates of hormone-dependent breast and endometrial cancers [64] and a lower incidence of menopausal symptoms and osteoporosis. Nevertheless, in Asian immigrants living in Western nations, whose diet includes more proteins and lipids and less fibers and soy, the risks for hormone-dependent cancers reach the same levels as the western population [65].

The main groups of phytoestrogens are lignans, coumestans, stilbenes and isoflavones.

Lignans, as components of plant cell walls, are found in many fiber-rich foods such as seeds (flax, pumpkin, sunflower, and sesame), whole grains (such as rye, oat, and barley), bran (such as wheat, oat, and rye), beans, fruits (especially berries), and cruciferous vegetables like broccoli and cabbage [66].

The richest dietary source of plant lignans is flaxseed (*Linum usatissimum*), and crushing or milling flaxseed can increase lignan bioavailability [67].

Compared to isoflavones and lignans, coumestans are less prevalent in the human diet. Coumestans are primarily found in legume shoots and sprouts, primarily in clover and alfalfa, though small amounts have also been found in spinach and brussel sprouts [68]. Coumestrol is also found in trace levels in a variety of legumes, including split peas, pinto beans, lima beans, and

soybean sprouts. Additionally, it has been noted that after an insect and fungal attack, the coumestrol levels in legumes rise. [68].

The most prevalent and studied stilbene, resveratrol, may be found in a number of plants and acts as a phytoalexin to ward off fungus infections. The skin of grapes (Vitis vinifera), red wine, and other highly pigmented fruit juices are the most recognized sources of resveratrol. Resveratrol is also present in pistachios, notably the papery skin surrounding the nut, and peanuts (Arachis). While flavonoids and resveratrol both have vascular effects that are frequently addressed, only the trans isomers of resveratrol have been found to have some phytoestrogenic effects [69].

Isoflavones are present in berries, wine, grains, and nuts, but are most abundant in soybeans, soy products, and other legumes [60,61].

Studies have shown that phytoestrogens, mainly the isoflavones, have both agonistic and antagonistic effects on ERβ and ERα receptors, depending on their concentration and their affinity for different estrogen receptors [70]. This mechanism explains the dual effect of phytoestrogens in ER-positive breast cancer cells, resulting in a growth stimulation at low concentrations and inhibition at higher concentrations [71]. Coumestrol, genistein, and equol have a stronger affinity for ERβ [72,73].

Altogether, the phytoestrogens and their analogs inhibit cell cycle progression in various breast carcinomas either by decreasing mRNA or protein expression levels of cyclins (D1, E), and CDKs (1, 2, 4, 6) and by increasing their inhibitors (p21, p27, p57) and tumor suppressor genes (APC, ATM, PTEN, SERPINB5) [66]. Even isoflavones, lignan, and resveratrol analogs modulate the expressions of cell cycle regulators, affecting various types of BC cell lines in vitro [74]. They also inhibit the expression of oncogenic cyclin D1, increase a number of cyclin-dependent kinase inhibitors (p21, p27, and p57) and phytoestrogens and their analogs and derivatives may also affect BC behavior by inhibiting estrogen synthesis and metabolism, as well as exerting antiangiogenic, antimetastatic, and epigenetic effects. Furthermore, these bioactive compounds may reverse multi-drug resistance [74].

Despite a huge number of studies, the question of whether or not phytoestrogens are beneficial or harmful for patients diagnosed with BC remains unresolved: the answers are complex and may depend on age, health status and even the composition of gut microbiota [75] (Table 1).

Table 1. Interplay between phytoestrogens and their metabolites with microrganism.

Chemical family	Molecules	Microrganisms	References
Lignans	Anhydrosecoisolariciresinol Secoisolariciresinol diglucoside Syringaresinol	*C. methoxybenzovorans* *B. pseudocatenulatum* WC 401 Firmicutes Bacteroidetes	[101,102, 103,122]
Isoflavones	Coumestrol Genistein Equol Daidzein	*F. prausnitzii* *Lactobacillus* *Enterococcus*	[119]
Steroids	Estradiol Estrone	*Collinsella, Edwardsiella, Alistipes, Bacteroides, Bifidobacterium, Citrobacter, Clostridium, Dermabacter, Escherichia, Faecalibacterium, Lactobacillus, Marvinbryantia, Propionibacterium, Roseburia, Tannerella*	[22,82–86]
Prenylflavonoids	Xanthohumol Desmethyxanthohumol	*E. limosum*	[106]
Stilbenes	Resveratrol Trans-resveratrol Dihydroresveratrol 3,4′–dihydroxybibenzyl, 3,4′-dihydroxy-trans-stilbene	*Firmicutes* *Bacteroidetes,* *Actinobacteria* *Verrucomicrobia,* *Cyanobacteria*	[123–127]

3. Estrobolome

Gut microbiota is a regulator of circulating levels and bioavailability of estrogens, steroid hormones and cytokines [76,77], which are involved in the onset, progression and outcomes of the majority of BCs [78–81]. In addition to steroid hormones, BC is also influenced by hormones derived from the adipose tissue, such as leptin and insulin, which are also regulated by gut microbiota.

Two main pathways have been identified through which microbiome influences the sexual hormonal balance. In the deconjugation-independent pathway, some phytoestrogens contained in food, such as plant lignans, are metabolized by specific intestinal bacteria into bioactive compounds. In the deconjugation-dependent pathway, several *genera* like *Collinsella, Edwardsiella, Alistipes, Bacteroides, Bifidobacterium, Citrobacter, Clostridium, Dermabacter, Escherichia, Faecalibacterium, Lactobacillus, Marvinbryantia, Propionibacterium, Roseburia, Tannerella* , constituting the so called "estrobolome", by the means of hydrolytic enzymes such as ß -glucuronidases and ß –glucosidases, can deconjugate estrogens excreted by the liver into the intestinal lumen as well as endocrine active food components, increasing their reabsorption through the entero-hepatic circulation [22,82–84]. Gut microbiota can also regulates the bioavailability of progesterone and testosterone: the sulfatase activity of certain enteric commensals can convert inactive circulating steroids into active hormones [84–86].

A pioneeristic study comparing premenopausal women consuming a "Western diet" (with high saturated fat intake), with vegetarians with a high fiber and moderate fat diet, showed estrogen levels three times higher in vegetarians' feces and 15% to 20% lower in serum [87]. In another study, Asian immigrants, consuming a low-fat diet, had systemic estrogen levels 30% lower compared to American women eating a high-fat diet [88], possibly via the estrobolome, although additional factors including lifestyle and oral supplements may contribute [89]. Changes in the estrobolome composition induced by lifestyles, antibiotics and chemotherapeutics affect the systemic levels of estrogen and its metabolites, and the entero-hepatic circulation of estrogens [90] has been linked to cancer progression in hormonal dependent BC patients and survivors [85,91,92].

Several studies showed that cancerogenesis can also be promoted by enhanced local exposures of breast tissue to hormonal triggers, both from estrogen and progesterone metabolites: an abundance of β -glucuronidase signaling has been found in nipple aspirate fluid of BC survivors [93], while BC tissue shows higher concentrations of estrogen metabolites compared to normal breast tissue [88,94]. In addition, BC tissue has elevated 5a-reductase activity, which results in significantly higher total levels of 5a-pregnanes (5aP) compared to normal tissue [95,96]. Among the possible mechanisms leading to an increased production of progesterone metabolites in tumour microenvironment, *Bacillus cereus* seem to play a role in promoting cancer cells proliferation [95,97,98]. Among the gram-negative family of *Sphingomonadaceae, Sphyngomonas yanoikuyae*, relatively enriched in paired normal breast tissue as compared to cancer tissue [99], has shown the ability to digest monocyclic compounds and degrade estrogens within the breast tissue [100], which could interfere with cancerogenesis through the local estrogen bioavailability.

4. Interplay between human microbiota, endocrine disruptors, and phytoestrogens

The complex relashionship between microbiota and endocrine active compounds derived from diet act in a bidirectional way: enteric commensals can metabolize EDs into biologically active or inactive forms, while EDs may selectively induce the growth of specific bacterial populations.

An interesting example of the microbiota's impact on xenobiotic metabolism is the biotrasformation of lignans, such as anhydrosecoisolariciresinol, by the gram-positive bacterium *Clostridium methoxybenzovorans* [101,102] , or the secoisolariciresinol diglucoside by *B. pseudocatenulatum* WC 401 and other *Bifidobacterium* strains through deglucosylation [103] . Among prenylflavonoids, a subgroup of chalcones and flavanones, the most significant are xanthohumol (XN) and desmethyxanthohumol (DMX) derived from hops, which are widely used in beer industry [104] :

XN's metabolite 8-prenylnaringenin (8-PN), produced in the gut by the commensal, [105] is one of the most potent phytoestrogen [106] , with a remarkable affinity for the ERα receptor [107,108] .

These dietary-induced interactions between gut microbiota and hormonal balance may lead to a dysbiosis, thus affecting human health and diseases [109].

5. Role of the endocrine disruptors on microbiota composition

Several studies underline the association between EDs exposure and metabolic disorders, diabetes, obesity, and some neurobehavioral disorders [110], which have been related to gut dysbiosis, suggesting a role of gut microbiome and its products (post-biotics) as mediators of the effects induced by EDs in human metabolism [111].

Both the exposure to EDs and their bioactive metabolites may disrupt the microbiota composition and lead to dysbiosis [112], but also alter the microbiome functions and metabolic activities [113]. Data from animal models suggest that the alterations in gut microbiota not only affect the levels of microbial enzymes, but also the levels of hepatic enzymes in the host [114].

Several EDs have been shown to promote dysbiosis or to inhibit bacterial growth both *in vitro* and *in vivo* [111], exerting a deep impact on the gut colonization, which will ultimately affect host health. In addition, a "leaky gut" wall let the circulating EDs enter directly the intestinal milieu and, by interacting with the enteric nervous system, may affect the composition and functions of gut microbiome [115–117].

Clavel et al. showed that the isoflavone daidzein and its metabolites modulate the composition of gut microbiota in postmenopausal women after 2 months supplementation, finding an association between the equol production and the increase of the *F. prausnitzii* and *Lactobacillus-Enterococcus* groups [118]. In a long-term study exploring the effects of isoflavones supplementation on the faecal microbiota of healthy menopausal women, a significant change of microbial populations was recorded, but without any difference between equol-producers and non-producers [119].

In another study on healthy volunteers, ellagitannin and its metabolites modulated the composition of gut microbiota (*Actinobacter, Firmicutes* and *Verrucomicrobia)*, after 4 weeks of supplementation of a pomegranate extract [120].

Luo et al. investigated the *in vivo* anti-obesity effect of flaxseed gums (FG) in obese rats and found the FG diet decreased the relative abundance of *Clostridiales* and increased the *Clostridium, Sutterella, Veillonella, Burkholderiales* and *Enterobacteriaceae* family in their gut microbiota [121]. The supplementation with syringaresinol, a plant lignan, increases the *Firmicutes*/*Bacteroidetes* ratio in an aging mouse model [122].

The resveratrol mechanisms of action are largely attributed to the modulation of gut microbiota and its metabolites. An *in vitro* study demonstrated a different conversion of trans-resveratrol into dihydroresveratrol, 3,4'–dihydroxybibenzyl, also known as lunularin, and 3,4'-dihydroxy-trans-stilbene, depending on the bacterial diversity of each individual's faecal samples [123]. Chen et al. (2016) observed that modulation of gut microbiota induced by resveratrol reduced the levels of trimethylamine-N-oxide (TMAO) by inhibiting microbial trimethylamine (TMA) production and increased hepatic bile acid (BA) *de novo* synthesis [124]. An increase in *Bacteroides*/*Firmicutes* ratio was also observed *in vivo* after resveratrol supplementation in animal studies along with other effects, such as anti-diabetic effect [125], improved carbohydrate metabolism [126] and glucose homeostasis [127]. Giuliani et al., using an advanced gastrointestinal stimulator, showed that an extract containing a combination of t-resveratrol and ε-viniferin induced changes in microbial functions and composition together with a strong decrease in the levels of SCFA and NH_4^+ [128].

6. Different metabolic pathways of endocrine disruptors depending on gut microbiota

Gut microbiota plays a key role in the metabolism of EDs and phytoestrogens into bioactive metabolites [129]. Isoflavones, ellagitannins, and lignans are metabolized by intestinal bacteria into equol, urolithins and enterolignans, respectively [102].

A model for the deconjugation-independent pathway is the enzimatic degradation of plant lignans, such as secoisolariciresinol, into phytoestrogens enterodiol and enterolactone by different

intestinal bacteria, like *Eggerthella lenta* and *Peptostreptococcus productus* [118]. Enterodiol and enterolactone may act as selective modulators of estrogens with protective effects against BC [19,130] and favorable prognostic impact in postmenopausal BC patients [131].

Van de Wiele et al. [132] reported that colonic microbiota can metabolize polyaromatic hydrocarbons into 1-hydroxy pyrene and 7 -hydroxybenzo[a]pyrene, biologically active estrogen metabolites.

A recent review of Velmurugan et al. [112] focused on the role of gut microbiota in glucose dysregulation, glucose intolerance and insulin resistance induced by several classes of EDs from plastics, pesticides, synthetic fertilizers, electronic waste and food additives. They included bisphenols, dioxins, phthalates, organochlorines, organophosphates, fungicides, polychlorinated biphenyls and polychlorinated dibenzofurans and other waste pollutants.

On the other hand, hyperglycemia induces changes of microbiota composition, favoring the growth of non-commensal germs, at the expense of beneficial phyla such as *Bacilli* (e.g. *Lactobacillus*), *Bacteroidetes*, *Proteobacteria* and *Actinobacteria* [112]. *Lactobacilli* can diminish the toxicity of pesticides and protect against EDs induced oxidative stress by inhibiting intestinal absorption of contaminants, reinforcing the tight junctions in the intestinal barrier, and stimulating host's immunity [133]. The exposure to EDs, such as polychlorinated biphenyls, may affect the integrity of gut permeability decreasing the expression of tight junctions' proteins [134,135].

Gut dysbiosis is linked with many disorders such as obesity, diabetes, endocrine and immunological diseases [109,136–141], which have been proven as risk factors for BC in both pre- and post-menopausal women [142,143].

In addition, all main classes of EDs (bisphenols, phthalates, polychlorinated biphenyls, organochlorine pesticides, dioxins and parabens) may act as obesogenic and increase the risk of developing insuline resistance and diabetes [144], by increasing adipogenesis through the mechanisms of hormone regulation of food intake, appetite and disruption of pancreatic β-cell function [145–150]. Even the fungicide tributyltin, which at least in mice decreased gut microbial biodiversity in the microbiome composition [151], induces adipogenesis by interacting with nuclear PPARγ and its heteromeric partner retinoid X receptor.

The interplay between EDs and human microbiota affects BC risk and clinical management not only through the sexual hormonal balance, but also through the innate as well as the acquired immunity [133,152–155], but these fundamental pathways are beyond the topic of the present review.

Beside this, a plethora of studies show that the gut microbiome affects the side effects, the toxicity and the outomes of anticancer treatments such as radiation therapy, chemotherapy, immunotherapy and hormone therapy. Pharmacomicrobiomics is defined as the effect of microbiome variations on drug absorption, distribution, metabolism, excretion, toxicity and overall response [95,156–158].

On the other hand, anticancer agents such as letrozole, an aromatase inhibitor, are associated with a time-dependent reduction of phylogenetic richness in the gut microbiota and a significant decrease in overall species [95].

These pharmacomicrobiomic studies might lead to the gut microbiota analysis as a means to predict patients' response to treatments, allowing a more personalized approach based on the microbiota-host-cancer triad.

8. Conclusions

Endocrine disruptors and phytoestrogens interact with the human microbiota both at the intestinal and the breast tissue levels, affecting estrogens' balance, bioavailability, and functions. This complex interplay results in a modification of BC cells behaviours, at least for hormonal dependent tumors, which account for more than 70% of cases globally.

A better understanding of this interplay, as well as the chance of modulating the exposure to EDs and targeting the microbiome composition, via dietary interventions and probiotics, could pave the way to a new oncobiotic approach in order to improve the clinical management of BC patients.

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