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A REVIEW OF ENDOCRINE-DISRUPTING COMPOUNDS AND BREAST CANCER DEVELOPMENT

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ABSTRACT
Endocrine-disrupting compounds (EDCs) are present in high amounts in the environment, they can get into food from the environment posing a high risk to human health due to their interactions with mammalian endocrine systems. Since these chemicals are similar in structure to hormones like estrogen, they can interfere with endocrine signaling, leading to harmful effects. Breast cancer is one of the most frequently diagnosed cancers among women and exposure to estrogenic EDC increases the risk for the development of breast cancer. However, the mechanisms that allow EDC to contribute to cancer remain elusive. Cancer cells undertake distinct metabolic pathways to utilize the nutrients in the tumor microenvironment and synthesize macromolecules de novo to undergo rapid proliferation. EDCs can lead to the development of breast cancer by dysregulating cell signaling pathways linked to metabolism. Metabolomics, an advancement in -omics technologies that interrogate molecular pathways favoring cancer development and progression can be used to analyze these altered pathways. This review will summarize recent discoveries regarding EDCs and how they facilitate the development of breast cancer by inducing metabolic alterations.

Keywords: Endocrine-disrupting compounds, Breast cancer, Metabolomics, Zeranol, Bisphenols, Phthalates

1. Introduction
Breast cancer is the most common form of cancer diagnosed in women [1,2]. Hereditary genetic mutations accounts for a small variety of breast cancers; the etiology for the most of the breast cancer variety are still unknown [3,4]. However, it is known that many factors are responsible for the development of breast cancer. The use of endocrine-disrupting compounds (EDC) in consumer products, their prevalence in the environment, and the incidence of breast cancers increased drastically in the last half-century [5]. One of the plausible reasons behind the increase in the prevalence of breast cancer could be related to the increased exposure to various EDCs. The major sources of EDC include industries; but they can also be found naturally in air, water, soil, and even in various types of household products, and medical devices, becoming ubiquitous in the environment. The estrogenic

effect of EDCs is a very high probable reason contributing to its possible role in development of breast cancer. The most notable EDCs with prominent estrogenic effect include phthalates, bisphenol A (BPA), and polychlorinated biphenyls (PCBs) [6]. However, there are many lesser-known EDCs, such as the mycotoxins produced by crop-contaminating fungi [7] and phytoestrogens produced by plants [8], which are considered to be a cause for concern because of their capability to bind and activate estrogen receptors (ERs) [9,10]. The increase in cancer cell proliferation, invasion, and metastasis linked to the downstream estrogen signaling induced by estrogenic EDCs, has been well-established [11-14]. These chemicals may result in development of mammary proliferation and subsequent progression into breast cancer.

Metabolomics utilizes computational biochemistry and bioinformatics to map the ratios of chemicals present in a sample. This can uncover novel underlying mechanisms of pathogenesis and prognosis of complex diseases like cancer. Study of metabolome has been a well established practice in cancer research for decades. In the late 1920s, Warburg described an altered metabolism in cancer cells of full oxidation where glucose is converted to lactate. [15], a phenomenon later called, "the Warburg effect." Since the initial discovery by Warburg, it has been shown by many researchers that the Warburg effect is not restricted to cancer cells. The Warburg effect explains rapid cell growth and proliferation, resulting in metabolic reorientation to sustain rapid growth, commonly seen in Budding yeasts, [16], rapidly developing tissues, [17] and even replicating pathogens [18]. Many explanations have been suggested justifying the involvement of Warburg's metabolism in cancer cells proliferation, along with the involvement of the tumor microenvironment, the speed of energy retrieval, and biomolecule synthesis [19-21]. However, sufficient evidence in support of why cancer cells use Warburg metabolism for proliferation could not be established. Besides Warburg metabolism, scientists have discovered many hallmarks of the metabolism of cancer cells, such as lipid turnover, alterations to mitochondrial metabolic pathways, and biosynthesis of nucleotides [22-24]. However, an elaborate explanation behind the mechanism of how these metabolic pathways aid cancer cell proliferation and survival, and ability of cancer cells to be resistant to treatment remains elusive [25,26].

To understand the metabolic mechanism of cancer cells, it is of utmost importance to have a thorough knowledge of the metabolite composition present within the tumor microenvironment [27], which directly affects an overall increase or decrease in survival. Tumor microenvironment heterogeneity of a cancer patient depends on their metabolic state alongside the organ of residence of cancer. It is also well-established, that pathological metabolic dysregulation is closely associated with the risk of cancer development [28]. Type II diabetes mellitus (DM) has been epidemiologically associated with the lifetime diagnosis of many cancers, including liver, breast, and pancreatic cancers [29]. This association of cancer development with Type II DM may be attributed to the prominent metabolic shifts, such as hyperlipidemia, hyperinsulinemia, and hyperglycemia [30].

Incidence of higher levels of lipids, glucose, and insulin are all correlated to cancer progression [31]. Increased generation of Reactive oxygen species (ROS) and subsequent hindrance to antioxidant protection associated with metabolic diseases may favor cancer progression [32]. So, the correlation of global metabolome and intrinsic cancer cell metabolic pathways may be considered to play a key role in cancer development.

2. Identifying cellular changes by Metabolomics

Metabolomics provides an in depth physiologically relevant perspective on how the body responds to a given stimulus [33]. It offers detailed insight into the changes in molecular pathways that precede a genetic mutation resulting in alterations in the "central dogma" of DNA, RNA, and protein signaling. The inclusion of metabolomics alongside other techniques like proteomics and transcriptomics can provide a cleared scenario in the study of cancer metabolic pathways which can lead to uncovering novel pathways due to perturbations. Any changes to the metabolomic signature subsequently effect the proteomics and ultimately leads to transcriptomic changes. This correlation validates the importance of inclusion of metabolomics as a tool to assess downstream molecular pathways. This

has been elucidated in breast cancer [34,35], cervical cancer [36], prostate cancer [37], and pancreatic cancer [38].

So, metabolomic analysis can be considered a strategically effective approach to understand progression and alterations in biological mechanisms involved in cancer initiation and progression.

Metabolomic analysis can be applied to biological samples to determine metabolite ratios, as in serum or in tumor explants. Metabolomics analysis of samples from in vitro cell models, or from extracellular media produced by colonies, can be done to identify intrinsic cellular metabolic pathways.

However, using in vitro cell culture for metabolomics analysis has severe drawbacks. Cellular metabolism is highly sensitive to any changes or disturbances in the microenvironment and results in rapid changes. Metabolite extracting process from cell culture can produce artifacts by introducing stress-based metabolomic responses [39]. Cellular metabolism pathways often vary due to the environment around it, so metabolic analysis of cells under physiological conditions and those under culture conditions are often different. Regardless of their limitations, in vitro studies are gaining increased popularity in the scientific community as limit unnecessary animal use, alongside being inexpensive and quick method of study and are quite efficiently used for generating hypotheses and compounds screening. However, cell culture studies results must be validated in animal and/or human studies.

Nuclear Magnetic Resonance (NMR) spectroscopy and mass spectrometry (MS) are commonly used to analyze metabolites ratios in sample [40]. In NMR spectroscopy, on applying an external magnetic field to a chemical, the electrically charged nuclei of each atom would spin in a direction that correlates with the chemical environment [41]. Hydrogen proton (^1H) is the most commonly used nucleus in NMR analysis. After the magnetic field is applied, the different resonant frequencies of each hydrogen atom in a compound are recorded and plotted in spectra [41]. The NMR peaks can be used to determine the original compound structure [41]. MS analysis adds electrical charges to the sample material by ionization. Then, an ion detector separates the ions based on their mass-to-charge ration(m/z) and their abundance is quantified in a sample [42]. The chemical structure can be deduced from this resulting spectrum. Although a complex sample preparation is required, a greater quantity of individual metabolites can be detected by MS [43]. There are two types of metabolomic analysis generated from NMR and MS:- targeted or untargeted. The targeted approach involves assessing known biomarkers for which NMR or MS peaks have been identified and established. The untargeted approach involves analyzing all analytes in a sample thoroughly and generating a vast data set increases the chance of novel discoveries [44]. After data collection, intricate statistical tools are used to interpret the data set. Two types of analysis are used by researchers to assess the data: supervised analysis and unsupervised analysis [45]. In supervised analysis, patterns are preinput, such as known cellular molecular pathways, to determine correlations from the data set. In unsupervised analysis, patterns are drawn from the data set without any preinput knowledge, treating all the data points as equal variables. This analysis is used on preliminary data sets and is useful for smaller data sets [46].

3. Metabolomics in Breast Cancer

Many metabolomic shifts have been identified in breast cancer [47-49]. In vitro studies involving metabolite studies pointed to changes in fatty acid and choline metabolism [50]. To survive with limited nutrients residual breast cancer cells from primary tumors change fatty acid synthesis [51]. An increase in the free fatty acid storage is noted in cancer cells, which aids in survivability of the cells in a nutrient deprived vasculature environment before angiogenesis occurs, to meet their high energy requirement [52]. Cancer cells undergo significant alterations in their metabolic pathways and cellular energy production pathways to adapt and survive to their constantly changing environment. Metabolomic analysis of samples from early and late stage breast cancer cells, show significant changes. Metabolite profiling of serum from patients with metastatic breast cancer showed increased glucose and lipids levels and lower levels of histidine. These profilings can be used as markers in identification of early stage cancers, in their operable stages. [53]. This study investigated the global metabolome of individuals rather than the metabolome of the individual breast cancer cells. The

increase in metabolite concentration could be due to metastatic breast cancer, or it reflects a global metabolic state that may have influenced the breast cancer metastasis. Metabolomic analysis profiling can thus be considered as a potential diagnostic identifier of early stage breast cancer. Plasma-free amino acid profiling (PFAA) is considered as one of the most efficient metabolomic biomarkers [54]. This diagnostic method considers the difference in the serum amino acid concentrations as profiled against different tumor node metastasis clinical stage in breast cancer patients [55]. Predictions of disease prognosis can be made based on the serum metabolite profile of the patient sample. However, they are not able to identify metabolomic mechanism that lead to breast cancer initiation and progression.

4. EDCs in Breast Cancer metabolome

"Endocrine disruptors or EDCs" mimics endogenous hormones and disrupts the endocrine functions by interacting with hormone receptors [56]. Most EDCs are structurally similar to β-estradiol and causes ER stress [57] (Figure 1). This structural similarity presents estrogenic EDCs with the ability to signal through estrogen pathways both as agonists and antagonists [58]. Direct and indirect interference in hormone signaling pathways caused due to EDCs exposure has been linked to many diseases like, breast cancer, thyroid disease, metabolomic disorders, and reproductive pathologies [59-68]. EDCs can capable of disrupting the metabolome which subsequently results in the onset of metabolic disorders like type II DM, obesity, and fatty liver disease [69]. However, the exact effect of EDCs on the breast cancer metabolome remains unclear (Table 1). It is important to determine the pathways that are affected due to EDC exposure in breast cancer development, so that proper risk assessment can be evaluated and accordingly therapeutic strategies and/or chemoprevention measures can be developed for a disease. This review will emphasize how various EDCs alter global and breast cancer metabolome.

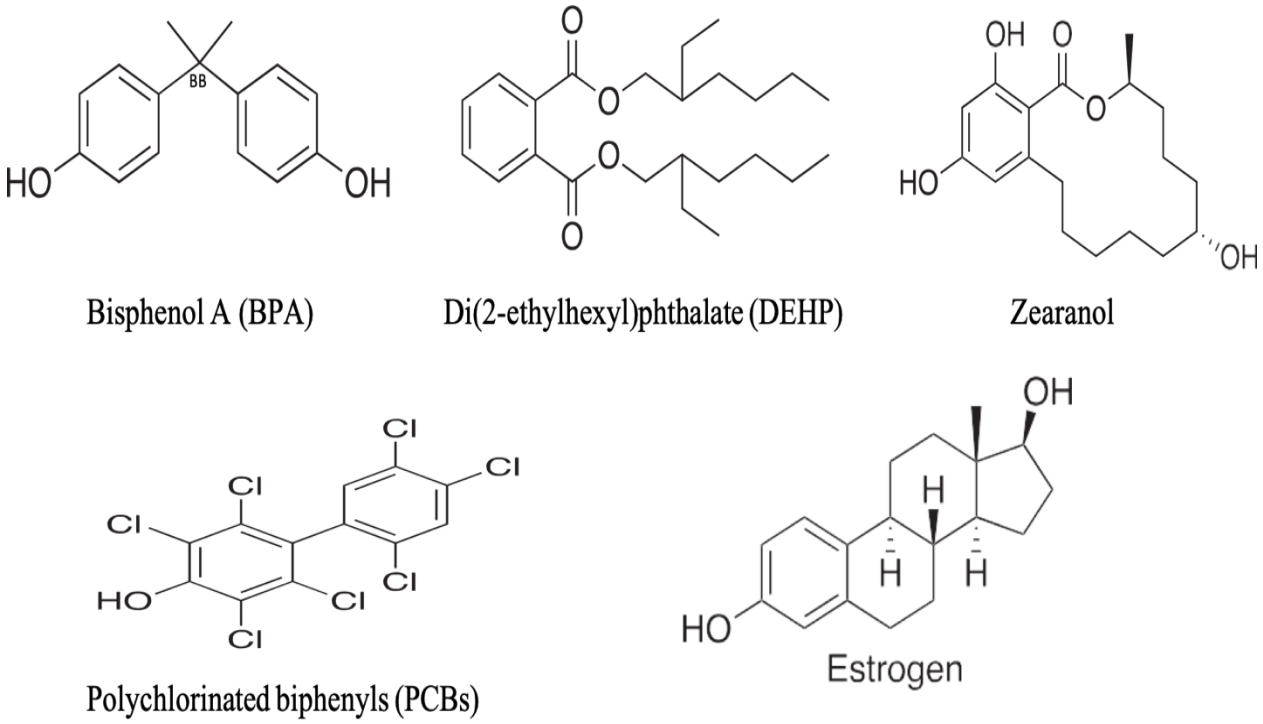

Figure 1: Chemical structures of environmentally relevant estrogenic endocrine-disrupting compounds. The structures of estrogen (beta-estradiol), bisphenol A, di(2-ethylhexyl)phthalate, alpha-zeranol, and polychlorinated biphenyls are shown.

Table 1: Metabolomic alterations induced by relevant environmental EDCs

Type of Study	Principle findings	Reference
PCBs	PCBs altered fatty acid biosynthesis pathways	[70]
Human	PCB metabolite PCB29-pQ induced aerobic glycolysis and upregulation of GLUT1 in cell culture, resulting in metastasis in a xenograft model	[71]
In vitro/in vivo	PCB exposure increased the metastatic potential of xenografts	
	BPA altered apolipoproteins, urea cycle, and Krebs cycle intermediates, resulting in changes in amino acid concentration in HepG2 cells.	[72]
In vivo	BPA impacted nucleotide synthesis in MCF-7 cells	
	BPA induced changes in purine and pyrimidine metabolism in MCF-7 cells in a "leave one out" approach	[73]
Bisphenols	In MCF-10A cells BPS dysregulated the citric acid cycle, purine metabolism, and lipid metabolism	
In vitro	TB-BPA and TC-BPA induced glycolytic intermediates and altered glutathione metabolism in MCF-10A cells	[74]
In vitro	BPF-induced changes in glutathione biosynthesis, glycerophospholipid, glycerolipid degradation, and glycolysis in MDA-MB-231 xenografted mice	[75]
In vitro	BPA changed the global metabolome in the whole body of CD-1 mouse pups exposed perinatally	[76]
In vitro	In the serum of pregnant women, phthalate metabolites correlated with the dysregulation of lipid	[77]
	DBP and BBP increased xenografted MDA-MB-231 tumor size	
In vitro	ZEN exposure increased the incidence of breast cancer in Tunisian women	[78]
In vivo	α-ZAL induced changes to protein biosynthesis, the urea cycle, methionine metabolism, and arginine/proline metabolism in MCF-7 cells	
	α-ZAL increased mammary proliferation in a rat model	[79]

In vivo		
Phthalates		[80]
Human		[14]
In vivo		
Zeranols		[81]
Humans		[82]
In vitro		
In vivo		[83]

Abbreviations: BBP, benzyl butyl phthalate; BPA, bisphenol A; BPF, bisphenol F; DBP, dibutyl phthalate; EDC, endocrine-disrupting compounds; PCB, polychlorinated biphenyl; TB-BPA, tetrabromo-BPA; TC-BPA, tetrachloro-BPA; ZAL, zearalanol; ZEN, zearalenone

4.1. PCBs

PCBs are structurally similar to 200 congener chemicals, containing biphenyl moieties with chlorine groups attached to the carbon ring [84]. Initially, they were used in the manufacture of electrical conductors and fluid coolants until 1979, when they were banned, upon discovery of their carcinogenic effects [85] (Figure 2). PCBs exposure still persists due to their environmental persistence and lipid bioaccumulation [86], and they are found in National Health and Nutrition Examination Survey (NHANES) biomonitoring studies [87]. According to epidemiology studies, many PCB congeners are likely to cause breast cancer [88-90]. In vivo studies point to PCBs playing a role in breast cancer development (Figure 3). PCB exposure in in nude mice increased the metastatic potential of MDA-MB-231 xenografts, with a significant observation of increase in the number and size of detectable metastases in distal organs. [72] (Figure 4). MDA-MB-231 is derived from a triple-negative breast adenocarcinoma, so it does not express the classical ER alpha. This observation can be directly correlated to the immunosuppressive effects of PCB [91]. However, the exact mechanism of increase of the metastatic potential remains unclear. In vitro studies show evidence of estrogenic effects of some PCBs in ER-positive breast cancer cell lines. A study reports, out of 17 PCB congeners

tested, one increased estrogenic signaling activity in an MCF-7 reporter assay, and another one congener antagonized estrogen signaling. In another study, four structurally different PCB congeners when tested all increased MCF-7 cell growth. On adding estrogen antagonist hydroxytamoxifen to the PCB congeners treated MCF-7 cells, the previously observed cell proliferation reversed marked, suggesting the increased proliferative effect was caused by estrogen signaling [92]. PCB metabolites have been identified as mutagens because they cause DNA damage in the liver [93].

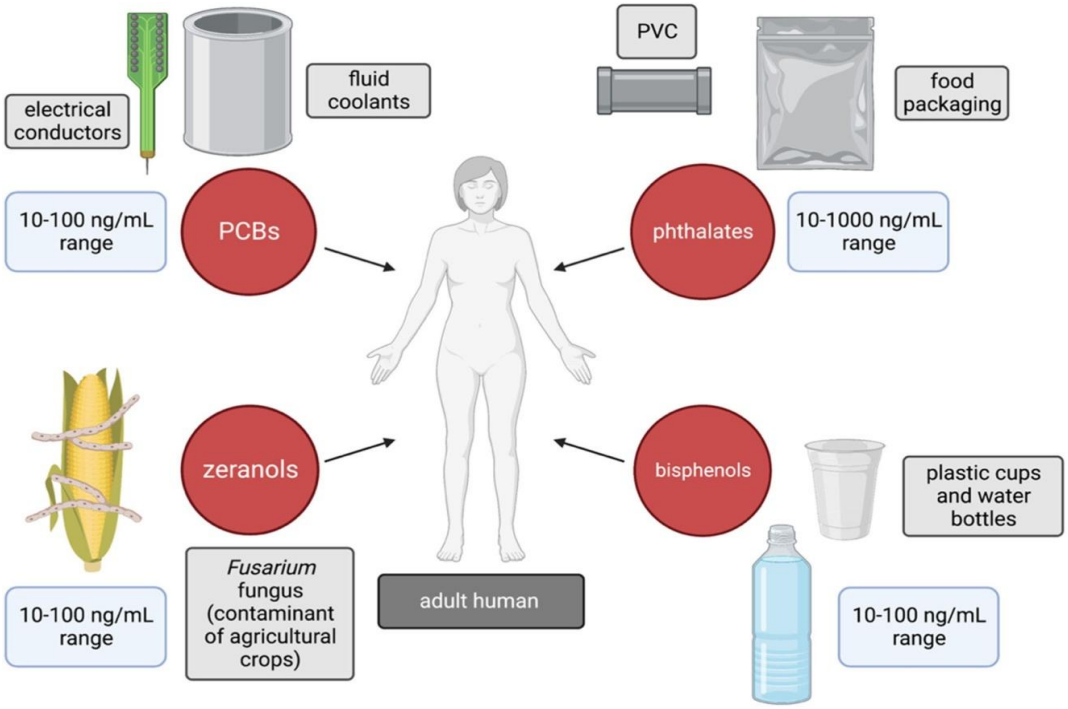

Figure 2: Environmental sources of endocrine disrupting compounds (EDCs). Humans are exposed to environmental EDCs from various sources. Historically, polychlorinated biphenyls (PCBs) were added to electrical conductors and fluid coolants. Phthalates are included in polyvinyl chloride (PVC) pipes and soft, malleable plastics, like food bagging. Bisphenols are incorporated into hard, stiff plastics, like water bottles. Zeranols are produced by the Fusarium fungus, a common contaminant of agricultural crops like corn and maize [94-97]. Human EDC exposure levels are shown.

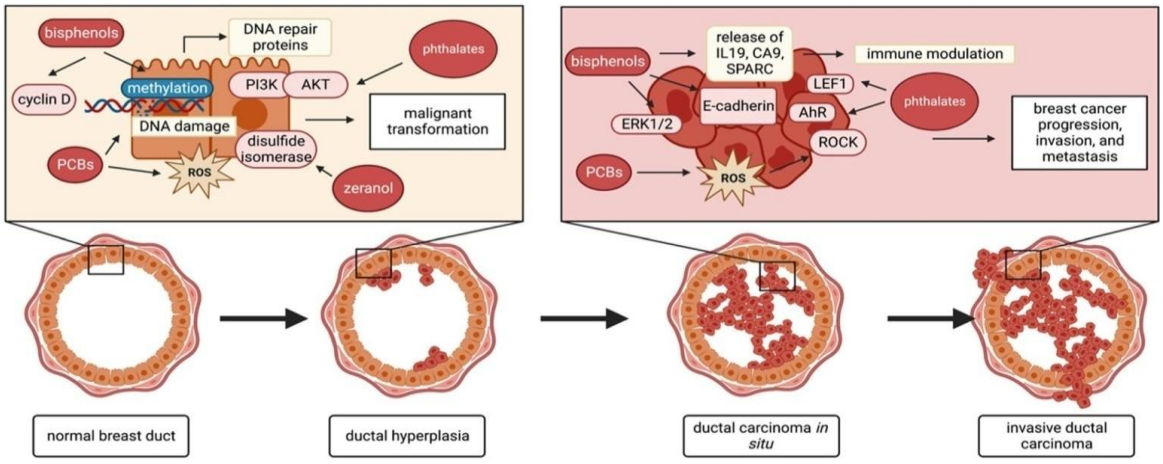

Figure 3: The role of endocrine disrupting compounds (EDCs) throughout breast cancer initiation, progression, and metastasis. EDCs likely have diverse mechanisms throughout carcinogenesis [14,72,98-106]. AhR, aryl-hydrocarbon receptor; AKT, protein kinase B; ERK 1/2, extracellular signal-regulated kinase 1/2; IL-19, interleukin 19; PCB, polychlorinated biphenyls; PI3K, phosphoinositide 3-kinases; ROS, reactive oxygen species.

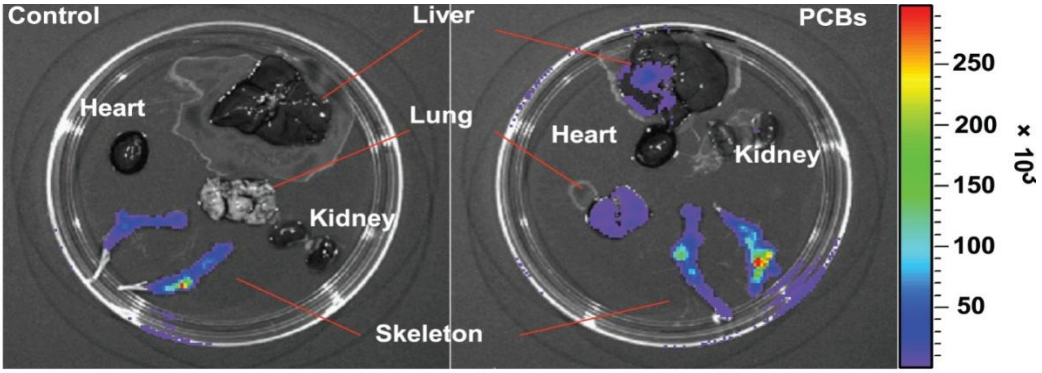

Figure 4: Representative images of metastases in mouse liver, lung, and skeleton from the bioluminescent imaging [72].

In a recent study, it was observed that PCB29-pQ, a quinone-type metabolite, drastically increased aerobic glycolysis in MDA-MB-231 cells. This conclusion was drawn on the basis of a marked increase in the mRNA expression of aerobic glycolysis enzymes [71]. PCB29-pQ treatment on MDA-MB-231 cells caused significant increase in the expression of GLUT1, a key transporter of glucose uptake. This increased expression of GLUT1 in turn activated the GLUT1/integrin B1/Src/FAK pathway, known to be crucial for the onset of epithelial-mesenchymal transition, extravasation, and metastasis [107,108]. In an in-vivo study conducted on LUC-1 nu/nu mice xenograft it was evidenced that inhibition of GLUT1 expression also prevented the metastatic effect of PCB29-pQ, concluding that both aerobic glycolysis and GLUT1 are involved in the progression of breast cancer [71]. These observations point that PCBs are regulate the mechanism of energy production via glycolysis affecting breast cancer metabolism (Figure 5).

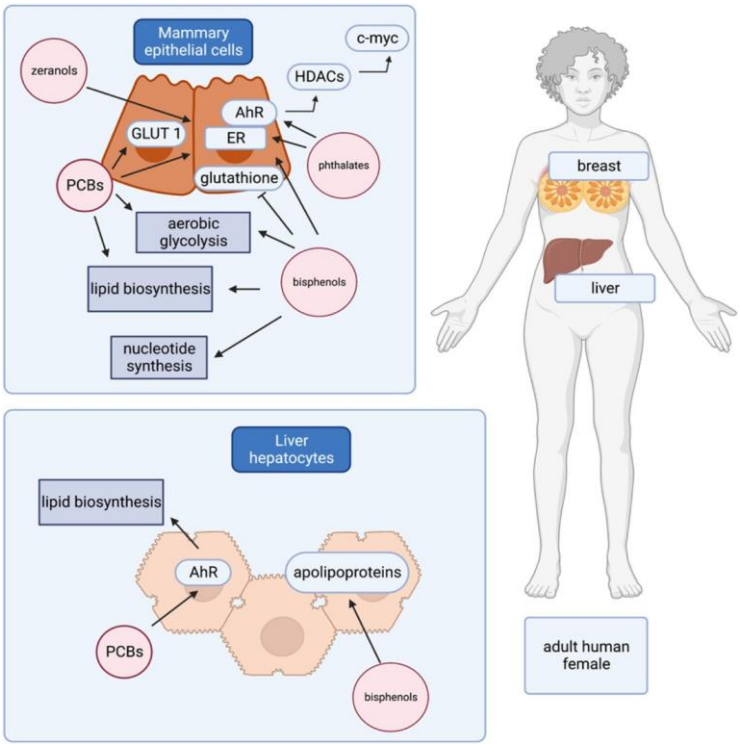

Figure 5: Major sites of action and molecular effects of endocrine disruptor exposure. EDCs can work through diverse molecular mechanisms upon arrival at a target site, though some pathways are conserved across various types of compounds. Bisphenols and PCBs both initiate aerobic glycolysis and lipid biosynthesis within the mammary gland. Phthalates and PCBs can both activate AhR in different target tissues. Other pathways, like nucleotide synthesis, are specific to certain compounds. AhR, aryl-hydrocarbon receptor; EDC, endocrine- disrupting compounds; ER, estrogen receptor; HDAC, histone deacetylases; PCB, polychlorinated biphenyls.

Besides the metabolome of breast cancer cells, PCBs may interact with global metabolism. PCBs are also linked to dysregulation of lipid metabolism, leading to chronic metabolic disorders like obesity and type II DM [109]. In a study conducted on serum samples with increased PCB concentration, marked increase in fatty acid concentration was evidenced leading to conclusion of role of PCB in fatty acid biosynthesis and fatty acid activation pathways. It was also found that other EDCs like dichlorodiphenyltrichloroethane (DDT) and per- and poly-fluoroalkyl substances (PFAS) also capable of regulating these pathways [70]. These EDCs have a synergistic effect on the global metabolome. These EDCs are proven to positively influence the rate of fatty acid biosynthesis and activation through the aryl hydrocarbon receptor (AhR), pregnane X receptor, and peroxisome proliferator-activated receptor nuclear transcription signaling [109]. Liphophilic EDCs like PCBs, DDT, and PFAS interact with nuclear transcription factors, fatty acid uptake proteins and lipid biosynthesis enzymes and lipid metabolizing enzymes. [109-111]. These EDCs thus are capable of regulating metabolic pathways and are linked to development and progression of metabolic disease, that subsequently increase the risk of development and progression of complex diseases, like breast cancer, prostate cancer, colon cancer and pancreatic cancer [112-115]. Increased lipid metabolism results in free circulating fatty acids, which highly contribute to increase in breast cancer proliferation and tumorigenicity in vivo [116,117].

However, the exact mechanism of how PCBs regulate pathways of lipid metabolism of both cancer and non-cancerous cells are yet to be understood. Factors related to PCB exposure like, Concentration and frequency of exposure, age of exposure and even secondary health factors and genetic susceptibility of patients are all needed to be considered while understanding the mechanism of PCB induced metabolic dysfunction that leads to development of breast cancer. Studies suggest a more prominent effect of PCBs on early developmental stages of breast cancer rather than the progression of the disease [118]. A late-life sampling of PCBs recapitulates exposures during early life poorly [119]. Another study suggests that early exposure to EDC, as early as in utero and postnatal stages, via lactation, may reprogram genetic makeup and metabolome in infants that later on progresses in breast cancer development in the individual's adulthood [120]. Effects of early EDC exposure upon interacting with other risk factors like lifestyle, diet and genetic polymorphisms can lead to a synergistic effect in increased chances of disease development.

4.2. Bisphenols

Bisphenols are a group of industrial chemicals used as plasticizers [121]. Their widespread use in almost every plastic consumer product makes their presence ubiquitous in the environment [122] (Figure 1). The most harmful among this class is BPA. Due to their disrupting effect on endocrine functioning, use of BPA has been banned in most countries and are being replaced with other bisphenols, like bisphenol F (BPF), bisphenol S (BPS), tetrabromo- BPA (TB-BPA), and tetracholoro-BPA (TC-BPA) [123]. These bisphenols also show endocrine function disrupting properties and are high degree of structural resemblance to BPA [124].

Many studies have successfully established the carcinogenic properties of BPA, but the mechanisms involved remains unclear. Low doses exposure of BPA in uterus of Sprague-Dawley rats resulted in development of neoplastic lesions and even carcinoma development in offspring [125].

BPA exposure increases susceptibility to development of breast cancer development, as observed in in-vivo studies (Figure 3). BPA along with other factors like lifestyle factors synergistically increases risk of breast cancer development, initiation and progression.

Another study shows that exposure to BPA in the uterus of FVB/N mice significantly increased the risk of developing 7,12-dimethylbenz(a)anthracene-induced tumors. The study also shows the role of BPA as a growth promoter in MCF-7 cells xenografted nu/nu mice [126]. However, this xenograft mice model presents with a limitation that cells from established cancer cell line were not directly injected in the mammary gland, but rather in the flank of the mice. Due to variation in the genetic makeup of human and mice, a direct extrapolation of these data from mice to humans is difficult and not absolutely precise. Heterogeneous collagen-rich stroma present in the human breast is absent in a comparatively simpler structure of the rodent mammary glands [127]. A study shows that perinatal

exposure of BPA in rhesus monkeys, shows significantly increased mammary bud density, however carcinogenic transformation was not observed [128]. A similar effect was observed in mammary glands of rodents upon BPA exposure, thus creating a basis of validation for these results.

Metabolomic analysis studies have been profoundly used in assessment of bisphenol-induced breast cancer, in both in vitro and in vivo studies. However, a challenge remains in mimicking the exact pathological conditions, in an on-vitro setup, of the diseased target organs from where the cell line was derived. In vitro models of diseases are clonal and offer limited genetic diversity, hindering the ability to conclude all pathological scenarios.

BPA exposure targets liver and disrupts systemic energy homeostasis, and alters metabolome of cells thus increasing incidence of breast cancer (Figure 5).

Upon exposing human hepatic cell line HepG2 to low doses of BPA in the micromolar to the picomolar range, estrogen-induced metabolic pathways were observed to get activated. Both BPA and β-estradiol showed similar effects in increasing the cellular concentrations of arginine, creatinine, and glutamine by regulation of the urea cycle and the Krebs cycle [73]. Increased cellular uptake and metabolism of arginine and glutamine have been previously related to development of many types of cancer [129]. Both BPA and β-estradiol disrupts lipid metabolism by alteration of the levels of apolipoproteins, which play important role in binding and trafficking lipids, that have established role in cancer invasion and proliferation [73, 130]. A study shows CD-1 mice livers when exposed to BPA, showed upregulation in *Apob and* downregulation of *ApocI*, subsequently leading to disfunction of apolipoprotein [131] (Figure 6). These observations thus can help in concluding the role of BPA in development and progression of breast cancer by alteration and disruption of lipid metabolism and amino acid metabolism and uptake.

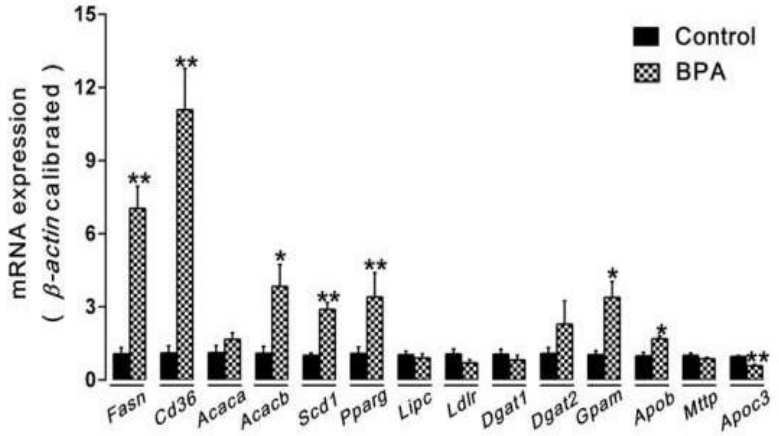

Figure 6: mRNA expression of lipogenesis-related genes (n=4/group). Levels of protein and mRNA were normalized to β-actin and were expressed as fold of values in control mice. Data were mean ± SE. *p<0.05 vs. control mice, **p<0.01 vs. control mice [126]. BPA, Bisphenol A.

Exposure to BPA altered nucleotide metabolism in the ER-positive cell line, MCF-7, evidenced by increases in the nucleotide precursors cytidine triphosphate (CTP) and uridine diphosphate (UDP) glucuronic acid [74]. A study that tested cocktails of exposures with a "leave one out" approach found that BPA was essential for altering purine and pyrimidine metabolism in MCF-7 cells, due to an increase in UDP, uridine triphosphate, cytidine diphosphate, and CTP [75]. In rapidly dividing cells, like cancer, nucleotides are quickly used so the nucleotide salvage pathway is more efficient for DNA synthesis [23]. However, when interpreting the results of these studies, it should be noted that the MCF-7 cell line was immortalized from a fully transformed breast cancer. Though the MCF-7 cell line is ER-positive making it an ideal candidate for EDC testing, it cannot mimic the unique features of cancer initiation. To conclude the role played by EDCs in facilitating a multi-step model of carcinogenesis, models that reflect early-timepoint initiation of breast cancer, and models that reflect promotion and/or progression of already existing breast cancer is essential.

Mice xenografted with MDA-MB-231 cells, an ER-negative cell line, [Zhao et al.] when exposed to BPF, BPA analog, prompted alterations in glutathione biosynthesis, glycerophospholipid and glycerolipids degradation, and glycolysis that subsequently led to development of larger tumors [78]. Down regulation of glutathione biosynthesis resulted in increase in cellular ROS levels that lead to DNA damage and subsequent development of carcinogenesis [132]. BPF increases formation of metabolic intermediates like lactate, pyruvate, fructose-6-phosphate, and glucose-6-phosphate that promote glycolysis [78]. The cause of these glycolytic changes is yet to be determined and thus cannot be directly correlated to proliferation induced by BPA or increased tumor size. MCF-10A cells show increased cancer cell proliferation due to alteration in the citric acid cycle, purine metabolism, and lipid metabolism, when exposed to BPS [76]. Similar results were observed in MCF-7 cells exposed to TB-BPA and TC-BPA. The study also showed increased formation of glycolytic intermediates and decreased glutathione concentrations upon exposure to TB-BPA and TC-BPA, leading to upregulated ROS production [77]. TB-BPA and TC-BPA also induced alternate energy metabolism pathways from amino acids via the glycolytic shunt pathway [77]. These findings emphasize the role of bisphenol analogs in alteration of metabolome of breast cancer cells, and thus highlight the dangers of using these chemicals in commercial products.

4.3. Phthalates

Phthalates are common additives in commercial plastic products used to manufacture vinyl, PVC, and food packaging (Figure 2). Phthalates are structurally similar to β-estradiol, and also act as endocrine disruptors (Figure 1). However, a direct correlation between urinary phthalate levels and development of breast cancer has not yet been established, according to a study conducted on 150,000 postmenopausal women [133]. In contrast to the previous result, another study conducted on a multi-ethnic population, a significantly increased risk of breast cancer incidence was correlated to urinary phthalate levels [134]. However, the sample size of this study was rather small and the analysis derived was based on a single urinary sample measurement.

In the absence of clear and reproducible results from epidemiological studies, in vitro and in vivo studies present data that shows increased risk of breast cancer development upon exposure to phthalates (Figures 3 and 5).

The most estrogenic phthalates are di(2-ethylhexyl)phthalate, dibutyl phthalate (DBP), and benzyl butyl phthalate (BBP). These phthalates even at low doses show marked increase in ER-alpha activation, cell viability, and proliferation in the MCF-7 cell line [106].

DBP and BBP exposure resulted in increased proliferation of ER-negative cell line MDA-MB-231 by activating AhR, that subsequently resulted in downstream signaling through a histone deacetylase enzyme (HDAC6), increasing expression levels of the oncogene and tumor promoter gene c-myc [14] (Figures 7,8).

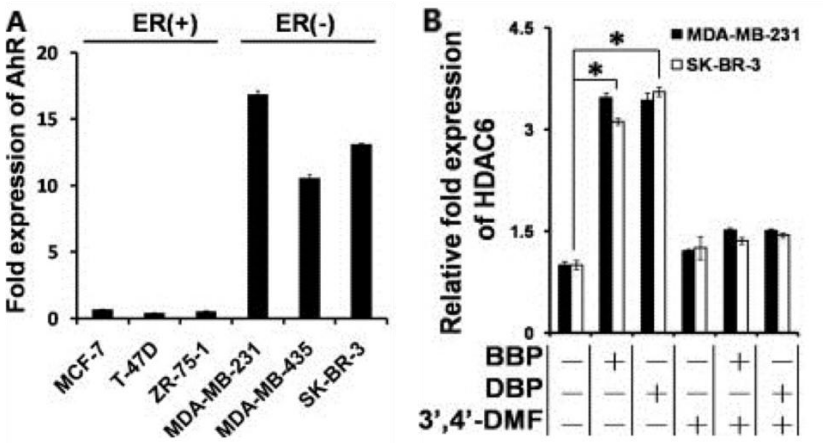

Figure 7: Phthalates mediate HDAC6 gene expression through the nongenomic function of AhR. A) Expression of AhR mRNA was determined by quantitative PCR in multiple breast cancer cell lines. B) Different cancer cell lines were pretreated with 3',4'-DMF(1μM) for 1h. Cells were then

treated with 1μM phthalates for 24 h, and expression of the HDAC6 gene was determined by quantitative PCR. *P<0.05. AhR, aryl-hydrocarbon receptor; HDAC6, histone deacetylase; BBP, benzyl butyl phthalate; DBP, dibutyl phthalate; 3',4'-DMF, 3,4-dimethoxyflavone [14].

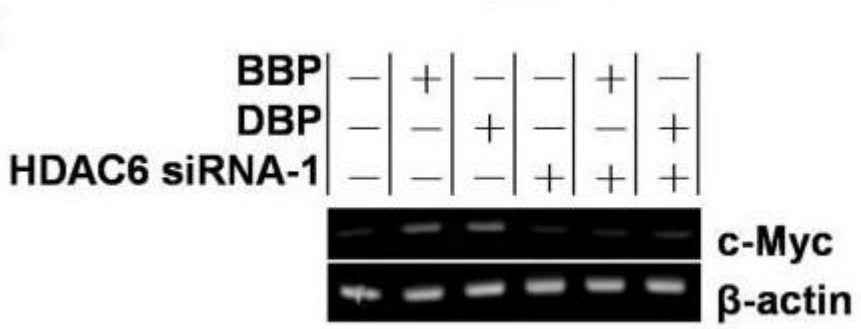

Figure 8: Phthalates mediate the c-Myc gene expression through HDAC6. The c-Myc gene expression was evaluated by quantitative PCR in cells treated with and without phthalates. For these experiments cells were transfected with HDAC6 siRNA-1 followed by stimulation of cells with either 1μM BBP or DBP for 24 hours. BBP, benzyl butyl phthalate; DBP, dibutyl phthalate; HDAC6 siRNA-1, histone deacetylate small interfering RNA [14].

Xenografted nu/nu mice when exposed to DBP and BBP, showed marked increase in MDA-MB-231 tumor size [14]. These results however don't reveal the underlying mechanisms of how phthalates initiate ER-negative breast cancer.

A study conducted on the serum of pregnant women with high phthalate urinary levels, shows altered levels of lipid constituents of the membrane, cholesterol, and sphingomyelin [78], which in turn increased the levels of triacylglycerols in serum and increased intermediate formation in sphingosine biosynthesis [78]. Thus, phthalate exposure causes significant metabolomic changes. These increased intermediate formations activate inflammatory signaling pathways. Zhao et. al also demonstrated a positive association between body mass index and urinary phthalate metabolite levels, implying that phthalates influence metabolism [78]. The hyperlipidemia induced in these pregnant women, upon exposure to pseudo-hormones like phthalates, results in increased incidence of breast cancer development. Phthalate exposure is also linked to development of other metabolic diseases like type II DM [135], which has been successfully established epidemiologically. A NHANES 2001-2010 study established a direct correlation between urinary levels of phthalate metabolites and development of metabolic syndrome [136]. Phthalate exposure results in the alteration of metabolome to conditions favoring hyperlipidemia which subsequently leads to cancer initiation, and thus increasing the risk of breast cancer development.

4.4. Zeranols

Zearalenones are mycotoxins produced by the fungus *Fusarium* that contaminate corn and grains (Figure 2). Humans consume this grain and zearalenone entering the metabolic pathway is metabolized to other beta-resorcyclic acid lactones (RALS) in the liver, some of them possessing stronger endocrine-disrupting properties than the parent compound [137]. Alpha-zearalenol is the most estrogenic metabolites of ZEN. Alpha-zearalenol is commercially manufactured into the synthetic hormone Zeranol^{TM}, used regularly for feeeding beef to increase growth of the animals and thus increase meat production rates. Consumption of these meat products routinely expose us to zearalenone, and many of its derivatives been found in human serum [138] and urine [139]. Zeranols, ZEN, and other RALS are chemically similar to endogenous beta-estradiol (Figure 1). These compounds and their analogues competitively bind to mammalian ER [140] due to the flexibility of the RAL ring structure [141]. Post receptor binding, zeranol initiates downstream estrogenic signaling pathways [142].

Epidemiological studies involving exposure to ZEN and its metabolites have established ZEN exposure to developmental defects and endocrine system disruption. Developmental defects due to ZEN exposure include delayed height and breast development [143]. In a 10-year longitudinal study, high serum levels of ZEN resulted in amenorrhea and also pubertal delays [96]. Increased levels of ZEN in urine have been directly correlated to increased incidence of breast cancer in Tunisia women [81]. However, the mechanism of onset of cancer initiation and progression as resulted from ZEN exposure is yet to be understood.

In vitro studies evidenced increased cell proliferation in various cancer cell lines, upon exposure to both ZEN and alpha-zearalenol [144]. There is evidence of cancer promotion during several distinct stages of breast cancer development (Figure 3). A study conducted in MCF-10A cells showed increased cell proliferation rates in the cell line by reduction in the cellular doubling time and occurrence of neoplastic transformation, when the cells were exposed to repeated doses of Zeranol [145]. MCF-10A is an immortalized non-cancerous normal breast cell line, found in the early proliferative stage of breast tissue. Zeranol at low concentrations downregulates formation of cell cycle inhibitor p21Cip1 and induces the growth of the ER-positive cancer cell lines MCF-7 and KPL-1 [146] (Figures 9,10).

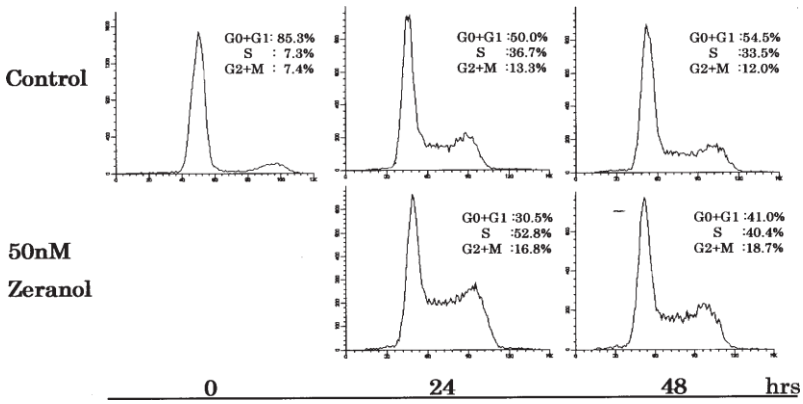

Figure 9: Low-dose (50nM) zeranol accelerates the cell cycle progression of estrogen receptor-positive MCF-7 human breast carcinoma cells [146].

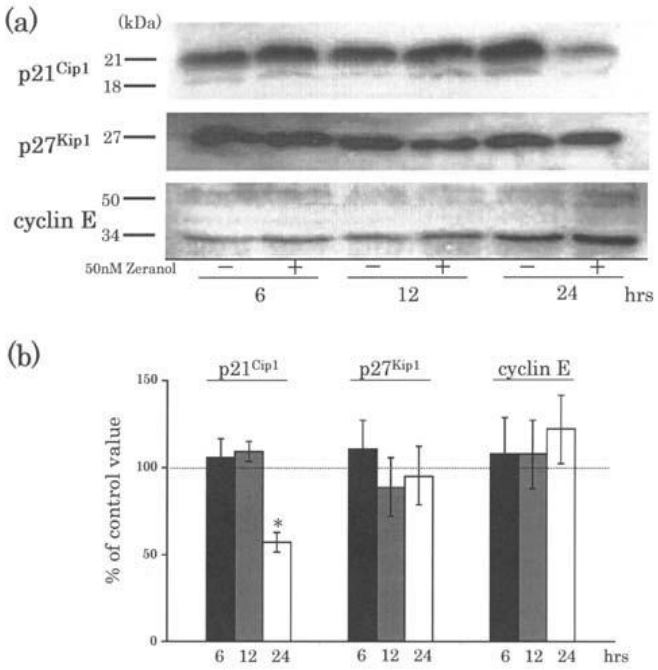

Figure 10: Western blotting. Representative results a) and quantitative data b) after 6-, 12-, and 24-h exposure of MCF-7 cells to low-dose (50nM) zeranol. After 24h exposure to low-dose zeranol the expression of the CDK inhibitor $p21^{Cip1}$ was significantly suppressed [146].

These cell lines show a growth pattern that depicts later stages of breast cancer development, when the tumor already attained invasiveness. Zeranol upon interaction with obesity hormone leptin, synergistically increases cell proliferation rates in the ER-positive breast adenocarcinoma cell line MCF-7. Zeranol is involved in inducing metabolomic dysfunction that induces metabolome characteristic changes that promotes tumor formation in the breast cells [147]. Similar changes have also been observed in primary breast cancer epithelial cells upon zeranol exposure [148].

In vivo study data of breast cancer models with zeranol exposures are very few. Of the few successful in vivo studies conducted, conclude that zeranol exhibits similar pathological effect to estrogen in increasing cell growth proliferation and subsequent transformation into carcinogenesis in animal models. In vivo studies in rhodents exposed to zeranol show increased cell proliferation rates in mammary gland [83], thus mimicking the cancer-promoting pattern similar to that of estrogen. Another study conducted on august Copenhagen Irish (ACI) rat model, show that zeranol may cause overt carcinogenesis. However, this study involves small sample size and the results are not very conclusive [149].

Understanding the distinction between carcinogenesis development and occurrence of hyperplasia by hormonal stimulation in mammary cancer model is very important. Estrogen activates downstream pathways that involves estrogenic targets in cell cycle control and promotes cell growth and proliferation. Estrogen is also involved induced generation of ROS that behaves as a genotoxic agent [150]. The exact pathway of ROS generation by estrogen still remains unclear, though certain hypotheses are proposed. One proposed mechanism of ROS generation by estrogen involves excessive hydrogen peroxide production and mitochondrial metabolism stimulation [151]. Studying the effects of estrogen in mammary glands of different animal models, including the ACI rat models, it can be conclusively stated that estrogen as a short-term effect induces mammary hyperplasia but long-term exposure induces development of carcinogenesis [152,153].

Studies conducted on animal models confirm the zeranol poses capabilities that activate ER and promote cell growth and proliferation; however, their role in initiation of carcinogenesis and direct DNA damage remains unclear. ZENs can induce DNA damage indirectly through the generation of ROS. A study conducted in CHO-K1 ovarian cells, showed DNA damage by ROS generation when the cells were exposed to ZEN and its metabolites [154]. This indirect approach of DNA damage attained by zeranol can further proceed into incidence of breast cancer development, further aided by cell proliferation properties of zeranol. However further extensive studies are needed to determine direct evidence in establishing these properties.

Only one in vitro study in cancel cells is available that studied the metabolomic changes caused due to zeranol. MCF-7, an estrogen-sensitive cell line, showed increased cell progression and invasion, and alteration in metabolic pathways, upon exposure to zeranol [82]. Zeranol exposure altered pathways like urea cycle, methionine metabolism, protein biosynthesis, and arginine/proline metabolism. The exposed cells also showed upregulated expression of glutathione and cysteine, as increased ROS produced stimulate cysteine and glutathione biosynthesis pathways. The cells also showed increase in choline levels, marking an increased in the number of invasive tumors [155,156]. These reports thus point an active role of zeranol in initiation, progression and promotion of breast cancer.

5. Conclusion

Endocrine disruptors have been previously linked to increased breast cancer incidence, prognosis, and metastasis. However, the scientific community has not been able to reach a consensus on the risk posed by these endocrine-disrupting chemicals, and how they may promote hormone induced cancers. A clearer understanding of the mechanism of how these chemicals induce their putative carcinogenic action(s) is needed. Metabolomic analysis has revealed that different well-known EDCs alter the metabolism in breast cancer cells by increasing the lipid metabolism to better suit the survival needs of the cancer cells. EDCs can also dysregulate global metabolism, leading to higher nutrient availability that could ultimately aid in cancer initiation and progression. These findings could also be used to identify and characterize the effects of other EDCs and cancer-causing toxicants more

accurately and efficiently. Further research is required that investigates potential mechanisms, both ER-dependent and independent, through which EDCs may alter breast cancer metabolism.

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7. References

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