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Role of dietary bioactive natural products in estrogen receptor-positive breast cancer

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Abstract

Estrogen receptor (ER)-positive breast cancer, including luminal-A and -B, is the most common type of breast cancer. Extended exposure to estrogen is associated with an increased risk of breast cancer. Both ER-dependent and ER-independent mechanisms have been implicated in estrogen-mediated carcinogenesis. The ER-dependent pathway involves cell growth and proliferation triggered by the binding of estrogen to the ER. The ER-independent mechanisms depend on the metabolism of estrogen to generate genotoxic metabolites, free radicals and reactive oxygen species to induce breast cancer. A better understanding of the mechanisms that drive ER-positive breast cancer will help optimize targeted approaches to prevent or treat breast cancer. A growing emphasis is being placed on alternative medicine and dietary approaches toward the prevention and treatment of breast cancer. Many natural products and bioactive compounds found in foods have been shown to inhibit breast carcinogenesis via inhibition of estrogen induced oxidative stress as well as ER signaling. This review summarizes the role of bioactive natural products that are involved in the prevention and treatment of estrogen-related and ER-positive breast cancer.

Keywords

estrogen; oxidative stress; stem cells; bioactive natural compounds; breast cancer

1. Introduction

Breast cancer is one of the most common cancers diagnosed among women [1]. There are many established risk factors for breast cancer, including age, genetic alterations, family history, mammographic breast density, menstrual and menopausal history, radiation

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Conflicts of interest

Authors have no potential conflicts of interest to disclose.

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exposure, and life style [2–4]. In particular, the hormones, estrogen and/or progesterone, are known to be capable of increasing breast cancer risk [2, 4]. Both ER-dependent and ER-independent pathways have been proposed for biological responses of estrogen [2, 5]. Estrogen binding to receptors results in their translocation to the nucleus, where they act as transcription factors leading to altered gene expression [6–8]. ER-dependent carcinogenic action of estrogen involves ER-mediated aberrant regulation of estrogen responsive genes that lead to increased cell proliferation and accumulation of DNA damage ultimately causing cell transformation [9]. The ER-independent pathway involves cytochrome P450 (CYP) mediated oxidative metabolisms of estrogen resulting in generation of genotoxic metabolites and ROS [10]. Since a large number of studies have demonstrated an inverse association between consumption of fruits and vegetables and the risk of breast cancer through suppression of ER signaling and reduction of oxidative stress, naturally occurring dietary compounds and phytochemicals have received increasing attention for treatment and prevention of breast cancer [11–15]. This review aims to summarize the potential of bioactive natural products in the prevention and treatment of estrogen-mediated and ER-positive breast cancer.

2. ER-positive breast cancer

ER expression is the main indicator of potential responses to hormonal therapy, and approximately 70–75% of human breast cancer is hormone-dependent and ER and/or progesterone receptor (PR) positive [16–19]. The ER-positive tumors express ER, ER-responsive genes, and other genes that encode characteristic proteins of luminal epithelial cells and, therefore, are termed “luminal group” [16]. Although sub-classification of luminal tumors is still contentious, there seems to be at least two groups of ER-positive breast cancers, commonly defined as luminal A and B tumors depending on the level of expression of the characteristic genes [16, 17]. Patients with luminal A breast cancer (ER/PR-positive and HER-2-negative) have a good prognosis with low histological grade, high survival rates and low recurrence rates [16, 17, 20, 21]. Luminal B tumors are ER-positive and/or PR-positive and HER- positive/negative [20]. At the cellular level, luminal B has low expression of ER and ER-related genes, high expression of proliferation and cell cycle-related genes such as Ki67, cyclin B (CCNB)1 and MYB-like (MYBL) 2 [20, 22]. The histological grade and proliferation index of the luminal B subtype is higher and prognosis is fairly poor than that for luminal A tumors [23]. In addition, patients with luminal B tumors have higher recurrence rates compared to those with luminal A tumors [24].

3. ER-dependent and -independent mechanisms

Estrogens have been implicated in breast carcinogenesis through receptor-dependent or -independent mechanisms [2, 5] (Fig. 1). The ER-dependent mechanism involves the binding of the hormone to nuclear ERs, which then form dimers and bind to estrogen response elements (ERE) in the regulatory regions of estrogen-responsive genes to alter gene expression, referred to as the classical genomic signaling pathway [5, 25, 26]. ER can also regulate cellular functions through nongenomic estrogen signaling [27]. Plasma membrane-associated ER increases the levels of second messengers and activates various tyrosine kinase receptors [28, 29]. The receptor-mediated cell divisions could increase cell

proliferation and accumulation of DNA damage with mutational events [30]. In the ER independent pathway, carcinogenic effects of estrogens are believed to occur through the actions of estrogen metabolites [2, 5, 31]. Estrogen metabolism regulated by phase I CYP enzymes mediates the hydroxylation of estradiols and estrones [2, 32]. The formation of catechol estrogens, 2-hydroxyestrone/estradiol (2-OH-E₁/E₂) or 4-hydroxyestrone/estradiol (4-OH-E₁/E₂), are catalyzed by CYP1A1 and CYP1B1, respectively [2, 5]. Further oxidative metabolism of the catechols leads to formation of 2,3- and 3,4-quinone that can cause DNA damage [33]. The 3,4-quinone forms unstable depurination adducts with adenine and guanine, 4-OH-E₂/E₁-1-N3 adenine and 4-OH-E₂/E₁-1-N7 guanine, whereas the 2,3-quinone forms relatively stable DNA adducts and depurination occurs uncommonly [9]. These quinones can be reduced to semiquinones by CYP reductase, and this process can establish a redox cycle to produce ROS that can cause oxidative DNA damage [34]. Phase II enzymes, including catechol-O-methyltransferase (COMT), glutathione S-transferase (GST) and quinone reductase (QR), can inactivate estrogen catechols, semiquinones and quinones by preventing formation of adducts and oxidative DNA damage [2, 5].

4. Estrogen and breast cancer stem cells

Cancer stem cells, defined by their ability to initiate the formation of tumors, self renew and differentiate, have been suggested to play a role in tumor initiation, maintenance, metastasis and resistance to therapies [35, 36]. Breast cancer stem cells were first identified as CD44⁺/CD24^{-/low} cell populations with an increased ability to form tumors [37]. Additional stem cell markers, such as high intracellular aldehyde dehydrogenase 1 (ALDH1) and epithelial specific antigen, have also been used in the identification of breast cancer stem cells [38]. Although the importance of estrogen in breast cancer is well-established, the role of estrogen in breast cancer stem cells is not fully understood. Some studies proposed that ER-positive cells are generated from a stem cell compartment that is directly stimulated by hormones, while others suggested that ER-positive cells may stimulate proliferation of a separate stem cell compartment in a paracrine manner [39, 40]. Several studies have reported that estrogen can modulate breast cancer stem cells via multiple pathways (Fig. 1). Major pathways involved in embryonic development, including Wnt/β-catenin, Hedgehog and Notch, have been identified to play pivotal roles in self-renewal behavior of breast cancer stem cells [41, 42]. Estrogen significantly increased the CD44⁺/CD24⁻ stem cell populations in MCF-7 and T47D as well as the size and number of the tumorsphere by targeting ERα.36 via the phosphoinositide-3-kinase (PI3K)/Akt/GSK-3β/β-catenin pathway [43]. Fillmore *et al.* [44] reported that estrogen-induced expansion of cancer stem cells *in vitro* could lead to a functional increase in breast cancer stem cells and tumorigenic phenotypes *in vivo* through the FGF/Tbx3 signaling pathway. In addition, estrogen induces the expansion of CD44⁺/CD24^{-/low} stem-like cells populations and produces larger spheres by up-regulating cancer stem cell-related genes such as ALDH1, glioma-associated oncogene homolog (Gli)-1, Shh, Nanog, SOX2 and Bmi-1 through a noncanonical ligand-independent Shh/Gli signaling pathway [45]. Furthermore, estrogen induces a dramatic increase of OCT4 expression and proliferation of mammospheres as well as the breast cancer stem cell population in MCF-7 mammospheres [46]. These results imply that estrogen can modulate various breast cancer stem cell signaling pathways. The bioactive natural compounds, including curcumin [47–

49], sulforaphane [50], soy isoflavone [51], epigallocatechin-3-gallate (EGCG) [52], resveratrol [53], indole-3-carbinol [54], luteolin [55], and 6-shogaol and pterostilbene [56], have the ability to inhibit breast cancer stem cells through regulation of self-renewal pathways such as Notch, Wnt/Gsk3 β / β -catenin, Hedgehog and PI3K/mTOR pathway. Currently, there are limited data available to conclude whether natural compounds can effectively suppress estrogen-induced breast cancer stem cells. Further studies are needed to identify the mechanisms of estrogen signaling related to breast cancer stem cells and the cancer inhibitory effects of natural compounds.

5. Natural products against ER-positive breast cancer

An increased understanding of the relationship between a healthy diet and lower incidence of a variety of cancers has led many researchers to focus on natural products for the prevention of cancer. A number of different terms are used to describe the many natural products currently being developed for health benefits. These include nutraceutical, functional food, pharmafoods, designer foods, dietary supplements and phytochemicals [57]. The terms functional food and nutraceutical are used interchangeably, and a number of definitions of what is included under these all-encompassing headings have been advanced [58]. Functional foods contain useful ingredients or compounds that have demonstrated physiological benefits; nutraceuticals (coined from “nutrition” and “pharmaceutical”) are naturally derived bioactive ingredients or compounds (usually as a supplement or extract) that provide health benefits [59]. Nutraceuticals and functional foods include many bioactive phytochemicals. Phytochemicals are natural bioactive compounds found in fruits, vegetables, herbal and medicinal plants which act as a defense system against several diseases [60, 61]. Phytochemicals from natural products cover a diverse range of chemical entities such as polyphenols, flavonoids, steroidal saponins, organosulphur compounds and vitamins [62]. Phytochemicals have been shown to exert beneficial effects with good safety profiles on many types of cancers including prostate, colon, breast, ovarian, and liver. Certain bioactive compounds have unique structural similarities to estrogen, and this review, therefore, focuses on phytochemicals that are exclusively involved in prevention and treatment of estrogen-related and ER-positive breast cancer. There are various animal models of ER-positive breast cancer that could be used to test existing and novel chemopreventive agents [63, 64]. The most widely studied are xenograft tumor models of established human breast cancer cell lines transplanted into athymic nude mice [65]. There are three major ER-positive cell lines commonly used, such as MCF-7 [66], T47D [67], and ZR-75-1 [68]. In addition, overexpression of genes involved in breast cancer and mutagenesis induced by the mouse mammary tumor virus (MMTV) or polyoma middle-T antigen (PyMT) [69], or treatment with chemical agents, such as 7,12-dimethylbenz(a)anthracene (DMBA) [70], medroxyprogesterone acetate (MPA) [71], or N-methyl-N-nitrosourea (NMU) [72], can induce ER-positive mammary tumors in experimental animals. Furthermore, estrogen-mediated mammary carcinogenesis models are based on long-term subcutaneous administration of estrogen using slow-release pellets or silastic tubes [73]. In Table 1, we review the effects of bioactive natural compounds against ER-positive breast cancer in experimental *in vivo* models.

5.1. Allyl isothiocyanate

Allyl isothiocyanate, which occurs in many cruciferous vegetables, has been reported to have chemopreventive activities in various cancer models [74]. Bioavailability of allyl isothiocyanate is high and absorbed allyl isothiocyanate is primarily eliminated in the urine in mice and rats [75–77]. Human absorption and disposition of allyl isothiocyanate appear to closely resemble that of animals, as studies showed that about 50% of the dose was recovered in the urine as a metabolite [78, 79]. Allyl isothiocyanate inhibited mammary tumor incidence and tumor growth in DMBA-treated female Sprague Dawley (SD) rats [80]. In this study, allyl isothiocyanate decreased lipid peroxidation-related thiobarbituric acid reactive substances (TBARS) and lipid hydroperoxides (LOOH) as well as total cholesterol (TC), triglycerides (TG), glycopospholipid (PL), free fatty acids (FFA), low-density lipoprotein (LDL) and very-low density lipoprotein (VLDL) [80]. Decreased levels of CYP450 and increased activities of phase II and antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), GST and glutathione reductase (GR), have been shown in liver and mammary tissues of allyl isothiocyanate-treated rats [80]. These data suggest that allyl isothiocyanate exerts chemopreventive activity against DMBA-induced mammary carcinogenesis mainly via activation of antioxidant response.

5.2. Apigenin

Apigenin is a natural flavonoid commonly found in fruits and vegetables such as parsley, celery, thyme, and oranges. The chemical structure of apigenin is similar to estrogen, and it may act as a mimic of estrogen. Therefore, extensive studies have shown that apigenin has potent antioxidant and anticancer activities in ER-positive and ER-negative breast cancer [81–83]. Apigenin in its pure form is unstable and insoluble in water or organic solvents. In its natural form, apigenin is present in foods mostly as glycoside conjugates and various acylated derivatives, which are more soluble than the parent compound. Therefore, apigenin bound to β -glycoside provides high bioavailability [84–86]. Several animal studies reported a decrease of estrogen-dependent tumorigenesis with apigenin containing diets. Mafuvadze *et al.* [87] determined whether apigenin inhibits the growth of aggressive BT-474 xenograft tumors in nude mice exposed to MPA, one of the most common hormone replacement therapies for postmenopausal women. In this study, apigenin inhibited progression and development of BT-474 xenograft tumors by inducing apoptosis, inhibiting cell proliferation, and reducing expression of Her2/neu, Ki-67 and vascular endothelial growth factor (VEGF) [87]. In another study using the DMBA model to examine the chemopreventive effect of dietary apigenin against MPA-accelerated mammary tumors in SD rats, apigenin decreased tumor incidence and tumor multiplicity [81]. Administration of apigenin reduced MPA-dependent tumor incidence and tumor multiplicity as well as MPA-dependent increase in VEGF and VEGF receptor-2 expression [88]. The direct binding of ER α to the ERE in the VEGF promoter region is known to decrease VEGF expression [89], suggesting that apigenin may provide a potent chemopreventive effect via ER-dependent pathway in breast cancer.

5.3. Berries

Dietary berries contain several phytochemicals such as cyanidin, delphinidin, quercetin, kaempferol, ellagic acid, resveratrol and pterostilbene, which have antioxidant properties and help to reduce the risk of breast cancer [90]. Bioavailability of anthocyanin is generally poor compared to other berry flavonoids, usually limited to less than a percent of the amount ingested. Proanthocyanidins also exhibit poor bioavailability. Flavonols in berries show better bioavailability than other flavonoids [91]. Aiyer *et al.* [92, 93] investigated the effects of dietary berries in estrogen-mediated mammary tumorigenesis. Black raspberry reduced the tumor volume and tumor multiplicity. Blueberry showed a reduction only in tumor volume [93]. The same group evaluated the ability of each of the mixed berries (strawberry, blueberry, blackberry, red raspberry, and black raspberry) and blueberry in reducing oxidative DNA damage in estrogen-treated ACI rats [94]. Their results indicated that 2.5% blueberry diet significantly reduced the estrogen-induced levels of 8-hydroxy-2-deoxyguanosine (8-OH-dG), P-1, P-2 and PL-1 subgroups [94]. Jayabalan *et al.* [95, 96] tested both preventive and therapeutic activities of diet supplemented with blueberry against estrogen-mediated mammary tumorigenesis. Administration of blueberry delayed the tumor latency and decreased the tumor incidence, tumor volume and tumor multiplicity in both modes. Administration of blueberry diet reduced the expression of CYP1A1, cyclin D1 and proliferating cell nuclear antigen (PCNA) and modulated the levels of miR-18a and miR-34c [95, 96]. These findings indicate that blueberry could modulate major estrogen-associated oxidative stress and proliferative markers, resulting in protective effects against mammary tumorigenesis in animals treated with estrogen.

5.4. Biochanin A

Biochanin A, an isoflavone isolated from red clover, is a natural phytoestrogen [97]. The chemical structure of biochanin A is similar to estrogen, enabling it to bind to ER. The effects of biochanin A include regulation of estrogen receptor, inhibition of cell proliferation, reduction of inducible nitric oxide (NO) synthase, and apoptosis stimulation in breast cancer [98, 99]. Biochanin A has low bioavailability in rats [100, 101]. Treatment with biochanin A decreased the tumor incidence and multiplicity in NMU-induced rat mammary carcinogenesis [102]. One study determined the effect of biochanin A, administered alone or in combination with the quercetin and epigallocatechin-3-gallate, on the growth of MCF-7 xenograft tumors. Treatment with biochanin A or the mixture of the three compounds resulted in a reduction in tumor incidence and tumor size [103]. Mishra *et al.* [104] investigated whether biochanin A inhibits mammary tumorigenesis via regulating anti-oxidant and xenobiotic metabolisms in DMBA-treated rats. Treatment with biochanin A suppressed tumor burden by increasing antioxidant enzymes, including SOD, CAT, GPx, GST, DT-diaphorase (DTD), and preventing the peroxidative damage, suggesting that protective effects of biochanin A are mediated by inhibiting oxidative stress and activating antioxidant response.

5.5. Caffeine

Caffeine, a natural chemical found in coffee beans, cacao, and tea leaves, has anticancer properties against both ER-dependent and ER-independent breast cancer cells [105, 106].

Several studies demonstrated that caffeine absorption from the gastrointestinal tract is rapid and complete with the bioavailability of 99 to 100% after oral administration [107–110]. Treatment with caffeine decreased the total number of mammary tumors in diethylstilbestrol (DES)-treated ACI rats [111]. Wolfrom *et al.* [112] assessed the influence of caffeine on the incidence of benign mammary tumors in DMBA-treated SD rats. Caffeine treatment significantly reduced the incidence of benign mammary fibroadenomas as well as the incidence of mammary gland cysts [112]. VanderPloeg *et al.* [113] explored the effect of chronic caffeine consumption on the initiation and promotion stages of DMBA and NMU-induced mammary tumorigenesis in female SD rats. Caffeine significantly suppressed the initiation stage of DMBA-induced rat mammary tumorigenesis, while there was no inhibitory effect in the promotion stage of NMU-induced mammary tumorigenesis [113]. Another study investigated the chemopreventive effects of caffeine on 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine (PhIP)-induced mammary carcinogenesis in SD rats. Administration of caffeine reduced tumor incidence and tumor size as well as tumor multiplicity [114]. Taken together, caffeine may reduce breast cancer by modifying metabolism of carcinogens *in vivo*.

5.6. Coumarin

Coumarin, a naturally occurring fragrant organic compound, is commonly found in many plants such as grass, orchids, citrus fruits and legumes [115]. The pattern of substitutions on the basic chemical structure of coumarin influences both pharmacological and biochemical properties, such as estrogenic activity [116]. However, coumarin has very low bioavailability in humans due to rapid absorption, metabolism, and extensive first-pass hepatic conversion to 7-hydroxycoumarin followed by glucuronidation [117, 118]. Prince *et al.* [119] investigated the ability of coumarin to block DMBA-induced DNA adduct formation in sensitive to carcinogenesis (SENCAR) mouse mammary gland. Coumarin inhibited DMBA-DNA adduct formation through inhibition of CYP450-1A1/1B1 and induction of hepatic GSTs [119], suggesting that coumarin can act via genotoxic pathway. Another study revealed that coumarin suppressed the incidence of adenocarcinomas, tumor growth, tumor size and tumor multiplicity when administered before DMBA. However, there was no effect when coumarin was given after DMBA treatment [120]. These results indicate coumarin as an effective chemopreventive agent against DMBA-induced carcinogenesis by reducing genotoxic pathway.

5.7. Curcumin

Curcumin, a yellow pigment of turmeric, has been reported to be an effective and safe natural compound for the prevention and treatment of breast cancer [121]. Despite much evidence of its efficacy and safety, curcumin has not yet been approved as a therapeutic agent due to its low bioavailability *in vivo* and in humans [122–124]. The daily dosage of curcumin generally seems safe in the range between 500 and 4000 mg, and no toxicity was observed even up to 8 g per day for 3 months, except for some individuals who had minor gastrointestinal side effects [125, 126]. Carroll *et al.* [127] revealed that curcumin delayed the first appearance of MPA-accelerated tumors, reduced tumor multiplicity in DMBA-induced and MPA-accelerated tumors, and decreased MPA-induced VEGF induction in hyperplastic lesions. Siddiqui *et al.* [128] demonstrated that combination of docosahexaenoic

acid and curcumin reduced the tumor incidence and tumor growth of DMBA-induced mammary tumorigenesis in SENCAR mice. Zhou *et al.* [129] also investigated the efficacy of curcumin in combination with mitomycin C in the MCF-7 xenograft model. Curcumin alone and curcumin plus mitomycin C treatment inhibited tumor growth, with increased G1 arrest associated with inhibition of cyclin D1, cyclin E, cyclin A, cyclin-dependent kinase (CDK) 2 and CDK4 via down-regulation of p38 mitogen-activated protein kinase (MAPK) pathway [129]. Bansal *et al.* [130] tested the potential chemopreventive effect of curcumin against estrogen-mediated mammary tumorigenesis when curcumin was given via diet or implants. Curcumin administered via implants resulted in significant reduction in both tumor multiplicity and tumor volume, while dietary curcumin was ineffective [130]. It may be because dietary curcumin increased hepatic CYP1A and CYP1B1, but not CYP3A4 activities, whereas curcumin given via implants increased CYP1A and CYP3A4, but decreased CYP1B1 activity in estrogen-treated ACI rats, generating non-carcinogenic estrogen metabolites [130]. Overall, these results indicate that curcumin inhibits mammary carcinogenesis by controlling estrogen-metabolism, apoptosis and MAPK pathway.

5.8. Diallyl sulfide

Allyl sulfides, such as diallyl sulfide, diallyl disulfide, and diallyl trisulfide, are major organosulfur compounds derived from garlic. These compounds have been shown to exert potent chemopreventive effects in several types of breast cancer [131, 132]. Oral administration of diallyl sulfide inhibited tumor growth in the MCF-7 xenograft model [132]. Green *et al.* [133] revealed that diallyl sulfide inhibited the DES-induced mtDNA adducts and caused a decrease in nDNA adduct formation in ACI rats. The same group investigated the effect of diallyl sulfide on the expression of phase I and phase II metabolizing genes involved in estrogen metabolism in the DES-induced ACI rats [134]. Their results indicated that diallyl sulfide treatment increased the expression of CYP1A1 and CYP1B1 as well as GST and SOD [134]. In addition, diallyl sulfide increased the expression of p53, Gadd45a, PCNA and DNA polymerase δ together, which are important in repairing DNA damage thus preventing cancer in DES-treated ACI rats [135]. Gued *et al.* [136] assessed the effect of diallyl sulfide on DES-induced ROS in ACI rats. Diallyl sulfide attenuated DES-induced LOOH and ROS production in breast and liver tissues. Overall, these data suggest that diallyl sulfide is a modulator of xenobiotic metabolic pathway involved in estrogen metabolism with a potential role in the prevention of breast cancer.

5.9. Diosgenin

Diosgenin, a naturally occurring steroid saponin found in legumes and yams, acts as a potential chemopreventive agent in ER-positive and ER-negative breast cancer [137]. Estrogenic effects of diosgenin have been hypothesized because of its structural similarities to estrogen. However, clinical application of diosgenin is limited due to undesirable pharmaceutical characteristics such as its poor solubility and low bioavailability [138]. An *in vivo* tumor study indicated that diosgenin significantly inhibited MCF-7 xenograft tumor growth in nude mice [137]. Jaqudeesan *et al.* [139] revealed that diosgenin has anticarcinogenic activity in NMU-induced mammary carcinogenesis in SD rats by reducing peroxidation reaction marker enzymes and antioxidant enzymes. These data imply that

diosgenin exhibits anticarcinogenic activity possibly through enhancing the antioxidant defense system.

5.10. Ellagic acid

Ellagic acid, a dietary flavonoid polyphenol present in berries, grapes, pomegranates and nuts, has anti-cancer effects through modulation of cell proliferation and apoptosis in ER-positive breast cancer cells [140]. Ellagic acid consists of phenolic rings and ortho-dihydroxyl groups, which allow receptor recognition and ER-mediated action [141]. However, the bioavailability of ellagic acid is very low due to poor absorption from the gut, rapid metabolism, and lack of transport to the target organs [142]. Treatment with ellagic acid reduced the tumor volume and multiplicity in estrogen-mediated mammary tumorigenesis in ACI rats, as reported by Aiyer *et al* [93]. The same group revealed that ellagic acid decreased the tumor incidence, volume and multiplicity as well as CYP1A1 activity in estrogen-induced ACI rats. Ellagic acid decreased 17 β -hydroxysteroid dehydrogenase (17 β HSD7) and COMT expression at early and intermediate phases of estrogen-induced mammary carcinogenesis [92]. Vadhanam *et al.* [143] investigated the potent chemopreventive effect of ellagic acid delivered by a subcutaneous implant compared with a dietary route against estrogen-induced mammary tumors. Ellagic acid delayed the first tumor appearance, tumor incidence, tumor burden, and tumor multiplicity by both the implant and dietary routes [143]. In addition, dietary and implant of ellagic acid significantly reduced the plasma prolactin levels and PCNA expression [143]. Ravoori *et al.* [96] explored the long-term effects of the berries supplemented in diets against estrogen-induced mammary tumorigenesis in ACI rats. Ellagic acid, present in black raspberry, delayed the first tumor appearance as well as reduced the tumor volume and multiplicity [96]. Ellagic acid reduced estrogen-induced serum estrogen and plasma prolactin levels while the expression levels of CYP1A1 and ER α were increased at 3 month and 3-, 7- month time points, respectively [96]. Munagala *et al.* [144] examined the role of ellagic acid on deregulated miRNAs during estrogen-induced mammary tumorigenesis. Administration of ellagic acid down-regulated the expression of ER α , Bcl-w, cyclin D1, cyclin G1 and antiproliferative factor RASD and up-regulated the expression of FOXO1 and FOXO3a. Overall, these data suggest that chemopreventive effects of ellagic acid may be associated with ER-dependent and antioxidant pathways.

5.11. EGCG

EGCG, one of the major polyphenols found in all tea preparations, possesses anti-proliferative, anti-mutagenic, and chemopreventive effects in cell culture and animal models of breast carcinogenesis [145, 146]. EGCG has poor bioavailability when taken orally in animals and humans [147–149]. However, some laboratory studies in mice and dogs have demonstrated the potential hepatotoxicity of acute oral bolus dosing with EGCG or green tea extracts [150, 151]. Although the underlying mechanisms of EGCG-induced hepatotoxicity remain to be investigated, it has been proposed that the acute oral doses of EGCG can result in oxidative stress leading to liver injury [152]. The human case studies also have reported an association between high doses of green tea-containing dietary supplements and hepatotoxicity [153], suggesting that genetic and/or life-style factors may play a role in susceptibility to EGCG-mediated hepatotoxicity. Chronic administration of EGCG or green

tea may influence the biotransformation and bioavailability of high doses of EGCG [154, 155]. EGCG can influence ER-dependent expression of estrogen target genes [156], ER-independent signaling pathway [157] as well as cellular signaling pathways [158, 159]. The growth of MCF-7 xenograft tumors was inhibited during the first week of injections of EGCG [160]. Treatment of EGCG increased uterine peroxidase activity compared to estrogen alone in C57BL/6 mice [161], suggesting that the effects of EGCG in estrogen-induced responses *in vivo* may be due to alterations in the absorption and metabolism of estrogen in target tissues.

5.12. Ferulic acid

Ferulic acid, a polyphenol abundantly present in fruits and vegetables, exerts anti-tumor properties against breast cancer [162]. The bioavailability of ferulic acid has been studied extensively. However, results are quite variable (0.4–98%), in part depending on the food source [163, 164]. Baskaran *et al.* [165] investigated the chemopreventive effect of ferulic acid on DMBA-induced mammary carcinogenesis in SD rats. Their results indicated that oral administration of ferulic acid prevented the tumor formation and decreased tumor volume. Further, ferulic acid decreased TBARS and enzymatic/non-enzymatic antioxidants, such as SOD, CAT, GPx, reduced glutathione (GSH), vitamin E and vitamin C activities, in plasma and mammary tissues [165]. The treatment with ferulic acid increased the levels of GSH and the activities of phase II detoxification enzymes, such as GST, GR and DTD, in the liver, whereas activities of GST, GR and DTD were decreased in the mammary tissues [165]. Oral administration of ferulic acid to DMBA-treated rats significantly down-regulated the expression of p53 and Bcl-2 [165]. Taken together, ferulic acid may alter the apoptosis pathway and detoxification pathway of the electrophilic intermediates that were formed during DMBA-induced carcinogenesis.

5.13. Flaxseed

Dietary flaxseed has numerous biological activities due to its high content of omega-3-fatty acid, α -linolenic acid and lignan, which have shown protective effects against breast cancer [166]. The main lignan in flaxseed is secoisolariciresinol diglucoside, which can modulate estrogen signaling due to its structural similarity to estrogen [167]. Chen *et al.* [168] determined the long-term effect of flaxseed with or without tamoxifen in ovariectomized athymic mice with MCF-7 xenografts. Flaxseed reduced tumor growth with or without tamoxifen by down-regulating the expression of estrogen-related genes such as cyclin D1, ER α and signal transduction pathways [168]. The same study group revealed that flaxseed inhibited MCF-7 xenografted tumor growth in a dose-dependent manner and enhanced the inhibitory effect of tamoxifen via modulating ER and growth factor signal transduction pathways [169, 170]. In a recent study conducted by Delman *et al.* [171], treatment with secoisolariciresinol diglucoside normalized several biomarkers in mammary gland tissues that had been altered by DMBA-induced carcinogenesis. Rickard *et al.* [172] determined the dose-dependent effects of flaxseed on NMU-induced mammary tumorigenesis in SD-rats. Administration of flaxseed decreased the tumor invasiveness and grade, suggesting that flaxseed appeared to delay the progression of NMU-induced mammary tumorigenesis [172]. Overall, these results indicated that flaxseed may be a potential chemopreventive agent against breast cancer via modulation of the ER-mediated signaling pathways.

5.14. Gallic acid

Gallic acid, a natural polyhydroxy phenolic compound, is commonly found in various foods and herbs that are well known as powerful antioxidants [173, 174]. Gallic acid was demonstrated to have anticancer effects by inhibiting cell proliferation and inducing apoptosis against ER-dependent and ER-independent cell lines [174, 175]. A few pharmacokinetic studies show that gallic acid has poor absorption profiles, low bioavailability and rapid elimination in humans and animals [176, 177]. Banerjee *et al.* [178] determined the molecular mechanisms underlying tumor cytotoxic activities of mango polyphenolics including gallic acid and gallotannins in the BT474 xenograft model. Treatment with mango polyphenolics significantly decreased tumor volume. Moreover, mango polyphenolics decreased the levels of p-PI3K, p-Akt, mTOR, hypoxia inducible factor 1 α (HIF- α), VEGF and nuclear factor κ B (NF κ B) (p65) as well as the expression of cancer-associated miRNAs including miR-126 in the xenograft tumors [178]. Gallic acid has a therapeutic potential against breast cancer, at least in part, mediated through the cancer-associated miRNAs and PI3K/Akt pathway.

5.15. Genistein

Genistein, a soy isoflavone, consists of two aromatic rings linked through a heterocyclic pyran ring. The chemical structure of genistein is similar to that of estrogen [179]. Animal and human pharmacokinetic studies show that genistein has low oral bioavailability [180, 181]. Michael *et al.* [182] tested the acute and chronic effects of oral genistein administration in rats. In this study, genistein was well tolerated at doses up to 500 mg/kg/day administered for up to 52 weeks [182]. In human studies, the toxicity studies on genistein suggested that it is safe for human consumption, even at the high concentration of 16 mg/kg body weight [183, 184]. Peng *et al.* [185] investigated the effect of prepubertal exposure to genistein on rat mammary carcinogenesis and the ErbB2/Akt signal pathway in DMBA-treated SD rats. In their study, genistein decreased tumor incidence, and its effect is associated with down-regulation of the expression of erbB2, p-Akt, AIB1 and PCNA as well as with low protein tyrosine-kinase (PTK) activity in the mammary tumors [185]. Kang *et al.* [186] found that genistein exerted anti-tumor and anti-angiogenic effects, which were evidenced by lower microvascular density, reduced plasma VEGF, and increased plasma endostatin levels in DMBA-treated SD rats. Park *et al.* [187] examined genistein-induced apoptosis in the presence of estrogen. Bcl-2/Bax ratios were decreased by genistein treatment in both estrogen-sufficient and estrogen-deficient SD rats [187]. Constantinou *et al.* [188] revealed that treatment with genistein diminished the tumorigenic potential of MCF-7 cells in nude mice. However, Andrade *et al.* [189] reported that long-term consumption of low doses of genistein (<500 ppm) promotes MCF-7 tumor growth into more aggressive and advanced growth phenotype in the MCF-7 xenograft mouse model. Fan *et al.* [190] also evaluated the efficacy of genistein suppressing tumor growth in the MCF-7 xenograft model. Genistein reduced tumor development and breast cancer stem-like population through down-regulation of the Hedgehog-Gli1 signaling pathway [190]. Overall data suggest that genistein inhibits tumor growth via multiple mechanisms including Hedgehog-Gli1 stem cell signaling, ErbB2/Akt and ER-dependent pathway.

5.16. Hesperetin

Hesperetin, found in citrus fruits, has potential anticarcinogenic activity through inhibiting cell proliferation, regulating aromatase transcription and inducing apoptosis by triggering accumulation of ROS and inducing cell cycle arrest in breast cancer cells [191–193]. Hesperetin does not bind to the ER, although it belongs to the flavanone, which is able to interact with the ERs [194]. A single hydroxyl group at the 4 position of the B-ring is hypothesized to be the one of the main features required for estrogenicity of a compound [195]. The 4-methoxy group at this very important position in hesperetin is likely to influence its binding to the ER. Although hesperetin is unable to bind to the ERs, it is effective in inhibiting cell proliferation of ER-positive cancer [192]. Ye *et al.* [196] evaluated the chemopreventive effects of apigenin, naringenin and hesperetin in the MCF-7 xenograft mouse model. Administration of hesperetin significantly decreased tumor volume as well as cell cycle-regulated proteins such as p57^{kip2}, cyclin A, cyclin E, CDK4 and Bcl-xL, while a null effect was observed in mice treated with apigenin and naringenin. In the same study, hesperetin reduced the serum levels of estrogen and down-regulated estrogen target genes and estrogen metabolism-related genes, such as pS2/TFF1 and CYP1A1 [196]. Hesperetin inhibits estrogen-induced breast carcinogenesis via ER-dependent mechanism as well as regulation of oxidative stress.

5.17. Indole-3-carbinol

Indole-3-carbinol, a naturally occurring compound in cruciferous vegetables of the Brassica genus such as broccoli and cabbage, has been indicated as a promising anticancer agent [197–199]. Indole-3-carbinol has poor bioavailability due to its instability in the gastrointestinal tract [200]. The results from short-term and long-term studies indicated that indole-3-carbinol is a relatively non-toxic compound [201, 202]. Indole-3-carbinol decreased the tumor incidence against MMTV-induced mammary tumors [203]. Chang *et al.* [204] investigated the effect of 3,3'-diindolylmethane (DIM), a major acid-catalyzed product of indole-3-carbinol, on angiogenesis and tumorigenesis in the MCF-7 xenograft mouse model. In this study, DIM decreased the development of estrogen-dependent xenografted tumors in mice. In addition, DIM significantly inhibited mammary tumor growth and tumor volume in DMBA-induced mammary tumors in SD rats [205]. Ritter *et al.* [206] investigated the effects of indole-3-carbinol on the P450 CYP enzyme activities, P450-dependent metabolism of estradiol (E2) and estrone (E1), and interconversion of E1 and E2 catalyzed by 17 β -HSD. In this study, indole-3-carbinol increased activities of P450 enzymes, such as CYP1A1, CYP1A2, CYP3A, and CYP2B, as well as metabolism of E2 and E1 in the liver and mammary gland [206]. Overall, these data suggest that anti-carcinogenic effects of indole-3-carbinol may be associated not only with its alterations in estrogen metabolism, but also with its modulation of P450 enzymes via both ER-dependent and ER-independent pathways.

5.18. Luteolin

Luteolin, a common flavonoid in many types of fruits, vegetables and medicinal herbs, has numerous biological activities [207–209]. The hydroxyl moieties and carbon double bond are important structural features in luteolin that are associated with anti-cancer activity

through regulation of estrogen signaling in ER-positive breast cancer cells [210, 211]. Luteolin has low bioavailability due to poor solubility in water [212]. There was no evidence of systemic toxicity in animal models as evidenced by normal food intake and body weight [85]. Samy *et al.* [213] evaluated the anti-tumor effect of luteolin against DMBA-induced mammary carcinogenesis in Wistar rats. Luteolin inhibited tumor incidence, decreased tumor volume, inhibited lipid peroxide formation, but increased SOD, CAT and GPx activities in the liver, kidney and breast tissues [213]. Another study reported that administration of luteolin led to decrease cells in S phase compared with DES alone in the mammary gland of rats [214]. In addition, luteolin treatment reduced tumor growth through inhibition of MPA-induced VEGF secretion and blood-vessel density in the T47D xenograft model [55]. Because VEGF has been shown to protect cells from undergoing apoptosis [215], loss of VEGF by luteolin may increase tumor cell apoptosis and inhibit angiogenesis. These studies suggest that luteolin exerts chemopreventive and antiangiogenic activity by inducing the antioxidant defense system in DMBA- or DES-induced mammary tumors.

5.19. Lycopene

Lycopene, a natural red colored pigment produced in plants and microorganisms, is potentially effective in the prevention of breast cancer [216]. Lycopene ingested in its natural *trans* form is poorly absorbed; heat processing induces isomerization of lycopene from all-*trans* to *cis* configuration, which increases its bioavailability [217]. Toxicity studies showed that lycopene did not cause any adverse events in animals [218]. In humans, lycopene ranging from 10 to 120 mg was well tolerated with minimal side effects, which were mainly of minimal gastrointestinal toxicity [219]. Several animal studies reported the synergistic effects of lycopene and other natural compounds. Moselhy *et al.* [220] investigated the anti-tumor potential of lycopene alone or in combination with melatonin in DMBA-induced oxidative stress and mammary carcinogenesis in SD rats. Their results indicated that lycopene alone or combination decreased tumor incidence as well as malondialdehyde (MDA) and NO levels in serum and mammary tissues [220]. The activities of SOD, CAT and GPx in the treatment groups of lycopene alone or combination were found to be significantly higher than the DMBA treatment [220]. Another study conducted by Al-Malki *et al.* [221] reported that tumor formation and angiogenesis in DMBA-treated rats were ameliorated by lycopene and/or combined treatment with tocopherol. Further, lycopene alone or in combination with tocopherol decreased MDA and NO in serum and mammary tumor tissues but increased SOD, CAT and GPx in mammary tumor tissues [221]. Administration of lycopene and genistein in combination inhibited DMBA-induced mammary tumor development through suppressing oxidative stress markers, including MDA, 8-isoprostane and 8-OH-dG, in DMBA-treated rats [222]. Overall results suggest that supplementation of diet with lycopene or in combination with other bioactive compounds may provide the antioxidant defense system against DMBA-induced mammary carcinogenesis.

5.20. Morin

Morin is a flavonoid from Moraceae that exhibits anti-proliferative and antitumor effects in ER-positive, ER-negative and PR-negative human breast cancer cell lines [223, 224]. Morin, a phytoestrogen, has the 7- and 4- positions occupied by hydroxy groups; these two

positions correspond to the 3- and 4- positions of DES [225]. The bioavailability of morin after a single oral dose is very low due to low aqueous solubility and low intestinal permeability [226, 227]. Nanhakumar *et al.* [228] evaluated the anti-carcinogenic effect of morin against DMBA-induced mammary carcinogenesis. Administration of morin showed a decrease in PCNA expression and the number of AgNOR/nuclei [228]. Morin improved the enzymic and nonenzymic antioxidant activities, including SOD, CAT, GPx, GST, GR, GSH, G6PD, vitamin C, and vitamin E, and considerably decreased the lipid peroxidation and tumor markers, such as CA15-3, α -feto protein (AFP) and carcinoembryonic antigen (CEA), in serum as compared to DMBA-treated rats [228]. These data suggest that morin inhibits mammary carcinogenesis possibly through the antioxidant pathway.

5.21. Myricetin

Myricetin, a member of the flavonoids, is commonly derived from many fruits and vegetables that are known as powerful antioxidants [229]. Myricetin has low oral bioavailability in rats and in humans due to poor aqueous solubility [230, 231]. The structure of myricetin is similar to estrogen, and it acts as an agonist by activating the agonist-dependent activation of ER α and ER β , inducing the ER α nuclear translocation and regulating the expression of estrogen target genes in ER-dependent breast cancer cells [232]. Jayakumar *et al.* [233] assessed the protective effect of myricetin against oxidative damage in DMBA-treated Wistar rats. Myricetin decreased TBARS levels in plasma and mammary tissues and increased SOD levels in erythrocyte lysates and mammary tissues [233], indicating that myricetin was effective in preventing oxidative damage induced by the carcinogen DMBA.

5.22. Phenethyl isothiocyanate

Phenethyl isothiocyanate, a naturally occurring isothiocyanate found in some cruciferous vegetables, has cancer prevention effects in breast cancer [234, 235]. Phenethyl isothiocyanate has high bioavailability, and it is likely that phenethyl isothiocyanate undergoes modest first-pass metabolism as metabolites of isothiocyanates can be generated by intestinal as well as hepatic enzymes [236]. Futakuchi *et al.* [234] revealed that phenethyl isothiocyanate exerts chemopreventive effect on the promotion and/or progression stage of DMBA-induced rat mammary carcinogenesis. In addition, phenethyl isothiocyanate reduced the tumor incidence and tumor burden in the NMU-induced breast cancer animal model [235]. McCune *et al.* [237] investigated the chemopreventive activity of phenethyl isothiocyanate in the PyMT transgenic model. The PyMT transgenic mouse model serves as an excellent model for studying progression of luminal subtype tumors [238]. Phenethyl isothiocyanate inhibited tumor initiation and delayed progression by regulating ER α , forkhead box protein A1 (FOXA1) and GATA binding protein 3 (GATA-3) transcriptional factors [237]. As these factors constitute a functional transcription factor network that determines estrogen dependence and response to anti-estrogen treatment [239], phenethyl isothiocyanate exerts chemopreventive effects possibly via the ER-dependent pathway.

5.23. Pomegranate

Pomegranate (*Punica granatum* L.) contains various bioactive phytochemicals that exert anti-proliferative [240], anti-angiogenic [241], anti-aromatase [242], proapoptotic [243] and

estrogenic activities in breast cancer cell lines and animal models [244, 245]. Despite many biological properties, punicalagin and ellagic acid, the major polyphenols in pomegranate, have poor absorption, low bioavailability and short retention time [246, 247]. In addition, pomegranate seeds are known to contain the estrogenic compounds, estrone and estradiol, that are chemically identical to those biosynthesized in human body [248]. Treatment with pomegranate polyphenolics significantly decreased tumor volume and weight by decreasing Sp1, Sp3 and Sp4 as well as miR-27a in the BT474 xenograft model [249]. Recently, Bishayee *et al.* [250] reported that pomegranate emulsion reduced the tumor incidence, total burden and tumor weight in DMBA-treated rats with a concurrent inhibition of cell proliferation, induction of apoptosis, up-regulation of proapoptotic protein Bax, and down-regulation of antiapoptotic protein Bcl-2 in mammary tumors. The same group investigated the effects of pomegranate emulsion on ER and Wnt/ β -catenin signaling as well as expression of cyclin D1, a downstream target for both ER and Wnt signaling, in DMBA-treated mammary tumorigenesis [244]. Pomegranate emulsion downregulated the expression of ER α , ER β , β -catenin and cyclin D1 via ER and Wnt/ β -catenin signaling pathways [244]. These studies suggest that pomegranate exerts chemopreventive activity by inducing apoptotic and estrogen-dependent pathways.

5.24. Quercetin

Quercetin, a major representative of the flavonol subclass of flavonoids, is commonly found in fruits and vegetables including onions and apples [251]. The structure of quercetin is similar to estrogen, including two hydroxyl groups and a phenol ring [252]. Therefore, quercetin acts as a phytoestrogen that binds to the ER and participates in the regulation of cell growth and gene transcription through estrogen dependent pathway [253, 254] as well as via ER-independent pathway [157]. Quercetin has low bioavailability in humans [255]. In addition, the bioavailability of quercetin differs among food sources, depending on the type of glycosides they contain [255]. Tao *et al.* [251] evaluated the anti-tumor effects of quercetin in the MCF-7 xenograft model. Tumor volume was decreased by quercetin compared with control mice, and expression of miR-146a was up-regulated after treatment with quercetin [251]. Moon *et al.* [103] determined the effect of quercetin in combination with biochanin A and EGCG in the MCF-7 xenograft model. Mixture of these three compounds reduced the tumor incidence, whereas quercetin and EGCG administration did not affect tumor size [103]. In *in vivo* study by Steiner *et al.* [256], quercetin reduced tumor number and tumor volume in the C3(1)/SV40Tag transgenic mouse model of breast cancer. Quercetin suppressed tumor growth, decreased the serum levels of CEA, a potent marker for tumor growth and invasion, and reduced activities of acid phosphatase (ACP) and cathepsin D in DMBA-treated Wistar-albino rats [257]. However, Singh *et al.* [258] reported that quercetin does not confer protection against estrogen-mediated mammary carcinogenesis, does not inhibit estrogen-induced oxidative stress and may exacerbate breast carcinogenesis in estrogen-treated ACI rats, possibly due to the inhibition of COMT activity. Overall effects of phytoestrogens, such as quercetin, on breast cancer remain unclear. Depending on the doses, quercetin may differently affect antioxidant pathway in breast cancer.

5.25. Resveratrol

Resveratrol, a polyphenol naturally occurring in grapes and red wine, is structurally similar to the DES [259]. Resveratrol suppresses the proliferation of breast cancer cells, induces apoptosis, inhibits the breast cancer stem cells and induces autophagy via suppressing the Wnt/ β -catenin signaling pathway [53, 260, 261]. Resveratrol has low water solubility, leading to low bioavailability. However, resveratrol absorption can vary depending on food ingested [262]. Crowell *et al.* [263] reported that adverse effects occurred with higher doses and consisted mainly of nephrotoxicity in rats. In a recent study conducted by Williams *et al.* [264], low and high doses of resveratrol are well tolerated and non-toxic in rats. In addition, consumption of high-dose resveratrol did not cause serious adverse effects in humans [265, 266]. Resveratrol is well absorbed and rapidly metabolized into sulfo- and glucuronide conjugates which are eliminated in urine [267]. Therefore, resveratrol seems to be well tolerated without any marked toxicity. Administration of resveratrol significantly reduced the tumor number and increased the time to onset of DMBA-induced mammary tumors [268]. Treatment with resveratrol reduced cell proliferation and induced apoptotic index for epithelial cells in mammary terminal ductal structures [268]. Banerjee *et al.* [269] investigated the chemopreventive potential of resveratrol against DMBA-induced mammary carcinogenesis in SD rats. Treatment with resveratrol suppressed the DMBA-induced tumor incidence and tumor multiplicity, which correlates with down-regulation of NF κ B, cyclooxygenase (COX)-2 and matrix metalloproteinase (MMP)-9 expression [269]. Treatment with resveratrol at high concentration delayed tumorigenesis and decreased the tumor multiplicity in NMU-treated SD rats [270]. Histomorphology of mammary tumors showed that resveratrol increased alveolar and adipocyte differentiation of mammary tumor cells [270]. Singh *et al.* [271] reported that resveratrol inhibited estrogen-induced breast carcinogenesis via regulation of nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant genes, NAD(P)H dehydrogenase quinone 1 (NQO1), SOD3, oxidative DNA damage repair gene, 8-oxoguanine DNA glycosylase 1 (OGG1), and detoxification genes, aldehyde oxidase 1 (AOX1) and flavin monooxygenase 1 (FMO1). In this study, treatment with resveratrol also induced apoptosis and inhibited estrogen-mediated increase in DNA damage in estrogen-treated mammary tissues [271]. These results suggest that resveratrol inhibits estrogen-induced breast carcinogenesis via induction of Nrf2-mediated protective pathways as well as ER-dependent mechanisms.

5.26. Sesamin

Sesamin, a lignan isolated from sesame seeds, possesses chemopreventive effects against breast cancer and other chronic diseases through ER-dependent pathway and NF κ B pathways [272–274]. Treatment with sesamin significantly reduced the cumulative number of palpable mammary tumors in DMBA-treated SD rats [275]. The levels of lipid peroxides, fatty acid compositions, tumor phosphatidylcholine and prostaglandin E2 were decreased while peripheral blood mononuclear cells (PBMC) were increased by sesamin [275]. Truan *et al.* [276] revealed that sesamin reduced MCF-7 xenograft tumor growth at high levels of circulating estrogen in athymic mice. In this study, sesamin increased apoptosis via regulating human epidermal growth factor receptor 2 (HER2) and endothelial growth factor receptor expression and MAPK pathway [276]. The inhibitory effect of sesamin against

mammary carcinogenesis may be due to increased antioxidant pathway and several cellular defense pathways in addition to ER-dependent mechanism.

5.27. Sulforaphane

Sulforaphane, an isothiocyanate naturally rich in cruciferous vegetables such as broccoli, broccoli sprouts, cabbage and kale, has been shown to reduce the risk of developing many common cancers [277]. Sulforaphane has anti-cancer activity against various breast cancer cell lines via regulating cytochrome P450 involved in estrogen metabolism [278], Nrf2-related antioxidant pathway [279], Akt/mTOR-S6K1 pro-survival pathway, ERK1/2-IKK α and NAK-IKK β [280], ErbB2/ER-PI3K/Akt-mTOR-S6K1 signaling [281] and cancer stem cell pathway [50, 280]. Sulforaphane has shown high bioavailability, as determined by significant intracellular and plasma concentrations in rats and humans [282, 283].

Kanematsu *et al.* [284] revealed that sulforaphane inhibited cell growth, induced apoptosis and reduced primary tumor growth, tumor volume and tumor weight in the KPL-1 breast cancer xenograft model. Furthermore, sulforaphane decreased breast cancer stem cells *in vivo*, thereby abrogating tumor growth after the reimplantation of primary tumor cells into the secondary mice via Wnt/ β -catenin self-renewal pathway [50]. These results indicate that sulforaphane inhibits the mammary tumor growth through the antioxidant pathway as well as Wnt/ β -catenin self-renewal pathway.

5.28. Tangeretin

Tangeretin, a flavonoid found in the peel of citrus fruits, induces the apoptosis of ER-dependent cells mainly through caspase-dependent or -independent pathways [285]. Despite its widely documented bioactivities, tangeretin has relatively low bioavailability due to its low water solubility, which is a major factor limiting its application as a nutraceutical [286]. A safety assessment indicated that oral administration of tangeretin did not show any adverse effects [287]. Arivazhagan *et al.* [288] investigated the therapeutic effect of tangeretin against DMBA-induced rat mammary carcinogenesis. Treatment with tangeretin decreased tumor weight and reduced serum levels of estradiol, progesterone, prolactin, lipid bound sialic acid (LSA), total sialic acid (TSA), NO and protein carbonyls. Oral administration of tangeretin also effectively reduced the tumor cell proliferation markers such as PCNA, COX-2, Ki-67 and inhibited metastasis by suppressing MMP-2, MMP-9 and VEGF [288]. Periyasamy *et al.* [289] also investigated the chemopreventive and therapeutic effect of tangeretin on DMBA-induced oxidative stress in SD rats. The levels of oxidative stress markers, such as NO and LOOH, and breast cancer marker CEA were decreased, whereas the antioxidant enzymes such as SOD, CAT, GPx, GST, GSH, vitamin C and vitamin E were increased in tangeretin pre-treated and post-treated animals [289]. Tangeretin significantly suppressed DMBA-induced mammary tumors in rats as reported by Lakshmi *et al.* [290]. In this study, tangeretin decreased the activities of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), acid phosphatase (ACP), 5'-nucleotidase (5'-ND), γ -glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH) and levels of tumor markers in serum as well as TBARS and conjugated dienes (CD) in plasma and mammary tissues [290]. The levels of enzymatic/non-enzymatic antioxidant and phase II detoxification enzymes were increased significantly by the administration of tangeretin [290]. DMBA-treated rats showed higher expression of ER, PR and Her2/neu, whereas

tangeretin treatment to tumor bearing animals significantly decreased the expression of the hormones and their receptors [290]. These results suggest that the chemopreventive effects of tangeretin *in vivo* could be mediated by ER-dependent pathway as well as ER-independent mechanism.

5.29. Thymoquinone

Thymoquinone, a phytochemical compound found in plant *Nigella sativa*, has been shown anti-cancer effects via regulation of apoptosis, estrogen metabolism, MAPK and Akt signaling pathways in breast cancer [291–294]. Although thymoquinone has these biological effects, its administration remains problematic partly due to its poor water solubility, leading to low absorptivity and bioavailability [295]. Thymoquinone regulates the expression of genes involved in estrogen metabolism including CYP1A1 [293]. Linjawi *et al.* [296] reported that thymoquinone reduced tumor markers, the levels of MDA and lactate dehydrogenase as well as alkaline phosphatase (ALP) and AST activities. In addition, treatment with thymoquinone decreased the expression of breast cancer (BRCA)1, BRCA2, Id-1 and p53 mutations in mammary tissues of DMBA-treated rats [296]. These data suggest that thymoquinone exerts a protective effect against mammary carcinogenesis by regulating the antioxidant pathway.

5.30. Tocopherols

Vitamin E consists of eight different forms which include four tocopherols (α -, β -, γ -, and δ -forms) and four tocotrienols (α -, β -, γ -, and δ -forms) [297]. The major dietary sources of tocopherols are vegetable oils, such as corn, soybean, sesame and canola oils [297]. α -Tocopherol has a higher bioavailability than other forms of vitamin E. Because the acetate form is less susceptible to oxidative destruction, α -tocopherol acetate is widely used as source of vitamin E [298]. In addition, the bioavailability of natural-source vitamin E is approximately twice that of synthetic form of vitamin E [299]. Iuliano *et al.* [300] studied the bioavailability of tocopherols in relation to food intake. Consumption of tocopherols after food intake increases its bioavailability. γ -Tocopherol-rich mixture of tocopherols (γ -TmT), a byproduct of refined vegetable oil, is a naturally occurring tocopherol mixture rich in γ -tocopherol [301]. γ -TmT, containing 57% γ -tocopherol, 24% δ -tocopherol and 13% α -tocopherol, inhibited tumorigenesis in NMU-treated animals through antioxidant dependent pathway [302]. Dietary administration of 0.1%, 0.3%, or 0.5% γ -TmT suppressed mammary tumor growth and tumor multiplicity through the regulation of ER, peroxisome proliferator-activated receptor γ (PPAR γ) and Akt signaling [303, 304]. Smolarek *et al.* [305] reported that treatment with dietary γ -TmT inhibited cell proliferation, down-regulated the expression of ER α , ER β , PCNA, COX-2 and level of serum estrogen, while γ -TmT up-regulated the levels of cleaved-caspase 3, PPAR γ , Nrf2 and Phase II detoxifying enzymes in hyperplastic mammary tissues of ACI rats with sustained release estrogen pellets. In addition, Das Gupta *et al.* [306] demonstrated that dietary administration of 0.3% γ -TmT reduced estrogen-induced oxidative/nitrosative stress markers including nitrotyrosine, 8-OH-dG and 8-isoprostane and up-regulated Nrf2 as well as Nrf2-dependent oxidative response genes such as SOD1, GPx and CAT in early mammary hyperplasia. A recent study determined the efficacy of dietary γ -TmT on estrogen-induced mammary tumors in two different *in vivo* models [301]. In the first study, γ -TmT up-regulated the estrogen-

metabolizing enzyme, CYP1A1, Nrf2-dependent antioxidant enzymes as well as PPAR γ and its downstream genes while down-regulated oxidative stress and cell proliferation markers at early, intermediate and late stages of mammary tumorigenesis in ACI rats [301]. In a second study, 0.05% to 0.5% dietary doses of γ -TmT inhibited the mammary tumor growth in MCF-7 xenografted mice [301]. Smolarek *et al.* [302] reported that γ - and δ -tocopherol, but not α -tocopherol, reduced levels of nitrotyrosine and 8-OH-dG stress markers while increased levels of phosphatase and tensin homologue (PTEN), p53 pathway, PPAR γ , Nrf2/phase II detoxifying and antioxidant enzymes in NMU-treated SD rats. Taken together, γ -TmT as well as γ - and δ -tocopherol work through antioxidant and/or ER-dependent mechanisms, leading to the inhibition of mammary tumorigenesis.

5.31. Xanthohumol

Xanthohumol is a type of flavonoid isolated from the hops and beer [307]. Several studies demonstrated that xanthohumol is able to modulate estrogen synthesis and estrogen metabolism in breast cancer [308–310]. Xanthohumol has poor absorption, low systemic bioavailability and short retention time [311, 312]. Toxicological studies in animals revealed that xanthohumol did not affect the major organ functions, sex hormones or cause blood clotting [287, 313, 314]. Monteiro *et al.* [315] investigated the effect of oral administration of xanthohumol in the MCF-7 xenograft model. Xanthohumol reduced the inflammatory cell number and focal proliferation areas by increasing percentage of apoptotic cells and decreasing microvessel density [315]. Decreased immunostaining for NF κ B, phosphorylated-inhibitor of κ B and interleukin-1 β was also observed [315]. In addition, Yoshimaru *et al.* [307] determined the antitumor activity of xanthohumol in KPL-3C orthotopic breast cancer xenografted mice. Their results indicated that xanthohumol inhibited estrogen-induced tumor growth by inducing G1-arrest via targeting the guanine nucleotide-exchange protein 3 (BIG3)-tumor suppressor prohibition 2 (PHB2) interaction [307]. BIG3-PHB2 complex play a pivotal role in estrogen signaling modulation in ER α -positive breast cancer [316], suggesting that xanthohumol may be a promising natural compound to regulate estrogen receptor signaling and NF κ B signaling pathway.

6. Bioactive natural products targeting estrogen-mediated mechanisms

Based on bioactive natural products reviewed in experimental *in vivo* models of ER-positive breast cancer, we summarized bioactive natural products targeting estrogen-mediated mechanisms in ER-positive breast cancer cells in Table 2. The estrogen-responsive breast cancer cell lines, such as MCF-7, T47D, BT474 and ZR-75-1, have been used to test the estrogenicity as well as anti-estrogenic activities of various bioactive natural compounds. Among many bioactive natural compounds, genistein and resveratrol have been the most widely studied, and reports showed that both compounds inhibited estrogen-induced DNA synthesis and proliferation of ER-positive breast cancer cells [317–326]. However, genistein and resveratrol could differently modify ERE-dependent transcription and expression of ERE-mediated genes, such as ER, PR, and pS2/Trefoil factor 1(TFF1) in the presence and absence of estrogen [97, 270, 319, 324–327]. These effects of genistein and resveratrol could be mediated through both ER-dependent and ER-independent pathways. Shao *et al.* [328] reported that curcumin inhibits the expression of ER downstream genes including pS1

and transforming growth factor (TGF)- β and ERE activity induced by estrogen in MCF-7 cells, suggesting that curcumin inhibits MCF-7 cell proliferation via an ER-dependent pathway. Anthocyanidins, delphinidin and pelargonidin in berries bind to ERs and significantly reduce estrogen-induced ERE-luciferase activity, similar to the action of antiestrogens [329]. Several studies clearly demonstrated that indole-3-carbinol exerted anti-estrogenic effect by intervention of estrogen and/or ER signal transduction pathways, by alterations in estrogen metabolism, and by regulation of the estrogen-responsive genes such as pS2, cathepsin D via an ER-dependent pathway [330–334]. Sesamin also significantly decreased the estrogen-induced ERE activation and pS2/TFF1 gene expression [274]. Pomegranate extract inhibited the binding of estradiol to ER and suppressed the estrogen-induced proliferation as well as estrogen-responsive receptor gene expression via an ER-dependent pathway in MCF-7 cells [335]. The dietary carotenoids, lycopene and β -carotene inhibited estrogen signaling pathways by decreasing estrogen-induced transactivation of ERE and regulating both ER α and ER β [336]. γ -Tocopherol, δ -tocopherol and γ -TmT suppressed the estrogen-induced cell proliferation and ER α expression and increased the transactivation of PPAR γ in both MCF-7 and T47D cells [303]. Since ER α binds to the PPAR response element and represses transactivation of PPAR γ [337], it is likely that activation of PPAR γ may mediate the anti-estrogenic action of γ - and δ -tocopherol. Xanthohumol treatment prevented the BIG3-PHB2 interaction, thereby releasing PHB2 to directly bind to both nuclear- and cytoplasmic ER α [316]. This event led to the suppression of the estrogen signaling pathways by inhibiting estrogen-induced ERE activation and pS2/TFF1 and CCND1 expression [316]. Several compounds, including apigenin, biochanin A, EGCG, ferulic acid, quercetin, and α -linolenic acid in flaxseed were distinct, in that their antiestrogenic activity did not appear to correlate with binding to ER [317, 338] and, therefore, their suppression of estrogen-induced cell proliferation may occur independent of direct antagonism of the receptor. Taken together, cancer preventive activities of bioactive natural compounds may occur through ER-dependent and ER-independent mechanisms.

7. Clinical trials of bioactive natural products in breast cancer

According to the *in vivo* and *in vitro* experimental studies, numerous natural products have been reported to have anticancer activities against ER-positive breast cancer. The current information about completed or ongoing clinical trials of bioactive natural products on breast cancer is summarized in Table 3. Bayet-Robert *et al.* [339] investigated the tolerability of the combination of curcumin and docetaxel in phase I clinical trial. Curcumin was given orally for seven consecutive days, and docetaxel (100 mg/m²) was administered as intravenous infusion every 3 week for six cycles. Based on this study, the recommended dose of curcumin is 6,000 mg/day for seven consecutive days every 3 week in combination with a standard dose of docetaxel [339]. Thompson *et al.* [166] conducted a randomized, placebo-controlled, double-blinded, prospective study. Patients with breast cancer in the treatment group (n = 19) ate one muffin daily containing 25 g of flaxseed included in their usual diet. The results of this study showed that daily intake of 25 g flaxseed has the potential to reduce tumor growth by reducing cell proliferation and increasing apoptosis in patients with breast cancer [166]. A clinical trial was conducted to evaluate the effects of high oral dose of soy isoflavone administered daily for 84 days to healthy postmenopausal

women. Genistein appears to be safe and well tolerated in healthy postmenopausal women at doses of 900 mg per day [340]. Recently, Shike *et al.* [341] investigated the effect of soy supplementation on modulating gene expression in one hundred-forty patients with early-stage breast cancer. Treatment with soy protein supplementation upregulated the expression of cell cycle transcripts, including those that promote cell proliferation, such as fibroblast growth factor receptor 2, E2 factor 5, BUB1, CCNB2, MYBL2, CDK1, and CDC20 [341]. Gregory *et al.* [342] conducted the phase I clinical trial of indole-3-carbinol in seventeen women from a high-risk breast cancer cohort. Patients received 400 mg and 800 mg of indole-3-carbinol per day for four weeks. Daily administration of indole-3-carbinol at doses of 400 and 800 mg were tolerated well by all subjects [342]. In addition, a randomized, placebo-controlled, double-blind, crossover trial was conducted to evaluate whether tomato-derived lycopene supplementation decreases serum levels of total IGF-I in premenopausal women with a history of breast cancer and a high familial breast cancer risk [343]. They received 30 mg of lycopene daily for 2 months. In this trial, lycopene effects were discordant between the two study populations showing beneficial effects in women with a family history of breast cancer but not in breast cancer survivors [343]. Nesaretnam *et al.* [344] conducted a double-blinded, placebo-controlled pilot trial study to examine the effect of adjuvant tocotrienol therapy in combination with tamoxifen for five years in women with early breast cancer. Two hundred-forty women with either tumor node metastasis Stage I or II breast cancer with ER-positive tumors were assigned to two groups and then administered tocotrienol-rich fraction plus tamoxifen [344]. The results indicated no association between adjuvant tocotrienol therapy and breast cancer specific survival in women with early breast cancer [344]. Currently, limited intervention studies are on-going or completed to determine the beneficial effects of natural products in patients with breast cancer. With a better understanding of the mechanisms of action of bioactive natural products in estrogen-mediated breast cancer, future intervention studies with bioactive natural products could be designed to evaluate their roles in the treatment and prevention of breast cancer in humans.

8. Conclusion and future directions

Current chemopreventive strategies for ER-positive breast cancer have targeted the ER, estrogen, or estrogen metabolites. It is well-established that many bioactive natural products have beneficial effects on estrogen driven breast cancer. These natural products have shown promise in preventive and therapeutic settings and point toward tumor initiation and progression as points of intervention. However, use of natural products and derivatives has many hurdles as chemopreventive agents because of low bioavailability, poor absorption and lack of specific cellular targets. Due to the role of breast cancer stem cells in tumor initiation, maintenance, and progression, stem cells have become a new area of interest in the study of estrogen-mediated breast carcinogenesis. Recent studies are identifying possible estrogen-mediated mechanisms of stem cell expansion. However, the currently available reports provide only limited information whether natural compounds may inhibit estrogen-induced cancer stem cells. As cancer stem cell signaling pathways become more evident, it will be important to identify inhibitors of estrogen-mediated signaling to effectively target the breast cancer stem cell subpopulation. The bioactive natural products identified in this review serve as good starting points for further investigation since their effects on estrogen

signaling in breast cancer have already been established. In order to effectively prevent or treat estrogen-driven breast cancers, it is important to consider not only targeting classical estrogen signaling but also identifying natural compounds effective in inhibiting breast cancer stem cells.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015; 65:5–29. [PubMed: 25559415]
2. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. *N Engl J Med.* 2006; 354:270–82. [PubMed: 16421368]
3. Armstrong K, Eisen A, Weber B. Assessing the risk of breast cancer. *N Engl J Med.* 2000; 342:564–71. [PubMed: 10684916]
4. Clemons M, Goss P. Estrogen and the risk of breast cancer. *N Engl J Med.* 2001; 344:276–85. [PubMed: 11172156]
5. Yue W, Yager JD, Wang JP, Jupe ER, Santen RJ. Estrogen receptor-dependent and independent mechanisms of breast cancer carcinogenesis. *Steroids.* 2013; 78:161–70. [PubMed: 23178278]
6. Brzozowski AM, Pike AC, Dauter Z, Hubbard RE, Bonn T, Engstrom O, et al. Molecular basis of agonism and antagonism in the oestrogen receptor. *Nature.* 1997; 389:753–8. [PubMed: 9338790]
7. Kumar V, Chambon P. The estrogen receptor binds tightly to its responsive element as a ligand-induced homodimer. *Cell.* 1988; 55:145–56. [PubMed: 3167974]
8. McInerney EM, Katzenellenbogen BS. Different regions in activation function-1 of the human estrogen receptor required for antiestrogen- and estradiol-dependent transcription activation. *J Biol Chem.* 1996; 271:24172–8. [PubMed: 8798658]
9. Cavalieri E, Chakravarti D, Guttentplan J, Hart E, Ingle J, Jankowiak R, et al. Catechol estrogen quinones as initiators of breast and other human cancers: implications for biomarkers of susceptibility and cancer prevention. *Biochim Biophys Acta.* 2006; 1766:63–78. [PubMed: 16675129]
10. Mahalingaiah PK, Ponnusamy L, Singh KP. Chronic oxidative stress causes estrogen-independent aggressive phenotype, and epigenetic inactivation of estrogen receptor alpha in MCF-7 breast cancer cells. *Breast Cancer Res Treat.* 2015; 153:41–56. [PubMed: 26208486]
11. Reuben SC, Gopalan A, Petit DM, Bishayee A. Modulation of angiogenesis by dietary phytoconstituents in the prevention and intervention of breast cancer. *Mol Nutr Food Res.* 2012; 56:14–29. [PubMed: 22125182]
12. Sinha D, Biswas J, Sung B, Aggarwal BB, Bishayee A. Chemopreventive and chemotherapeutic potential of curcumin in breast cancer. *Curr Drug Targets.* 2012; 13:1799–819. [PubMed: 23140290]
13. Vadodkar AS, Suman S, Lakshmanaswamy R, Damodaran C. Chemoprevention of breast cancer by dietary compounds. *Anticancer Agents Med Chem.* 2012; 12:1185–202. [PubMed: 22583403]
14. Parikh NR, Mandal A, Bhatia D, Siveen KS, Sethi G, Bishayee A. Oleanane triterpenoids in the prevention and therapy of breast cancer: current evidence and future perspectives. *Phytochem Rev.* 2014; 13:793–810. [PubMed: 25395898]
15. Siddiqui JA, Singh A, Chagtoo M, Singh N, Godbole MM, Chakravarti B. Phytochemicals for breast cancer therapy: current status and future implications. *Curr Cancer Drug Targets.* 2015; 15:116–35. [PubMed: 25544650]
16. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. *Nature.* 2000; 406:747–52. [PubMed: 10963602]

17. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA*. 2006; 295:2492–502. [PubMed: 16757721]
18. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A*. 2001; 98:10869–74. [PubMed: 11553815]
19. Puhalla S, Bhattacharya S, Davidson NE. Hormonal therapy in breast cancer: a model disease for the personalization of cancer care. *Mol Oncol*. 2012; 6:222–36. [PubMed: 22406404]
20. Inic Z, Zegarac M, Inic M, Markovic I, Kozomara Z, Djuricic I, et al. Difference between Luminal A and Luminal B Subtypes According to Ki-67, Tumor Size, and Progesterone Receptor Negativity Providing Prognostic Information. *Clin Med Insights Oncol*. 2014; 8:107–11. [PubMed: 25249766]
21. Metzger-Filho O, Sun Z, Viale G, Price KN, Crivellari D, Snyder RD, et al. Patterns of Recurrence and outcome according to breast cancer subtypes in lymph node-negative disease: results from international breast cancer study group trials VIII and IX. *J Clin Oncol*. 2013; 31:3083–90. [PubMed: 23897954]
22. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. *J Natl Cancer Inst*. 2009; 101:736–50. [PubMed: 19436038]
23. Yersal O, Barutca S. Biological subtypes of breast cancer: Prognostic and therapeutic implications. *World J Clin Oncol*. 2014; 5:412–24. [PubMed: 25114856]
24. Shim HJ, Kim SH, Kang BJ, Choi BG, Kim HS, Cha ES, et al. Breast cancer recurrence according to molecular subtype. *Asian Pac J Cancer Prev*. 2014; 15:5539–44. [PubMed: 25081661]
25. Thongprakaisang S, Thiantanawat A, Rangkadilok N, Suriyo T, Satayavivad J. Glyphosate induces human breast cancer cells growth via estrogen receptors. *Food Chem Toxicol*. 2013; 59:129–36. [PubMed: 23756170]
26. van der Velpen V, Geelen A, Schouten EG, Hollman PC, Afman LA, van 't Veer P. Estrogen receptor-mediated effects of isoflavone supplementation were not observed in whole-genome gene expression profiles of peripheral blood mononuclear cells in postmenopausal, equol-producing women. *J Nutr*. 2013; 143:774–80. [PubMed: 23616509]
27. Marino M, Galluzzo P, Ascenzi P. Estrogen signaling multiple pathways to impact gene transcription. *Curr Genomics*. 2006; 7:497–508. [PubMed: 18369406]
28. Ishida M, Mitsui T, Izawa M, Arita J. Activation of D2 dopamine receptors inhibits estrogen response element-mediated estrogen receptor transactivation in rat pituitary lactotrophs. *Mol Cell Endocrinol*. 2013; 375:58–67. [PubMed: 23701824]
29. Mohamood AS, Gyles P, Balan KV, Hollis VW, Eckberg WR, Asseffa A, et al. Estrogen receptor, growth factor receptor and protooncogene protein activities and possible signal transduction crosstalk in estrogen dependent and independent breast cancer cell lines. *J Submicrosc Cytol Pathol*. 1997; 29:1–17. [PubMed: 9066137]
30. Williamson LM, Lees-Miller SP. Estrogen receptor alpha-mediated transcription induces cell cycle-dependent DNA double-strand breaks. *Carcinogenesis*. 2011; 32:279–85. [PubMed: 21112959]
31. Hemachandra LP, Patel H, Chandrasena RE, Choi J, Piyankarage SC, Wang S, et al. SERMs attenuate estrogen-induced malignant transformation of human mammary epithelial cells by upregulating detoxification of oxidative metabolites. *Cancer Prev Res (Phila)*. 2014; 7:505–15. [PubMed: 24598415]
32. Cribb AE, Knight MJ, Dryer D, Guernsey J, Hender K, Tesch M, et al. Role of polymorphic human cytochrome P450 enzymes in estrone oxidation. *Cancer Epidemiol Biomarkers Prev*. 2006; 15:551–8. [PubMed: 16537715]
33. Belous AR, Hachey DL, Dawling S, Roodi N, Parl FF. Cytochrome P450 1B1-mediated estrogen metabolism results in estrogen-deoxyribonucleoside adduct formation. *Cancer Res*. 2007; 67:812–7. [PubMed: 17234793]
34. Santen RJ, Yue W, Wang JP. Estrogen metabolites and breast cancer. *Steroids*. 2015; 99:61–6. [PubMed: 25168343]

35. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. *Nature*. 2001; 414:105–11. [PubMed: 11689955]
36. Liu S, Dontu G, Wicha MS. Mammary stem cells, self-renewal pathways, and carcinogenesis. *Breast Cancer Res*. 2005; 7:86–95. [PubMed: 15987436]
37. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. *Proc Natl Acad Sci U S A*. 2003; 100:3983–8. [PubMed: 12629218]
38. Ginestier C, Hur MH, Charafe-Jauffret E, Monville F, Dutcher J, Brown M, et al. ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. *Cell Stem Cell*. 2007; 1:555–67. [PubMed: 18371393]
39. Sleeman KE, Kendrick H, Robertson D, Isacke CM, Ashworth A, Smalley MJ. Dissociation of estrogen receptor expression and in vivo stem cell activity in the mammary gland. *J Cell Biol*. 2007; 176:19–26. [PubMed: 17190790]
40. Mallepell S, Krust A, Chambon P, Briskin C. Paracrine signaling through the epithelial estrogen receptor alpha is required for proliferation and morphogenesis in the mammary gland. *Proc Natl Acad Sci U S A*. 2006; 103:2196–201. [PubMed: 16452162]
41. Valkenburg KC, Graveel CR, Zylstra-Diegel CR, Zhong Z, Williams BO. Wnt/beta-catenin Signaling in Normal and Cancer Stem Cells. *Cancers (Basel)*. 2011; 3:2050–79. [PubMed: 24212796]
42. Velasco-Velazquez MA, Homsí N, De La Fuente M, Pestell RG. Breast cancer stem cells. *Int J Biochem Cell Biol*. 2012; 44:573–7. [PubMed: 22249027]
43. Deng H, Zhang XT, Wang ML, Zheng HY, Liu LJ, Wang ZY. ER-alpha36-mediated rapid estrogen signaling positively regulates ER-positive breast cancer stem/progenitor cells. *PLoS One*. 2014; 9:e88034. [PubMed: 24558373]
44. Fillmore CM, Gupta PB, Rudnick JA, Caballero S, Keller PJ, Lander ES, et al. Estrogen expands breast cancer stem-like cells through paracrine FGF/Tbx3 signaling. *Proc Natl Acad Sci U S A*. 2010; 107:21737–42. [PubMed: 21098263]
45. Sun Y, Wang Y, Fan C, Gao P, Wang X, Wei G, et al. Estrogen promotes stemness and invasiveness of ER-positive breast cancer cells through Gli1 activation. *Mol Cancer*. 2014; 13:137. [PubMed: 24889938]
46. Jung JW, Park SB, Lee SJ, Seo MS, Trosko JE, Kang KS. Metformin represses self-renewal of the human breast carcinoma stem cells via inhibition of estrogen receptor-mediated OCT4 expression. *PLoS One*. 2011; 6:e28068. [PubMed: 22132214]
47. Zhou Q, Ye M, Lu Y, Zhang H, Chen Q, Huang S, et al. Curcumin Improves the Tumoricidal Effect of Mitomycin C by Suppressing ABCG2 Expression in Stem Cell-Like Breast Cancer Cells. *PLoS One*. 2015; 10:e0136694. [PubMed: 26305906]
48. Charpentier MS, Whipple RA, Vitolo MI, Boggs AE, Slovic J, Thompson KN, et al. Curcumin targets breast cancer stem-like cells with microtentacles that persist in mammospheres and promote reattachment. *Cancer Res*. 2014; 74:1250–60. [PubMed: 24371229]
49. Kakarala M, Brenner DE, Korkaya H, Cheng C, Tazi K, Ginestier C, et al. Targeting breast stem cells with the cancer preventive compounds curcumin and piperine. *Breast Cancer Res Treat*. 2010; 122:777–85. [PubMed: 19898931]
50. Li Y, Zhang T, Korkaya H, Liu S, Lee HF, Newman B, et al. Sulforaphane, a dietary component of broccoli/broccoli sprouts, inhibits breast cancer stem cells. *Clin Cancer Res*. 2010; 16:2580–90. [PubMed: 20388854]
51. Montales MT, Rahal OM, Kang J, Rogers TJ, Prior RL, Wu X, et al. Repression of mammosphere formation of human breast cancer cells by soy isoflavone genistein and blueberry polyphenolic acids suggests diet-mediated targeting of cancer stem-like/progenitor cells. *Carcinogenesis*. 2012; 33:652–60. [PubMed: 22219179]
52. Mineva ND, Paulson KE, Naber SP, Yee AS, Sonenshein GE. Epigallocatechin-3-gallate inhibits stem-like inflammatory breast cancer cells. *PLoS One*. 2013; 8:e73464. [PubMed: 24039951]
53. Fu Y, Chang H, Peng X, Bai Q, Yi L, Zhou Y, et al. Resveratrol inhibits breast cancer stem-like cells and induces autophagy via suppressing Wnt/beta-catenin signaling pathway. *PLoS One*. 2014; 9:e102535. [PubMed: 25068516]

54. Tin AS, Park AH, Sundar SN, Firestone GL. Essential role of the cancer stem/progenitor cell marker nucleostemin for indole-3-carbinol anti-proliferative responsiveness in human breast cancer cells. *BMC Biol.* 2014; 12:72. [PubMed: 25209720]
55. Cook MT, Liang Y, Besch-Williford C, Goyette S, Mafuvadze B, Hyder SM. Luteolin inhibits progesterin-dependent angiogenesis, stem cell-like characteristics, and growth of human breast cancer xenografts. *Springerplus.* 2015; 4:444. [PubMed: 26312209]
56. Wu CH, Hong BH, Ho CT, Yen GC. Targeting cancer stem cells in breast cancer: potential anticancer properties of 6-shogaol and pterostilbene. *J Agric Food Chem.* 2015; 63:2432–41. [PubMed: 25686711]
57. Nasri H, Baradaran A, Shirzad H, Rafieian-Kopaei M. New concepts in nutraceuticals as alternative for pharmaceuticals. *Int J Prev Med.* 2014; 5:1487–99. [PubMed: 25709784]
58. Coppens P, da Silva MF, Pettman S. European regulations on nutraceuticals, dietary supplements and functional foods: a framework based on safety. *Toxicology.* 2006; 221:59–74. [PubMed: 16469424]
59. Cencic A, Chingwaru W. The role of functional foods, nutraceuticals, and food supplements in intestinal health. *Nutrients.* 2010; 2:611–25. [PubMed: 22254045]
60. Huq F, Yu JQ, Beale P, Chan C, Arzuman L, Nessa MU, et al. Combinations of platinum and selected phytochemicals as a means of overcoming resistance in ovarian cancer. *Anticancer Res.* 2014; 34:541–5. [PubMed: 24403514]
61. Tucker KL. Dietary Intake and Coronary Heart Disease: A Variety of Nutrients and Phytochemicals Are Important. *Curr Treat Options Cardiovasc Med.* 2004; 6:291–302. [PubMed: 15212724]
62. Vasanthi HR, ShriShriMal N, Das DK. Phytochemicals from plants to combat cardiovascular disease. *Curr Med Chem.* 2012; 19:2242–51. [PubMed: 22414106]
63. Mohibi S, Mirza S, Band H, Band V. Mouse models of estrogen receptor-positive breast cancer. *J Carcinog.* 2011; 10:35. [PubMed: 22279420]
64. Lumachi F, Brunello A, Maruzzo M, Basso U, Basso SM. Treatment of estrogen receptor-positive breast cancer. *Curr Med Chem.* 2013; 20:596–604. [PubMed: 23278394]
65. Clarke R. Human breast cancer cell line xenografts as models of breast cancer. The immunobiologies of recipient mice and the characteristics of several tumorigenic cell lines. *Breast Cancer Res Treat.* 1996; 39:69–86. [PubMed: 8738607]
66. Divisova J, Kuitse I, Lazard Z, Weiss H, Vreeland F, Hadsell DL, et al. The growth hormone receptor antagonist pegvisomant blocks both mammary gland development and MCF-7 breast cancer xenograft growth. *Breast Cancer Res Treat.* 2006; 98:315–27. [PubMed: 16541323]
67. Hartman J, Lindberg K, Morani A, Inzunza J, Strom A, Gustafsson JA. Estrogen receptor beta inhibits angiogenesis and growth of T47D breast cancer xenografts. *Cancer Res.* 2006; 66:11207–13. [PubMed: 17145865]
68. Fleming JM, Miller TC, Meyer MJ, Ginsburg E, Vonderhaar BK. Local regulation of human breast xenograft models. *J Cell Physiol.* 2010; 224:795–806. [PubMed: 20578247]
69. Kavanaugh C, Green JE. The use of genetically altered mice for breast cancer prevention studies. *J Nutr.* 2003; 133:2404S–9S. [PubMed: 12840216]
70. Batcioglu K, Uyumlu AB, Satilmis B, Yildirim B, Yucel N, Demirtas H, et al. Oxidative stress in the in vivo DMBA rat model of breast cancer: suppression by a voltage-gated sodium channel inhibitor (RS100642). *Basic Clin Pharmacol Toxicol.* 2012; 111:137–41. [PubMed: 22429688]
71. Lanari C, Lamb CA, Fabris VT, Helguero LA, Soldati R, Bottino MC, et al. The MPA mouse breast cancer model: evidence for a role of progesterone receptors in breast cancer. *Endocr Relat Cancer.* 2009; 16:333–50. [PubMed: 19190078]
72. Chan MM, Lu X, Merchant FM, Iglehart JD, Miron PL. Gene expression profiling of NMU-induced rat mammary tumors: cross species comparison with human breast cancer. *Carcinogenesis.* 2005; 26:1343–53. [PubMed: 15845649]
73. Ingberg E, Theodorsson A, Theodorsson E, Strom JO. Methods for long-term 17beta-estradiol administration to mice. *Gen Comp Endocrinol.* 2012; 175:188–93. [PubMed: 22137913]
74. Zhang Y. Allyl isothiocyanate as a cancer chemopreventive phytochemical. *Mol Nutr Food Res.* 2010; 54:127–35. [PubMed: 19960458]

75. Ioannou YM, Burka LT, Matthews HB. Allyl isothiocyanate: comparative disposition in rats and mice. *Toxicol Appl Pharmacol*. 1984; 75:173–81. [PubMed: 6474456]
76. Bollard M, Stribbling S, Mitchell S, Caldwell J. The disposition of allyl isothiocyanate in the rat and mouse. *Food Chem Toxicol*. 1997; 35:933–43. [PubMed: 9463527]
77. Munday R, Zhang Y, Fahey JW, Jobson HE, Munday CM, Li J, et al. Evaluation of isothiocyanates as potent inducers of carcinogen-detoxifying enzymes in the urinary bladder: critical nature of in vivo bioassay. *Nutr Cancer*. 2006; 54:223–31. [PubMed: 16898867]
78. Shapiro TA, Fahey JW, Wade KL, Stephenson KK, Talalay P. Human metabolism and excretion of cancer chemoprotective glucosinolates and isothiocyanates of cruciferous vegetables. *Cancer Epidemiol Biomarkers Prev*. 1998; 7:1091–100. [PubMed: 9865427]
79. Jiao D, Ho CT, Foiles P, Chung FL. Identification and quantification of the N-acetylcysteine conjugate of allyl isothiocyanate in human urine after ingestion of mustard. *Cancer Epidemiol Biomarkers Prev*. 1994; 3:487–92. [PubMed: 8000299]
80. Rajakumar T, Pugalandhi P, Thilagavathi S. Dose response chemopreventive potential of allyl isothiocyanate against 7,12-dimethylbenz(a)anthracene induced mammary carcinogenesis in female Sprague-Dawley rats. *Chem Biol Interact*. 2015; 231:35–43. [PubMed: 25744308]
81. Mafuvadze B, Cook M, Xu Z, Besch-Williford CL, Hyder SM. Effects of dietary apigenin on tumor latency, incidence and multiplicity in a medroxyprogesterone acetate-accelerated 7,12-dimethylbenz(a)anthracene-induced breast cancer model. *Nutr Cancer*. 2013; 65:1184–91. [PubMed: 24127693]
82. Seo HS, Ku JM, Choi HS, Woo JK, Jang BH, Go H, et al. Apigenin induces caspase-dependent apoptosis by inhibiting signal transducer and activator of transcription 3 signaling in HER2-overexpressing SKBR3 breast cancer cells. *Mol Med Rep*. 2015; 12:2977–84. [PubMed: 25936427]
83. Scherbakov AM, Andreeva OE. Apigenin Inhibits Growth of Breast Cancer Cells: The Role of ERalpha and HER2/neu. *Acta Naturae*. 2015; 7:133–9. [PubMed: 26483970]
84. Hollman PC, Katan MB. Health effects and bioavailability of dietary flavonols. *Free Radic Res*. 1999; 31(Suppl):S75–80. [PubMed: 10694044]
85. Ross JA, Kasum CM. Dietary flavonoids: bioavailability, metabolic effects, and safety. *Annu Rev Nutr*. 2002; 22:19–34. [PubMed: 12055336]
86. Patel D, Shukla S, Gupta S. Apigenin and cancer chemoprevention: progress, potential and promise (review). *Int J Oncol*. 2007; 30:233–45. [PubMed: 17143534]
87. Mafuvadze B, Liang Y, Besch-Williford C, Zhang X, Hyder SM. Apigenin induces apoptosis and blocks growth of medroxyprogesterone acetate-dependent BT-474 xenograft tumors. *Horm Cancer*. 2012; 3:160–71. [PubMed: 22569706]
88. Mafuvadze B, Benakanakere I, Lopez Perez FR, Besch-Williford C, Ellersieck MR, Hyder SM. Apigenin prevents development of medroxyprogesterone acetate-accelerated 7,12-dimethylbenz(a)anthracene-induced mammary tumors in Sprague-Dawley rats. *Cancer Prev Res (Phila)*. 2011; 4:1316–24. [PubMed: 21505181]
89. Kawai H, Li H, Chun P, Avraham S, Avraham HK. Direct interaction between BRCA1 and the estrogen receptor regulates vascular endothelial growth factor (VEGF) transcription and secretion in breast cancer cells. *Oncogene*. 2002; 21:7730–9. [PubMed: 12400015]
90. Aiyer HS, Warri AM, Woode DR, Hilakivi-Clarke L, Clarke R. Influence of berry polyphenols on receptor signaling and cell-death pathways: implications for breast cancer prevention. *J Agric Food Chem*. 2012; 60:5693–708. [PubMed: 22300613]
91. Koli R, Erlund I, Julia A, Marniemi J, Mattila P, Alfthan G. Bioavailability of various polyphenols from a diet containing moderate amounts of berries. *J Agric Food Chem*. 2010; 58:3927–32. [PubMed: 20073463]
92. Aiyer HS, Gupta RC. Berries and ellagic acid prevent estrogen-induced mammary tumorigenesis by modulating enzymes of estrogen metabolism. *Cancer Prev Res (Phila)*. 2010; 3:727–37. [PubMed: 20501861]
93. Aiyer HS, Srinivasan C, Gupta RC. Dietary berries and ellagic acid diminish estrogen-mediated mammary tumorigenesis in ACI rats. *Nutr Cancer*. 2008; 60:227–34. [PubMed: 18444155]

94. Aiyer HS, Kichambare S, Gupta RC. Prevention of oxidative DNA damage by bioactive berry components. *Nutr Cancer*. 2008; 60(Suppl 1):36–42. [PubMed: 19003579]
95. Jeyabalan J, Aqil F, Munagala R, Annamalai L, Vadhanam MV, Gupta RC. Chemopreventive and therapeutic activity of dietary blueberry against estrogen-mediated breast cancer. *J Agric Food Chem*. 2014; 62:3963–71. [PubMed: 24245576]
96. Ravoori S, Vadhanam MV, Aqil F, Gupta RC. Inhibition of estrogen-mediated mammary tumorigenesis by blueberry and black raspberry. *J Agric Food Chem*. 2012; 60:5547–55. [PubMed: 22571764]
97. Lin CC, Tsai YL, Ho CT, Teng SC. Determination of the differential estrogenicity of isoflavonoids by E2-ER-ERE-dependent gene expression in recombinant yeast and MCF-7 human breast cancer cells. *Food Chem*. 2008; 108:719–26. [PubMed: 26059153]
98. Chen J, Ge B, Wang Y, Ye Y, Zeng S, Huang Z. Biochanin A promotes proliferation that involves a feedback loop of microRNA-375 and estrogen receptor alpha in breast cancer cells. *Cell Physiol Biochem*. 2015; 35:639–46. [PubMed: 25613180]
99. Hsu JT, Ying C, Chen CJ. Regulation of inducible nitric oxide synthase by dietary phytoestrogen in MCF-7 human mammary cancer cells. *Reprod Nutr Dev*. 2000; 40:11–8. [PubMed: 10737547]
100. Jia X, Chen J, Lin H, Hu M. Disposition of flavonoids via enteric recycling: enzyme-transporter coupling affects metabolism of biochanin A and formononetin and excretion of their phase II conjugates. *J Pharmacol Exp Ther*. 2004; 310:1103–13. [PubMed: 15128864]
101. Moon YJ, Sagawa K, Frederick K, Zhang S, Morris ME. Pharmacokinetics and bioavailability of the isoflavone biochanin A in rats. *AAPS J*. 2006; 8:E433–42. [PubMed: 17025260]
102. Gotoh T, Yamada K, Yin H, Ito A, Kataoka T, Dohi K. Chemoprevention of N-nitroso-N-methylurea-induced rat mammary carcinogenesis by soy foods or biochanin A. *Jpn J Cancer Res*. 1998; 89:137–42. [PubMed: 9548440]
103. Moon YJ, Shin BS, An G, Morris ME. Biochanin A inhibits breast cancer tumor growth in a murine xenograft model. *Pharm Res*. 2008; 25:2158–63. [PubMed: 18454305]
104. Mishra P, Kale RK, Kar A. Chemoprevention of mammary tumorigenesis and chemomodulation of the antioxidative enzymes and peroxidative damage in prepubertal Sprague Dawley rats by Biochanin A. *Mol Cell Biochem*. 2008; 312:1–9. [PubMed: 18273562]
105. Rosendahl AH, Perks CM, Zeng L, Markkula A, Simonsson M, Rose C, et al. Caffeine and Caffeic Acid Inhibit Growth and Modify Estrogen Receptor and Insulin-like Growth Factor I Receptor Levels in Human Breast Cancer. *Clin Cancer Res*. 2015; 21:1877–87. [PubMed: 25691730]
106. Sisti JS, Hankinson SE, Caporaso NE, Gu F, Tamimi RM, Rosner B, et al. Caffeine, coffee, and tea intake and urinary estrogens and estrogen metabolites in premenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2015; 24:1174–83. [PubMed: 26063478]
107. Arnaud MJ. The pharmacology of caffeine. *Prog Drug Res*. 1987; 31:273–313. [PubMed: 3326033]
108. Bonati M, Latini R, Galletti F, Young JF, Tognoni G, Garattini S. Caffeine disposition after oral doses. *Clin Pharmacol Ther*. 1982; 32:98–106. [PubMed: 7083737]
109. Sawynok J, Yaksh TL. Caffeine as an analgesic adjuvant: a review of pharmacology and mechanisms of action. *Pharmacol Rev*. 1993; 45:43–85. [PubMed: 8475169]
110. Teekachunhatean S, Tosri N, Rojanasthien N, Srichairatanakool S, Sangdee C. Pharmacokinetics of Caffeine following a Single Administration of Coffee Enema versus Oral Coffee Consumption in Healthy Male Subjects. *ISRN Pharmacol*. 2013; 2013:147238. [PubMed: 23533801]
111. Petrek JA, Sandberg WA, Cole MN, Silberman MS, Collins DC. The inhibitory effect of caffeine on hormone-induced rat breast cancer. *Cancer*. 1985; 56:1977–81. [PubMed: 4027928]
112. Wolfrom DM, Rao AR, Welsch CW. Caffeine inhibits development of benign mammary gland tumors in carcinogen-treated female Sprague-Dawley rats. *Breast Cancer Res Treat*. 1991; 19:269–75. [PubMed: 1777646]
113. Vanderploeg LC, Wolfrom DM, Welsch CW. Influence of caffeine on development of benign and carcinomatous mammary gland tumors in female rats treated with the carcinogens 7,12-dimethylbenz(a)anthracene and N-methyl-N-nitrosourea. *Cancer Res*. 1991; 51:3399–404. [PubMed: 1905195]

114. Hirose M, Nishikawa A, Shibutani M, Imai T, Shirai T. Chemoprevention of heterocyclic amine-induced mammary carcinogenesis in rats. *Environ Mol Mutagen*. 2002; 39:271–8. [PubMed: 11921198]
115. Musa MA, Cooperwood JS, Khan MO. A review of coumarin derivatives in pharmacotherapy of breast cancer. *Curr Med Chem*. 2008; 15:2664–79. [PubMed: 18991629]
116. Jacquot Y, Bermont L, Giorgi H, Refouvelet B, Adessi GL, Daubrosse E, et al. Substituted benzopyranobenzothiazinones. Synthesis and estrogenic activity on MCF-7 breast carcinoma cells. *Eur J Med Chem*. 2001; 36:127–36. [PubMed: 11311744]
117. Hoult JR, Paya M. Pharmacological and biochemical actions of simple coumarins: natural products with therapeutic potential. *Gen Pharmacol*. 1996; 27:713–22. [PubMed: 8853310]
118. Gao S, Hu M. Bioavailability challenges associated with development of anti-cancer phenolics. *Mini Rev Med Chem*. 2010; 10:550–67. [PubMed: 20370701]
119. Prince M, Campbell CT, Robertson TA, Wells AJ, Kleiner HE. Naturally occurring coumarins inhibit 7,12-dimethylbenz[a]anthracene DNA adduct formation in mouse mammary gland. *Carcinogenesis*. 2006; 27:1204–13. [PubMed: 16387742]
120. Feuer G, Kellen JA, Kovacs K. Suppression of 7,12-dimethylbenz(alpha) anthracene-induced breast carcinoma by coumarin in the rat. *Oncology*. 1976; 33:35–9. [PubMed: 824591]
121. Lv ZD, Liu XP, Zhao WJ, Dong Q, Li FN, Wang HB, et al. Curcumin induces apoptosis in breast cancer cells and inhibits tumor growth in vitro and in vivo. *Int J Clin Exp Pathol*. 2014; 7:2818–24. [PubMed: 25031701]
122. Yang KY, Lin LC, Tseng TY, Wang SC, Tsai TH. Oral bioavailability of curcumin in rat and the herbal analysis from *Curcuma longa* by LC-MS/MS. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2007; 853:183–9.
123. Pan MH, Huang TM, Lin JK. Biotransformation of curcumin through reduction and glucuronidation in mice. *Drug Metab Dispos*. 1999; 27:486–94. [PubMed: 10101144]
124. Dhillon N, Aggarwal BB, Newman RA, Wolff RA, Kunnumakkara AB, Abbruzzese JL, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin Cancer Res*. 2008; 14:4491–9. [PubMed: 18628464]
125. Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res*. 2001; 21:2895–900. [PubMed: 11712783]
126. Sharma RA, McLelland HR, Hill KA, Ireson CR, Euden SA, Manson MM, et al. Pharmacodynamic and pharmacokinetic study of oral *Curcuma* extract in patients with colorectal cancer. *Clin Cancer Res*. 2001; 7:1894–900. [PubMed: 11448902]
127. Carroll CE, Benakanakere I, Besch-Williford C, Ellersieck MR, Hyder SM. Curcumin delays development of medroxyprogesterone acetate-accelerated 7,12-dimethylbenz[a]anthracene-induced mammary tumors. *Menopause*. 2010; 17:178–84. [PubMed: 19629015]
128. Siddiqui RA, Harvey KA, Walker C, Altenburg J, Xu Z, Terry C, et al. Characterization of synergistic anti-cancer effects of docosahexaenoic acid and curcumin on DMBA-induced mammary tumorigenesis in mice. *BMC Cancer*. 2013; 13:418. [PubMed: 24034496]
129. Zhou QM, Wang XF, Liu XJ, Zhang H, Lu YY, Su SB. Curcumin enhanced antiproliferative effect of mitomycin C in human breast cancer MCF-7 cells in vitro and in vivo. *Acta Pharmacol Sin*. 2011; 32:1402–10. [PubMed: 21986579]
130. Bansal SS, Kausar H, Vadhanam MV, Ravoori S, Pan J, Rai SN, et al. Curcumin implants, not curcumin diet, inhibit estrogen-induced mammary carcinogenesis in ACI rats. *Cancer Prev Res (Phila)*. 2014; 7:456–65. [PubMed: 24501322]
131. McCaskill ML, Rogan E, Thomas RD. Diallyl sulfide inhibits diethylstilbestrol induced DNA damage in human breast epithelial cells (MCF-10A). *Steroids*. 2014; 92:96–100. [PubMed: 25278253]
132. Na HK, Kim EH, Choi MA, Park JM, Kim DH, Surh YJ. Diallyl trisulfide induces apoptosis in human breast cancer cells through ROS-mediated activation of JNK and AP-1. *Biochem Pharmacol*. 2012; 84:1241–50. [PubMed: 22981381]

133. Green M, Wilson C, Newell O, Sadrud-Din S, Thomas R. Diallyl sulfide inhibits diethylstilbesterol-induced DNA adducts in the breast of female ACI rats. *Food Chem Toxicol.* 2005; 43:1323–31. [PubMed: 15989972]
134. Green M, Newell O, Aboyade-Cole A, Darling-Reed S, Thomas RD. Diallyl sulfide induces the expression of estrogen metabolizing genes in the presence and/or absence of diethylstilbestrol in the breast of female ACI rats. *Toxicol Lett.* 2007; 168:7–12. [PubMed: 17129689]
135. Green M, Newell O, Aboyade-Cole A, Darling-Reed S, Thomas RD. Diallyl sulfide induces the expression of nucleotide excision repair enzymes in the breast of female ACI rats. *Toxicol Lett.* 2007; 168:40–4. [PubMed: 17125941]
136. Gued LR, Thomas RD, Green M. Diallyl sulfide inhibits diethylstilbestrol-induced lipid peroxidation in breast tissue of female ACI rats: implications in breast cancer prevention. *Oncol Rep.* 2003; 10:739–43. [PubMed: 12684652]
137. Srinivasan S, Koduru S, Kumar R, Venguswamy G, Kyprianou N, Damodaran C. Diosgenin targets Akt-mediated prosurvival signaling in human breast cancer cells. *Int J Cancer.* 2009; 125:961–7. [PubMed: 19384950]
138. Okawara M, Hashimoto F, Todo H, Sugibayashi K, Tokudome Y. Effect of liquid crystals with cyclodextrin on the bioavailability of a poorly water-soluble compound, diosgenin, after its oral administration to rats. *Int J Pharm.* 2014; 472:257–61. [PubMed: 24954725]
139. Jagadeesan J, Nandakumar N, Rengarajan T, Balasubramanian MP. Diosgenin, a steroidal saponin, exhibits anticancer activity by attenuating lipid peroxidation via enhancing antioxidant defense system during NMU-induced breast carcinoma. *J Environ Pathol Toxicol Oncol.* 2012; 31:121–9. [PubMed: 23216637]
140. Chen HS, Bai MH, Zhang T, Li GD, Liu M. Ellagic acid induces cell cycle arrest and apoptosis through TGF-beta/Smad3 signaling pathway in human breast cancer MCF-7 cells. *Int J Oncol.* 2015; 46:1730–8. [PubMed: 25647396]
141. Papoutsi Z, Kassi E, Tsiapara A, Fokialakis N, Chrousos GP, Moutsatsou P. Evaluation of estrogenic/antiestrogenic activity of ellagic acid via the estrogen receptor subtypes ERalpha and ERbeta. *J Agric Food Chem.* 2005; 53:7715–20. [PubMed: 16190622]
142. Zhang HM, Zhao L, Li H, Xu H, Chen WW, Tao L. Research progress on the anticarcinogenic actions and mechanisms of ellagic acid. *Cancer Biol Med.* 2014; 11:92–100. [PubMed: 25009751]
143. Vadhanam MV, Ravoori S, Aqil F, Gupta RC. Chemoprevention of mammary carcinogenesis by sustained systemic delivery of ellagic acid. *Eur J Cancer Prev.* 2011; 20:484–91. [PubMed: 21768881]
144. Munagala R, Aqil F, Vadhanam MV, Gupta RC. MicroRNA ‘signature’ during estrogen-mediated mammary carcinogenesis and its reversal by ellagic acid intervention. *Cancer Lett.* 2013; 339:175–84. [PubMed: 23791885]
145. Tran PL, Kim SA, Choi HS, Yoon JH, Ahn SG. Epigallocatechin-3-gallate suppresses the expression of HSP70 and HSP90 and exhibits anti-tumor activity in vitro and in vivo. *BMC Cancer.* 2010; 10:276. [PubMed: 20537126]
146. Manjegowda MC, Deb G, Kumar N, Limaye AM. Expression profiling of genes modulated by estrogen, EGCG or both in MCF-7 breast cancer cells. *Genom Data.* 2015; 5:210–2. [PubMed: 26484257]
147. Lee MJ, Maliakal P, Chen L, Meng X, Bondoc FY, Prabhu S, et al. Pharmacokinetics of tea catechins after ingestion of green tea and (–)-epigallocatechin-3-gallate by humans: formation of different metabolites and individual variability. *Cancer Epidemiol Biomarkers Prev.* 2002; 11:1025–32. [PubMed: 12376503]
148. Bettuzzi S, Brausi M, Rizzi F, Castagnetti G, Peracchia G, Corti A. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. *Cancer Res.* 2006; 66:1234–40. [PubMed: 16424063]
149. Chow HH, Hakim IA, Vining DR, Crowell JA, Cordova CA, Chew WM, et al. Effects of repeated green tea catechin administration on human cytochrome P450 activity. *Cancer Epidemiol Biomarkers Prev.* 2006; 15:2473–6. [PubMed: 17164372]

150. Lambert JD, Kennett MJ, Sang S, Reuhl KR, Ju J, Yang CS. Hepatotoxicity of high oral dose (–)-epigallocatechin-3-gallate in mice. *Food Chem Toxicol.* 2010; 48:409–16. [PubMed: 19883714]
151. Kapetanovic IM, Crowell JA, Krishnaraj R, Zakharov A, Lindeblad M, Lyubimov A. Exposure and toxicity of green tea polyphenols in fasted and non-fasted dogs. *Toxicology.* 2009; 260:28–36. [PubMed: 19464566]
152. Lambert JD, Sang S, Yang CS. Possible controversy over dietary polyphenols: benefits vs risks. *Chem Res Toxicol.* 2007; 20:583–5. [PubMed: 17362033]
153. Mazzanti G, Menniti-Ippolito F, Moro PA, Cassetti F, Raschetti R, Santuccio C, et al. Hepatotoxicity from green tea: a review of the literature and two unpublished cases. *Eur J Clin Pharmacol.* 2009; 65:331–41. [PubMed: 19198822]
154. Lambert JD, Lee MJ, Lu H, Meng X, Hong JJ, Seril DN, et al. Epigallocatechin-3-gallate is absorbed but extensively glucuronidated following oral administration to mice. *J Nutr.* 2003; 133:4172–7. [PubMed: 14652367]
155. Chen L, Lee MJ, Li H, Yang CS. Absorption, distribution, elimination of tea polyphenols in rats. *Drug Metab Dispos.* 1997; 25:1045–50. [PubMed: 9311619]
156. Manjegowda CM, Deb G, Limaye AM. Epigallocatechin gallate induces the steady state mRNA levels of pS2 and PR genes in MCF-7 breast cancer cells. *Indian J Exp Biol.* 2014; 52:312–6. [PubMed: 24772933]
157. Moreira L, Araujo I, Costa T, Correia-Branco A, Faria A, Martel F, et al. Quercetin and epigallocatechin gallate inhibit glucose uptake and metabolism by breast cancer cells by an estrogen receptor-independent mechanism. *Exp Cell Res.* 2013; 319:1784–95. [PubMed: 23664836]
158. van Ginkel PR, Yan MB, Bhattacharya S, Polans AS, Kenealey JD. Natural products induce a G protein-mediated calcium pathway activating p53 in cancer cells. *Toxicol Appl Pharmacol.* 2015; 288:453–62. [PubMed: 26341291]
159. Khan HY, Zubair H, Faisal M, Ullah MF, Farhan M, Sarkar FH, et al. Plant polyphenol induced cell death in human cancer cells involves mobilization of intracellular copper ions and reactive oxygen species generation: a mechanism for cancer chemopreventive action. *Mol Nutr Food Res.* 2014; 58:437–46. [PubMed: 24123728]
160. Liao S, Umekita Y, Guo J, Kokontis JM, Hiipakka RA. Growth inhibition and regression of human prostate and breast tumors in athymic mice by tea epigallocatechin gallate. *Cancer Lett.* 1995; 96:239–43. [PubMed: 7585463]
161. Goodin MG, Fertuck KC, Zacharewski TR, Rosengren RJ. Estrogen receptor-mediated actions of polyphenolic catechins in vivo and in vitro. *Toxicol Sci.* 2002; 69:354–61. [PubMed: 12377984]
162. Choi YE, Park E. Ferulic acid in combination with PARP inhibitor sensitizes breast cancer cells as chemotherapeutic strategy. *Biochem Biophys Res Commun.* 2015; 458:520–4. [PubMed: 25677620]
163. Bourne L, Paganga G, Baxter D, Hughes P, Rice-Evans C. Absorption of ferulic acid from low-alcohol beer. *Free Radic Res.* 2000; 32:273–80. [PubMed: 10730826]
164. Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr.* 2005; 81:230S–42S. [PubMed: 15640486]
165. Baskaran N, Manoharan S, Balakrishnan S, Pugalendhi P. Chemopreventive potential of ferulic acid in 7,12-dimethylbenz[a]anthracene-induced mammary carcinogenesis in Sprague-Dawley rats. *Eur J Pharmacol.* 2010; 637:22–9. [PubMed: 20385116]
166. Thompson LU, Chen JM, Li T, Strasser-Weippl K, Goss PE. Dietary flaxseed alters tumor biological markers in postmenopausal breast cancer. *Clin Cancer Res.* 2005; 11:3828–35. [PubMed: 15897583]
167. Thompson LU, Boucher BA, Liu Z, Cotterchio M, Kreiger N. Phytoestrogen content of foods consumed in Canada, including isoflavones, lignans, and coumestanol. *Nutr Cancer.* 2006; 54:184–201. [PubMed: 16898863]
168. Chen J, Power KA, Mann J, Cheng A, Thompson LU. Dietary flaxseed interaction with tamoxifen induced tumor regression in athymic mice with MCF-7 xenografts by downregulating the

- expression of estrogen related gene products and signal transduction pathways. *Nutr Cancer*. 2007; 58:162–70. [PubMed: 17640162]
169. Chen J, Power KA, Mann J, Cheng A, Thompson LU. Flaxseed alone or in combination with tamoxifen inhibits MCF-7 breast tumor growth in ovariectomized athymic mice with high circulating levels of estrogen. *Exp Biol Med (Maywood)*. 2007; 232:1071–80. [PubMed: 17720953]
 170. Chen J, Hui E, Ip T, Thompson LU. Dietary flaxseed enhances the inhibitory effect of tamoxifen on the growth of estrogen-dependent human breast cancer (mcf-7) in nude mice. *Clin Cancer Res*. 2004; 10:7703–11. [PubMed: 15570004]
 171. Delman DM, Fabian CJ, Kimler BF, Yeh H, Petroff BK. Effects of Flaxseed Lignan Secoisolaricresinol Diglucoside on Preneoplastic Biomarkers of Cancer Progression in a Model of Simultaneous Breast and Ovarian Cancer Development. *Nutr Cancer*. 2015; 67:857–64. [PubMed: 26010915]
 172. Rickard SE, Yuan YV, Chen J, Thompson LU. Dose effects of flaxseed and its lignan on N-methyl-N-nitrosourea-induced mammary tumorigenesis in rats. *Nutr Cancer*. 1999; 35:50–7. [PubMed: 10624706]
 173. Parihar S, Gupta A, Chaturvedi AK, Agarwal J, Luqman S, Changkija B, et al. Gallic acid based steroidal phenstatin analogues for selective targeting of breast cancer cells through inhibiting tubulin polymerization. *Steroids*. 2012; 77:878–86. [PubMed: 22503714]
 174. Wang K, Zhu X, Zhang K, Zhu L, Zhou F. Investigation of gallic acid induced anticancer effect in human breast carcinoma MCF-7 cells. *J Biochem Mol Toxicol*. 2014; 28:387–93. [PubMed: 24864015]
 175. Hsu JD, Kao SH, Ou TT, Chen YJ, Li YJ, Wang CJ. Gallic acid induces G2/M phase arrest of breast cancer cell MCF-7 through stabilization of p27(Kip1) attributed to disruption of p27(Kip1)/Skp2 complex. *J Agric Food Chem*. 2011; 59:1996–2003. [PubMed: 21299246]
 176. Shahrzad S, Aoyagi K, Winter A, Koyama A, Bitsch I. Pharmacokinetics of gallic acid and its relative bioavailability from tea in healthy humans. *J Nutr*. 2001; 131:1207–10. [PubMed: 11285327]
 177. Ferruzzi MG, Lobo JK, Janle EM, Cooper B, Simon JE, Wu QL, et al. Bioavailability of gallic acid and catechins from grape seed polyphenol extract is improved by repeated dosing in rats: implications for treatment in Alzheimer's disease. *J Alzheimers Dis*. 2009; 18:113–24. [PubMed: 19625746]
 178. Banerjee N, Kim H, Krenek K, Talcott ST, Mertens-Talcott SU. Mango polyphenolics suppressed tumor growth in breast cancer xenografts in mice: role of the PI3K/AKT pathway and associated microRNAs. *Nutr Res*. 2015; 35:744–51. [PubMed: 26194618]
 179. Pons DG, Nadal-Serrano M, Torrens-Mas M, Oliver J, Roca P. The Phytoestrogen Genistein Affects Breast Cancer Cells Treatment Depending on the ERalpha/ERbeta Ratio. *J Cell Biochem*. 2015
 180. Setchell KD, Brown NM, Desai P, Zimmer-Nechemias L, Wolfe BE, Brashear WT, et al. Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. *J Nutr*. 2001; 131:1362S–75S. [PubMed: 11285356]
 181. Larkin T, Price WE, Astheimer L. The key importance of soy isoflavone bioavailability to understanding health benefits. *Crit Rev Food Sci Nutr*. 2008; 48:538–52. [PubMed: 18568859]
 182. Michael McClain R, Wolz E, Davidovich A, Pfannkuch F, Edwards JA, Bausch J. Acute, subchronic and chronic safety studies with genistein in rats. *Food Chem Toxicol*. 2006; 44:56–80. [PubMed: 16213646]
 183. Busby MG, Jeffcoat AR, Bloedon LT, Koch MA, Black T, Dix KJ, et al. Clinical characteristics and pharmacokinetics of purified soy isoflavones: single-dose administration to healthy men. *Am J Clin Nutr*. 2002; 75:126–36. [PubMed: 11756070]
 184. Bloedon LT, Jeffcoat AR, Lopaczynski W, Schell MJ, Black TM, Dix KJ, et al. Safety and pharmacokinetics of purified soy isoflavones: single-dose administration to postmenopausal women. *Am J Clin Nutr*. 2002; 76:1126–37. [PubMed: 12399289]

185. Peng JH, Zhu JD, Mi MT, Li FJ, Cai L, Dong JZ, et al. Prepubertal genistein exposure affects erbB2/Akt signal and reduces rat mammary tumorigenesis. *Eur J Cancer Prev.* 2010; 19:110–9. [PubMed: 20051871]
186. Kang X, Jin S, Zhang Q. Antitumor and antiangiogenic activity of soy phytoestrogen on 7,12-dimethylbenz[alpha]anthracene-induced mammary tumors following ovariectomy in Sprague-Dawley rats. *J Food Sci.* 2009; 74:H237–42. [PubMed: 19895476]
187. Park OJ, Shin JI. Proapoptotic potentials of genistein under growth stimulation by estrogen. *Ann N Y Acad Sci.* 2004; 1030:410–8. [PubMed: 15659824]
188. Constantinou AI, Krygier AE, Mehta RR. Genistein induces maturation of cultured human breast cancer cells and prevents tumor growth in nude mice. *Am J Clin Nutr.* 1998; 68:1426S–30S. [PubMed: 9848511]
189. Andrade JE, Ju YH, Baker C, Doerge DR, Helferich WG. Long-term exposure to dietary sources of genistein induces estrogen-independence in the human breast cancer (MCF-7) xenograft model. *Mol Nutr Food Res.* 2015; 59:413–23. [PubMed: 24668689]
190. Fan P, Fan S, Wang H, Mao J, Shi Y, Ibrahim MM, et al. Genistein decreases the breast cancer stem-like cell population through Hedgehog pathway. *Stem Cell Res Ther.* 2013; 4:146. [PubMed: 24331293]
191. Palit S, Kar S, Sharma G, Das PK. Hesperetin Induces Apoptosis in Breast Carcinoma by Triggering Accumulation of ROS and Activation of ASK1/JNK Pathway. *J Cell Physiol.* 2015; 230:1729–39. [PubMed: 25204891]
192. Choi EJ. Hesperetin induced G1-phase cell cycle arrest in human breast cancer MCF-7 cells: involvement of CDK4 and p21. *Nutr Cancer.* 2007; 59:115–9. [PubMed: 17927510]
193. Li F, Ye L, Lin SM, Leung LK. Dietary flavones and flavonones display differential effects on aromatase (CYP19) transcription in the breast cancer cells MCF-7. *Mol Cell Endocrinol.* 2011; 344:51–8. [PubMed: 21741436]
194. Zava DT, Blen M, Duwe G. Estrogenic activity of natural and synthetic estrogens in human breast cancer cells in culture. *Environ Health Perspect.* 1997; 105(Suppl 3):637–45. [PubMed: 9168008]
195. Miksicek RJ. Interaction of naturally occurring nonsteroidal estrogens with expressed recombinant human estrogen receptor. *J Steroid Biochem Mol Biol.* 1994; 49:153–60. [PubMed: 8031711]
196. Ye L, Chan FL, Chen S, Leung LK. The citrus flavonone hesperetin inhibits growth of aromatase-expressing MCF-7 tumor in ovariectomized athymic mice. *J Nutr Biochem.* 2012; 23:1230–7. [PubMed: 22209285]
197. Marconett CN, Singhal AK, Sundar SN, Firestone GL. Indole-3-carbinol disrupts estrogen receptor-alpha dependent expression of insulin-like growth factor-1 receptor and insulin receptor substrate-1 and proliferation of human breast cancer cells. *Mol Cell Endocrinol.* 2012; 363:74–84. [PubMed: 22835548]
198. Caruso JA, Campana R, Wei C, Su CH, Hanks AM, Bornmann WG, et al. Indole-3-carbinol and its N-alkoxy derivatives preferentially target ERalpha-positive breast cancer cells. *Cell Cycle.* 2014; 13:2587–99. [PubMed: 25486199]
199. Tiwari RK, Guo L, Bradlow HL, Telang NT, Osborne MP. Selective responsiveness of human breast cancer cells to indole-3-carbinol, a chemopreventive agent. *J Natl Cancer Inst.* 1994; 86:126–31. [PubMed: 8271295]
200. Reed GA, Arneson DW, Putnam WC, Smith HJ, Gray JC, Sullivan DK, et al. Single-dose and multiple-dose administration of indole-3-carbinol to women: pharmacokinetics based on 3,3'-diindolylmethane. *Cancer Epidemiol Biomarkers Prev.* 2006; 15:2477–81. [PubMed: 17164373]
201. Horn TL, Reichert MA, Bliss RL, Malejka-Giganti D. Modulations of P450 mRNA in liver and mammary gland and P450 activities and metabolism of estrogen in liver by treatment of rats with indole-3-carbinol. *Biochem Pharmacol.* 2002; 64:393–404. [PubMed: 12147290]
202. Leibelt DA, Hedstrom OR, Fischer KA, Pereira CB, Williams DE. Evaluation of chronic dietary exposure to indole-3-carbinol and absorption-enhanced 3,3'-diindolylmethane in sprague-dawley rats. *Toxicol Sci.* 2003; 74:10–21. [PubMed: 12730619]

203. Malloy VL, Bradlow HL, Orentreich N. Interaction between a semisynthetic diet and indole-3-carbinol on mammary tumor incidence in Balb/c/c3H mice. *Anticancer Res.* 1997; 17:4333–7. [PubMed: 9494529]
204. Chang X, Tou JC, Hong C, Kim HA, Riby JE, Firestone GL, et al. 3,3'-Diindolylmethane inhibits angiogenesis and the growth of transplantable human breast carcinoma in athymic mice. *Carcinogenesis.* 2005; 26:771–8. [PubMed: 15661811]
205. Chen I, McDougal A, Wang F, Safe S. Aryl hydrocarbon receptor-mediated antiestrogenic and antitumorigenic activity of diindolylmethane. *Carcinogenesis.* 1998; 19:1631–9. [PubMed: 9771935]
206. Ritter CL, Prigge WF, Reichert MA, Malejka-Giganti D. Oxidations of 17beta-estradiol and estrone and their interconversions catalyzed by liver, mammary gland and mammary tumor after acute and chronic treatment of rats with indole-3-carbinol or beta-naphthoflavone. *Can J Physiol Pharmacol.* 2001; 79:519–32. [PubMed: 11430590]
207. Zhang YC, Gan FF, Shelar SB, Ng KY, Chew EH. Antioxidant and Nrf2 inducing activities of luteolin, a flavonoid constituent in *Ixeris sonchifolia* Hance, provide neuroprotective effects against ischemia-induced cellular injury. *Food Chem Toxicol.* 2013; 59:272–80. [PubMed: 23770353]
208. Ashokkumar P, Sudhandiran G. Protective role of luteolin on the status of lipid peroxidation and antioxidant defense against azoxymethane-induced experimental colon carcinogenesis. *Biomed Pharmacother.* 2008; 62:590–7. [PubMed: 18692983]
209. Park SH, Ham S, Kwon TH, Kim MS, Lee DH, Kang JW, et al. Luteolin induces cell cycle arrest and apoptosis through extrinsic and intrinsic signaling pathways in MCF-7 breast cancer cells. *J Environ Pathol Toxicol Oncol.* 2014; 33:219–31. [PubMed: 25272060]
210. Wang LM, Xie KP, Huo HN, Shang F, Zou W, Xie MJ. Luteolin inhibits proliferation induced by IGF-1 pathway dependent ERalpha in human breast cancer MCF-7 cells. *Asian Pac J Cancer Prev.* 2012; 13:1431–7. [PubMed: 22799344]
211. Markaverich BM, Shoulars K, Rodriguez MA. Luteolin Regulation of Estrogen Signaling and Cell Cycle Pathway Genes in MCF-7 Human Breast Cancer Cells. *Int J Biomed Sci.* 2011; 7:101–11. [PubMed: 21731475]
212. Majumdar D, Jung KH, Zhang H, Nannapaneni S, Wang X, Amin AR, et al. Luteolin nanoparticle in chemoprevention: in vitro and in vivo anticancer activity. *Cancer Prev Res (Phila).* 2014; 7:65–73. [PubMed: 24403290]
213. Samy RP, Gopalakrishnakone P, Ignacimuthu S. Anti-tumor promoting potential of luteolin against 7,12-dimethylbenz(a)anthracene-induced mammary tumors in rats. *Chem Biol Interact.* 2006; 164:1–14. [PubMed: 17064676]
214. Colerangle J, Roy D. The antiproliferative effect of luteolin against diethylstilbestrol-induced cell-proliferation in the mammary-gland of rat. *Int J Oncol.* 1995; 7:1361–6. [PubMed: 21552973]
215. Liang Y, Brekken RA, Hyder SM. Vascular endothelial growth factor induces proliferation of breast cancer cells and inhibits the anti-proliferative activity of anti-hormones. *Endocr Relat Cancer.* 2006; 13:905–19. [PubMed: 16954439]
216. Gloria NF, Soares N, Brand C, Oliveira FL, Borojevic R, Teodoro AJ. Lycopene and beta-carotene induce cell-cycle arrest and apoptosis in human breast cancer cell lines. *Anticancer Res.* 2014; 34:1377–86. [PubMed: 24596385]
217. Micozzi MS, Brown ED, Edwards BK, Bieri JG, Taylor PR, Khachik F, et al. Plasma carotenoid response to chronic intake of selected foods and beta-carotene supplements in men. *Am J Clin Nutr.* 1992; 55:1120–5. [PubMed: 1595584]
218. Jonker D, Kuper CF, Fraile N, Estrella A, Rodriguez Otero C. Ninety-day oral toxicity study of lycopene from *Blakeslea trispora* in rats. *Regul Toxicol Pharmacol.* 2003; 37:396–406. [PubMed: 12758219]
219. Gustin DM, Rodvold KA, Sosman JA, Diwadkar-Navsariwala V, Stacewicz-Sapuntzakis M, Viana M, et al. Single-dose pharmacokinetic study of lycopene delivered in a well-defined food-based lycopene delivery system (tomato paste-oil mixture) in healthy adult male subjects. *Cancer Epidemiol Biomarkers Prev.* 2004; 13:850–60. [PubMed: 15159319]

220. Moselhy SS, Al mslmani MA. Chemopreventive effect of lycopene alone or with melatonin against the genesis of oxidative stress and mammary tumors induced by 7,12 dimethyl(a)benzanthracene in sprague dawely female rats. *Mol Cell Biochem.* 2008; 319:175–80. [PubMed: 18682897]
221. Al-Malki AL, Moselhy SS, Refai MY. Synergistic effect of lycopene and tocopherol against oxidative stress and mammary tumorigenesis induced by 7,12-dimethyl[a]benzanthracene in female rats. *Toxicol Ind Health.* 2012; 28:542–8. [PubMed: 22033431]
222. Sahin K, Tuzcu M, Sahin N, Akdemir F, Ozercan I, Bayraktar S, et al. Inhibitory effects of combination of lycopene and genistein on 7,12- dimethyl benz(a)anthracene-induced breast cancer in rats. *Nutr Cancer.* 2011; 63:1279–86. [PubMed: 21958026]
223. Kondath S, Srinivas Raghavan B, Anantanarayanan R, Rajaram R. Synthesis and characterisation of morin reduced gold nanoparticles and its cytotoxicity in MCF-7 cells. *Chem Biol Interact.* 2014; 224C:78–88. [PubMed: 25446498]
224. Jin H, Lee WS, Eun SY, Jung JH, Park HS, Kim G, et al. Morin, a flavonoid from Moraceae, suppresses growth and invasion of the highly metastatic breast cancer cell line MDA-MB231 partly through suppression of the Akt pathway. *Int J Oncol.* 2014; 45:1629–37. [PubMed: 24993541]
225. Fang H, Tong W, Shi LM, Blair R, Perkins R, Branham W, et al. Structure-activity relationships for a large diverse set of natural, synthetic, and environmental estrogens. *Chem Res Toxicol.* 2001; 14:280–94. [PubMed: 11258977]
226. Zhang J, Peng Q, Shi S, Zhang Q, Sun X, Gong T, et al. Preparation, characterization, and in vivo evaluation of a self-nanoemulsifying drug delivery system (SNEDDS) loaded with morin-phospholipid complex. *Int J Nanomedicine.* 2011; 6:3405–14. [PubMed: 22267925]
227. Choi YA, Yoon YH, Choi K, Kwon M, Goo SH, Cha JS, et al. Enhanced oral bioavailability of morin administered in mixed micelle formulation with PluronicF127 and Tween80 in rats. *Biol Pharm Bull.* 2015; 38:208–17. [PubMed: 25747979]
228. Nandhakumar R, Salini K, Niranjali Devaraj S. Morin augments anticarcinogenic and antiproliferative efficacy against 7,12-dimethylbenz(a)-anthracene induced experimental mammary carcinogenesis. *Mol Cell Biochem.* 2012; 364:79–92. [PubMed: 22350814]
229. Deepa M, Sureshkumar T, Sateeshkumar PK, Priya S. Antioxidant rich Morus alba leaf extract induces apoptosis in human colon and breast cancer cells by the downregulation of nitric oxide produced by inducible nitric oxide synthase. *Nutr Cancer.* 2013; 65:305–10. [PubMed: 23441618]
230. Thilakarathna SH, Rupasinghe HP. Flavonoid bioavailability and attempts for bioavailability enhancement. *Nutrients.* 2013; 5:3367–87. [PubMed: 23989753]
231. Yao Y, Xie Y, Hong C, Li G, Shen H, Ji G. Development of a myricetin/hydroxypropyl-beta-cyclodextrin inclusion complex: preparation, characterization, and evaluation. *Carbohydr Polym.* 2014; 110:329–37. [PubMed: 24906763]
232. Maggiolini M, Recchia AG, Bonofiglio D, Catalano S, Vivacqua A, Carpino A, et al. The red wine phenolics piceatannol and myricetin act as agonists for estrogen receptor alpha in human breast cancer cells. *J Mol Endocrinol.* 2005; 35:269–81. [PubMed: 16216908]
233. Jayakumar JK, Nirmala P, Praveen Kumar BA, Kumar AP. Evaluation of protective effect of myricetin, a bioflavonoid in dimethyl benzanthracene-induced breast cancer in female Wistar rats. *South Asian J Cancer.* 2014; 3:107–11. [PubMed: 24818105]
234. Futakuchi M, Hirose M, Miki T, Tanaka H, Ozaki M, Shirai T. Inhibition of DMBA-initiated rat mammary tumour development by 1-O-hexyl-2,3,5-trimethylhydroquinone, phenylethyl isothiocyanate, and novel synthetic ascorbic acid derivatives. *Eur J Cancer Prev.* 1998; 7:153–9. [PubMed: 9818778]
235. Aras U, Gandhi YA, Masso-Welch PA, Morris ME. Chemopreventive and anti-angiogenic effects of dietary phenethyl isothiocyanate in an N-methyl nitrosourea-induced breast cancer animal model. *Biopharm Drug Dispos.* 2013; 34:98–106. [PubMed: 23138465]
236. Konsue N, Kirkpatrick J, Kuhnert N, King LJ, Ioannides C. Repeated oral administration modulates the pharmacokinetic behavior of the chemopreventive agent phenethyl isothiocyanate in rats. *Mol Nutr Food Res.* 2010; 54:426–32. [PubMed: 19866468]

237. McCune K, Mehta R, Thorat MA, Badve S, Nakshatri H. Loss of ERalpha and FOXA1 expression in a progression model of luminal type breast cancer: insights from PyMT transgenic mouse model. *Oncol Rep.* 2010; 24:1233–9. [PubMed: 20878115]
238. Lin EY, Jones JG, Li P, Zhu L, Whitney KD, Muller WJ, et al. Progression to malignancy in the polyoma middle T oncoprotein mouse breast cancer model provides a reliable model for human diseases. *Am J Pathol.* 2003; 163:2113–26. [PubMed: 14578209]
239. Eeckhoutte J, Keeton EK, Lupien M, Krum SA, Carroll JS, Brown M. Positive cross-regulatory loop ties GATA-3 to estrogen receptor alpha expression in breast cancer. *Cancer Res.* 2007; 67:6477–83. [PubMed: 17616709]
240. Shirode AB, Kovvuru P, Chittur SV, Henning SM, Heber D, Reliene R. Antiproliferative effects of pomegranate extract in MCF-7 breast cancer cells are associated with reduced DNA repair gene expression and induction of double strand breaks. *Mol Carcinog.* 2014; 53:458–70. [PubMed: 23359482]
241. Dana N, Javanmard Sh H, Rafiee L. Antiangiogenic and antiproliferative effects of black pomegranate peel extract on melanoma cell line. *Res Pharm Sci.* 2015; 10:117–24. [PubMed: 26487888]
242. Adams LS, Zhang Y, Seeram NP, Heber D, Chen S. Pomegranate ellagitannin-derived compounds exhibit antiproliferative and antiaromatase activity in breast cancer cells in vitro. *Cancer Prev Res (Phila).* 2010; 3:108–13. [PubMed: 20051378]
243. Dahlawi H, Jordan-Mahy N, Clench M, McDougall GJ, Maitre CL. Polyphenols are responsible for the proapoptotic properties of pomegranate juice on leukemia cell lines. *Food Sci Nutr.* 2013; 1:196–208. [PubMed: 24804028]
244. Mandal A, Bishayee A. Mechanism of Breast Cancer Preventive Action of Pomegranate: Disruption of Estrogen Receptor and Wnt/beta-Catenin Signaling Pathways. *Molecules.* 2015; 20:22315–28. [PubMed: 26703530]
245. Rocha A, Wang L, Penichet M, Martins-Green M. Pomegranate juice and specific components inhibit cell and molecular processes critical for metastasis of breast cancer. *Breast Cancer Res Treat.* 2012; 136:647–58. [PubMed: 23065001]
246. Seeram NP, Henning SM, Zhang Y, Suchard M, Li Z, Heber D. Pomegranate juice ellagitannin metabolites are present in human plasma and some persist in urine for up to 48 hours. *J Nutr.* 2006; 136:2481–5. [PubMed: 16988113]
247. Shirode AB, Bharali DJ, Nallanthighal S, Coon JK, Mousa SA, Reliene R. Nanoencapsulation of pomegranate bioactive compounds for breast cancer chemoprevention. *Int J Nanomedicine.* 2015; 10:475–84. [PubMed: 25624761]
248. Saravani M, Kazemi Mehrjerdi H, Mirshahi A, Afkhami Goli A. Protective effects of pomegranate seed oil on ovariectomized rats as a model of postmenopausal osteoporosis: A multi-detector computed tomography evaluation. *Vet Res Forum.* 2014; 5:263–7. [PubMed: 25610577]
249. Banerjee N, Talcott S, Safe S, Mertens-Talcott SU. Cytotoxicity of pomegranate polyphenolics in breast cancer cells in vitro and vivo: potential role of miRNA-27a and miRNA-155 in cell survival and inflammation. *Breast Cancer Res Treat.* 2012; 136:21–34. [PubMed: 22941571]
250. Bishayee A, Mandal A, Bhattacharyya P, Bhatia D. Pomegranate exerts chemoprevention of experimentally induced mammary tumorigenesis by suppression of cell proliferation and induction of apoptosis. *Nutr Cancer.* 2016; 68:120–30. [PubMed: 26699876]
251. Tao SF, He HF, Chen Q. Quercetin inhibits proliferation and invasion acts by up-regulating miR-146a in human breast cancer cells. *Mol Cell Biochem.* 2015; 402:93–100. [PubMed: 25596948]
252. Cao Y, Zhuang MF, Yang Y, Xie SW, Cui JG, Cao L, et al. Preliminary study of quercetin affecting the hypothalamic-pituitary-gonadal axis on rat endometriosis model. *Evid Based Complement Alternat Med.* 2014; 2014:781684. [PubMed: 25530789]
253. Chen FP, Chien MH. Phytoestrogens induce apoptosis through a mitochondria/caspase pathway in human breast cancer cells. *Climacteric.* 2014; 17:385–92. [PubMed: 24299158]
254. Huang C, Lee SY, Lin CL, Tu TH, Chen LH, Chen YJ, et al. Co-treatment with quercetin and 1,2,3,4,6-penta-O-galloyl-beta-D-glucose causes cell cycle arrest and apoptosis in human breast

- cancer MDA-MB-231 and AU565 cells. *J Agric Food Chem.* 2013; 61:6430–45. [PubMed: 23731217]
255. Cai X, Fang Z, Dou J, Yu A, Zhai G. Bioavailability of quercetin: problems and promises. *Curr Med Chem.* 2013; 20:2572–82. [PubMed: 23514412]
 256. Steiner J, Davis J, McClellan J, Enos R, Carson J, Fayad R, et al. Dose-dependent benefits of quercetin on tumorigenesis in the C3(1)/SV40Tag transgenic mouse model of breast cancer. *Cancer Biol Ther.* 2014; 15:1456–67. [PubMed: 25482952]
 257. Devipriya S, Ganapathy V, Shyamaladevi CS. Suppression of tumor growth and invasion in 9,10 dimethyl benz(a) anthracene induced mammary carcinoma by the plant bioflavonoid quercetin. *Chem Biol Interact.* 2006; 162:106–13. [PubMed: 16846595]
 258. Singh B, Mense SM, Bhat NK, Putty S, Guthiel WA, Remotti F, et al. Dietary quercetin exacerbates the development of estrogen-induced breast tumors in female ACI rats. *Toxicol Appl Pharmacol.* 2010; 247:83–90. [PubMed: 20600213]
 259. Chin YT, Hsieh MT, Yang SH, Tsai PW, Wang SH, Wang CC, et al. Anti-proliferative and gene expression actions of resveratrol in breast cancer cells in vitro. *Oncotarget.* 2014; 5:12891–907. [PubMed: 25436977]
 260. Khan A, Aljarbou AN, Aldebasi YH, Faisal SM, Khan MA. Resveratrol suppresses the proliferation of breast cancer cells by inhibiting fatty acid synthase signaling pathway. *Cancer Epidemiol.* 2014; 38:765–72. [PubMed: 25448084]
 261. Alayev A, Berger SM, Kramer MY, Schwartz NS, Holz MK. The combination of rapamycin and resveratrol blocks autophagy and induces apoptosis in breast cancer cells. *J Cell Biochem.* 2015; 116:450–7. [PubMed: 25336146]
 262. Vitaglione P, Sforza S, Galaverna G, Ghidini C, Caporaso N, Vescovi PP, et al. Bioavailability of trans-resveratrol from red wine in humans. *Mol Nutr Food Res.* 2005; 49:495–504. [PubMed: 15830336]
 263. Crowell JA, Korytko PJ, Morrissey RL, Booth TD, Levine BS. Resveratrol-associated renal toxicity. *Toxicol Sci.* 2004; 82:614–9. [PubMed: 15329443]
 264. Williams LD, Burdock GA, Edwards JA, Beck M, Bausch J. Safety studies conducted on high-purity trans-resveratrol in experimental animals. *Food Chem Toxicol.* 2009; 47:2170–82. [PubMed: 19505523]
 265. Boocock DJ, Faust GE, Patel KR, Schinas AM, Brown VA, Ducharme MP, et al. Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. *Cancer Epidemiol Biomarkers Prev.* 2007; 16:1246–52. [PubMed: 17548692]
 266. Almeida L, Vaz-da-Silva M, Falcao A, Soares E, Costa R, Loureiro AI, et al. Pharmacokinetic and safety profile of trans-resveratrol in a rising multiple-dose study in healthy volunteers. *Mol Nutr Food Res.* 2009; 53(Suppl 1):S7–15. [PubMed: 19194969]
 267. Cottart CH, Nivet-Antoine V, Laguillier-Morizot C, Beaudeau JL. Resveratrol bioavailability and toxicity in humans. *Mol Nutr Food Res.* 2010; 54:7–16. [PubMed: 20013887]
 268. Whitsett T, Carpenter M, Lamartiniere CA. Resveratrol, but not EGCG, in the diet suppresses DMBA-induced mammary cancer in rats. *J Carcinog.* 2006; 5:15. [PubMed: 16700914]
 269. Banerjee S, Bueso-Ramos C, Aggarwal BB. Suppression of 7,12-dimethylbenz(a)anthracene-induced mammary carcinogenesis in rats by resveratrol: role of nuclear factor-kappaB, cyclooxygenase 2, and matrix metalloprotease 9. *Cancer Res.* 2002; 62:4945–54. [PubMed: 12208745]
 270. Bhat KP, Lantvit D, Christov K, Mehta RG, Moon RC, Pezzuto JM. Estrogenic and antiestrogenic properties of resveratrol in mammary tumor models. *Cancer Res.* 2001; 61:7456–63. [PubMed: 11606380]
 271. Singh B, Shoulson R, Chatterjee A, Ronghe A, Bhat NK, Dim DC, et al. Resveratrol inhibits estrogen-induced breast carcinogenesis through induction of NRF2-mediated protective pathways. *Carcinogenesis.* 2014; 35:1872–80. [PubMed: 24894866]
 272. Harikumar KB, Sung B, Tharakan ST, Pandey MK, Joy B, Guha S, et al. Sesamin manifests chemopreventive effects through the suppression of NF-kappa B-regulated cell survival,

- proliferation, invasion, and angiogenic gene products. *Mol Cancer Res.* 2010; 8:751–61. [PubMed: 20460401]
273. Akl MR, Ayoub NM, Sylvester PW. Mechanisms mediating the synergistic anticancer effects of combined gamma-tocotrienol and sesamin treatment. *Planta Med.* 2012; 78:1731–9. [PubMed: 22987298]
 274. Pianjing P, Thiantanawat A, Rangkadilok N, Watcharasit P, Mahidol C, Satayavivad J. Estrogenic activities of sesame lignans and their metabolites on human breast cancer cells. *J Agric Food Chem.* 2011; 59:212–21. [PubMed: 21141889]
 275. Hirose N, Doi F, Ueki T, Akazawa K, Chijiwa K, Sugano M, et al. Suppressive effect of sesamin against 7,12-dimethylbenz[a]-anthracene induced rat mammary carcinogenesis. *Anticancer Res.* 1992; 12:1259–65. [PubMed: 1386971]
 276. Truan JS, Chen JM, Thompson LU. Comparative effects of sesame seed lignan and flaxseed lignan in reducing the growth of human breast tumors (MCF-7) at high levels of circulating estrogen in athymic mice. *Nutr Cancer.* 2012; 64:65–71. [PubMed: 22136581]
 277. Atwell LL, Beaver LM, Shannon J, Williams DE, Dashwood RH, Ho E. Epigenetic Regulation by Sulforaphane: Opportunities for Breast and Prostate Cancer Chemoprevention. *Curr Pharmacol Rep.* 2015; 1:102–11. [PubMed: 26042194]
 278. Licznarska B, Szafer H, Matuszak I, Murias M, Baer-Dubowska W. Modulating potential of L-sulforaphane in the expression of cytochrome p450 to identify potential targets for breast cancer chemoprevention and therapy using breast cell lines. *Phytother Res.* 2015; 29:93–9. [PubMed: 25234182]
 279. Lo R, Matthews J. The aryl hydrocarbon receptor and estrogen receptor alpha differentially modulate nuclear factor erythroid-2-related factor 2 transactivation in MCF-7 breast cancer cells. *Toxicol Appl Pharmacol.* 2013; 270:139–48. [PubMed: 23583297]
 280. Kim HN, Kim DH, Kim EH, Lee MH, Kundu JK, Na HK, et al. Sulforaphane inhibits phorbol ester-stimulated IKK-NF-kappaB signaling and COX-2 expression in human mammary epithelial cells by targeting NF-kappaB activating kinase and ERK. *Cancer Lett.* 2014; 351:41–9. [PubMed: 24747121]
 281. Pawlik A, Wiczak A, Kaczynska A, Antosiewicz J, Herman-Antosiewicz A. Sulforaphane inhibits growth of phenotypically different breast cancer cells. *Eur J Nutr.* 2013; 52:1949–58. [PubMed: 23389114]
 282. Clarke JD, Hsu A, Riedl K, Bella D, Schwartz SJ, Stevens JF, et al. Bioavailability and inter-conversion of sulforaphane and erucin in human subjects consuming broccoli sprouts or broccoli supplement in a cross-over study design. *Pharmacol Res.* 2011; 64:456–63. [PubMed: 21816223]
 283. Hanlon N, Coldham N, Gielbert A, Kuhnert N, Sauer MJ, King LJ, et al. Absolute bioavailability and dose-dependent pharmacokinetic behaviour of dietary doses of the chemopreventive isothiocyanate sulforaphane in rat. *Br J Nutr.* 2008; 99:559–64. [PubMed: 17868493]
 284. Kanematsu S, Yoshizawa K, Uehara N, Miki H, Sasaki T, Kuro M, et al. Sulforaphane inhibits the growth of KPL-1 human breast cancer cells in vitro and suppresses the growth and metastasis of orthotopically transplanted KPL-1 cells in female athymic mice. *Oncol Rep.* 2011; 26:603–8. [PubMed: 21617865]
 285. Wang J, Duan Y, Zhi D, Li G, Wang L, Zhang H, et al. Pro-apoptotic effects of the novel tangeretin derivate 5-acetyl-6,7,8,4'-tetramethylnortangeretin on MCF-7 breast cancer cells. *Cell Biochem Biophys.* 2014; 70:1255–63. [PubMed: 24938898]
 286. Ting Y, Jiang Y, Lan Y, Xia C, Lin Z, Rogers MA, et al. Viscoelastic Emulsion Improved the Bioaccessibility and Oral Bioavailability of Crystalline Compound: A Mechanistic Study Using in Vitro and in Vivo Models. *Mol Pharm.* 2015; 12:2229–36. [PubMed: 25984595]
 287. Vanhoecke BW, Delparte F, Van Braeckel E, Heyerick A, Depypere HT, Nuytinck M, et al. A safety study of oral tangeretin and xanthohumol administration to laboratory mice. *In Vivo.* 2005; 19:103–7. [PubMed: 15796161]
 288. Arivazhagan L, Sorimuthu Pillai S. Tangeretin, a citrus pentamethoxyflavone, exerts cytostatic effect via p53/p21 up-regulation and suppresses metastasis in 7,12-dimethylbenz(alpha)anthracene-induced rat mammary carcinoma. *J Nutr Biochem.* 2014; 25:1140–53. [PubMed: 25151216]

289. Periyasamy K, Baskaran K, Ilakkia A, Vanitha K, Selvaraj S, Sakthisekaran D. Antitumor efficacy of tangeretin by targeting the oxidative stress mediated on 7,12-dimethylbenz(a) anthracene-induced proliferative breast cancer in Sprague-Dawley rats. *Cancer Chemother Pharmacol.* 2015; 75:263–72. [PubMed: 25431347]
290. Lakshmi A, Subramanian S. Chemotherapeutic effect of tangeretin, a polymethoxylated flavone studied in 7, 12-dimethylbenz(a)anthracene induced mammary carcinoma in experimental rats. *Biochimie.* 2014; 99:96–109. [PubMed: 24299963]
291. Ng WK, Saiful Yazan L, Yap LH, Wan Nor Hafiza WA, How CW, Abdullah R. Thymoquinone-loaded nanostructured lipid carrier exhibited cytotoxicity towards breast cancer cell lines (MDA-MB-231 and MCF-7) and cervical cancer cell lines (HeLa and SiHa). *Biomed Res Int.* 2015; 2015:263131. [PubMed: 25632388]
292. Sutton KM, Greenshields AL, Hoskin DW. Thymoquinone, a bioactive component of black caraway seeds, causes G1 phase cell cycle arrest and apoptosis in triple-negative breast cancer cells with mutant p53. *Nutr Cancer.* 2014; 66:408–18. [PubMed: 24579801]
293. Motaghed M, Al-Hassan FM, Hamid SS. Thymoquinone regulates gene expression levels in the estrogen metabolic and interferon pathways in MCF7 breast cancer cells. *Int J Mol Med.* 2014; 33:8–16. [PubMed: 24270600]
294. Rajput S, Kumar BN, Dey KK, Pal I, Parekh A, Mandal M. Molecular targeting of Akt by thymoquinone promotes G(1) arrest through translation inhibition of cyclin D1 and induces apoptosis in breast cancer cells. *Life Sci.* 2013; 93:783–90. [PubMed: 24044882]
295. Odeh F, Ismail SI, Abu-Dahab R, Mahmoud IS, Al Bawab A. Thymoquinone in liposomes: a study of loading efficiency and biological activity towards breast cancer. *Drug Deliv.* 2012; 19:371–7. [PubMed: 23043626]
296. Linjawi SA, Khalil WK, Hassanane MM, Ahmed ES. Evaluation of the protective effect of *Nigella sativa* extract and its primary active component thymoquinone against DMBA-induced breast cancer in female rats. *Arch Med Sci.* 2015; 11:220–9. [PubMed: 25861310]
297. Smolarek AK, Suh N. Chemopreventive activity of vitamin E in breast cancer: a focus on gamma- and delta-tocopherol. *Nutrients.* 2011; 3:962–86. [PubMed: 22254089]
298. Borel P, Preveraud D, Desmarchelier C. Bioavailability of vitamin E in humans: an update. *Nutr Rev.* 2013; 71:319–31. [PubMed: 23731443]
299. Kormann AW, Bachmann H. Biodiscrimination of alpha-tocopherol stereoisomers in humans after oral administration. *Am J Clin Nutr.* 1998; 67:350–1. [PubMed: 9459387]
300. Iuliano L, Micheletta F, Maranghi M, Frati G, Diczfalusy U, Violi F. Bioavailability of vitamin E as function of food intake in healthy subjects: effects on plasma peroxide-scavenging activity and cholesterol-oxidation products. *Arterioscler Thromb Vasc Biol.* 2001; 21:E34–7. [PubMed: 11597949]
301. Das Gupta S, Sae-Tan S, Wahler J, So JY, Bak MJ, Cheng LC, et al. Dietary gamma-Tocopherol-Rich Mixture Inhibits Estrogen-Induced Mammary Tumorigenesis by Modulating Estrogen Metabolism, Antioxidant Response, and PPARgamma. *Cancer Prev Res (Phila).* 2015; 8:807–16. [PubMed: 26130252]
302. Smolarek AK, So JY, Burgess B, Kong AN, Reuhl K, Lin Y, et al. Dietary administration of delta- and gamma-tocopherol inhibits tumorigenesis in the animal model of estrogen receptor-positive, but not HER-2 breast cancer. *Cancer Prev Res (Phila).* 2012; 5:1310–20. [PubMed: 22964476]
303. Lee HJ, Ju J, Paul S, So JY, DeCastro A, Smolarek A, et al. Mixed tocopherols prevent mammary tumorigenesis by inhibiting estrogen action and activating PPAR-gamma. *Clin Cancer Res.* 2009; 15:4242–9. [PubMed: 19509159]
304. Suh N, Paul S, Lee HJ, Ji Y, Lee MJ, Yang CS, et al. Mixed tocopherols inhibit N-methyl-N-nitrosourea-induced mammary tumor growth in rats. *Nutr Cancer.* 2007; 59:76–81. [PubMed: 17927505]
305. Smolarek AK, So JY, Thomas PE, Lee HJ, Paul S, Dombrowski A, et al. Dietary tocopherols inhibit cell proliferation, regulate expression of ERalpha, PPARgamma, and Nrf2, and decrease serum inflammatory markers during the development of mammary hyperplasia. *Mol Carcinog.* 2013; 52:514–25. [PubMed: 22389237]

306. Das Gupta S, So JY, Wall B, Wahler J, Smolarek AK, Sae-Tan S, et al. Tocopherols inhibit oxidative and nitrosative stress in estrogen-induced early mammary hyperplasia in ACI rats. *Mol Carcinog.* 2015; 54:916–25. [PubMed: 24782330]
307. Yoshimaru T, Komatsu M, Tashiro E, Imoto M, Osada H, Miyoshi Y, et al. Xanthohumol suppresses oestrogen-signalling in breast cancer through the inhibition of BIG3-PHB2 interactions. *Sci Rep.* 2014; 4:7355. [PubMed: 25483453]
308. Monteiro R, Becker H, Azevedo I, Calhau C. Effect of hop (*Humulus lupulus* L.) flavonoids on aromatase (estrogen synthase) activity. *J Agric Food Chem.* 2006; 54:2938–43. [PubMed: 16608212]
309. Hemachandra LP, Madhubhani P, Chandrasena R, Esala P, Chen SN, Main M, et al. Hops (*Humulus lupulus*) inhibits oxidative estrogen metabolism and estrogen-induced malignant transformation in human mammary epithelial cells (MCF-10A). *Cancer Prev Res (Phila).* 2012; 5:73–81. [PubMed: 21997247]
310. Guerreiro S, Monteiro R, Martins MJ, Calhau C, Azevedo I, Soares R. Distinct modulation of alkaline phosphatase isoenzymes by 17 β -estradiol and xanthohumol in breast cancer MCF-7 cells. *Clin Biochem.* 2007; 40:268–73. [PubMed: 17126313]
311. Legette L, Ma L, Reed RL, Miranda CL, Christensen JM, Rodriguez-Proteau R, et al. Pharmacokinetics of xanthohumol and metabolites in rats after oral and intravenous administration. *Mol Nutr Food Res.* 2012; 56:466–74. [PubMed: 22147307]
312. Legette L, Karnpracha C, Reed RL, Choi J, Bobe G, Christensen JM, et al. Human pharmacokinetics of xanthohumol, an antihyperglycemic flavonoid from hops. *Mol Nutr Food Res.* 2014; 58:248–55. [PubMed: 24038952]
313. Dorn C, Bataille F, Gaebele E, Heilmann J, Hellerbrand C. Xanthohumol feeding does not impair organ function and homeostasis in mice. *Food Chem Toxicol.* 2010; 48:1890–7. [PubMed: 20427021]
314. van Breemen RB, Yuan Y, Banuvar S, Shulman LP, Qiu X, Alvarenga RF, et al. Pharmacokinetics of prenylated hop phenols in women following oral administration of a standardized extract of hops. *Mol Nutr Food Res.* 2014; 58:1962–9. [PubMed: 25045111]
315. Monteiro R, Calhau C, Silva AO, Pinheiro-Silva S, Guerreiro S, Gartner F, et al. Xanthohumol inhibits inflammatory factor production and angiogenesis in breast cancer xenografts. *J Cell Biochem.* 2008; 104:1699–707. [PubMed: 18348194]
316. Kim JW, Akiyama M, Park JH, Lin ML, Shimo A, Ueki T, et al. Activation of an estrogen/estrogen receptor signaling by BIG3 through its inhibitory effect on nuclear transport of PHB2/REA in breast cancer. *Cancer Sci.* 2009; 100:1468–78. [PubMed: 19496786]
317. Wang C, Kurzer MS. Effects of phytoestrogens on DNA synthesis in MCF-7 cells in the presence of estradiol or growth factors. *Nutr Cancer.* 1998; 31:90–100. [PubMed: 9770719]
318. Rajah TT, Du N, Drews N, Cohn R. Genistein in the presence of 17 β -estradiol inhibits proliferation of ER β breast cancer cells. *Pharmacology.* 2009; 84:68–73. [PubMed: 19556829]
319. Chen FP, Chien MH, Chern IY. Impact of lower concentrations of phytoestrogens on the effects of estradiol in breast cancer cells. *Climacteric.* 2015; 18:574–81. [PubMed: 25581323]
320. Pons DG, Nadal-Serrano M, Blanquer-Rossello MM, Sastre-Serra J, Oliver J, Roca P. Genistein modulates proliferation and mitochondrial functionality in breast cancer cells depending on ER α /ER β ratio. *J Cell Biochem.* 2014; 115:949–58. [PubMed: 24375531]
321. So FV, Guthrie N, Chambers AF, Carroll KK. Inhibition of proliferation of estrogen receptor-positive MCF-7 human breast cancer cells by flavonoids in the presence and absence of excess estrogen. *Cancer Lett.* 1997; 112:127–33. [PubMed: 9066718]
322. Lehmann L, Jiang L, Wagner J. Soy isoflavones decrease the catechol-O-methyltransferase-mediated inactivation of 4-hydroxyestradiol in cultured MCF-7 cells. *Carcinogenesis.* 2008; 29:363–70. [PubMed: 18192686]
323. Zhang S, Cao HJ, Davis FB, Tang HY, Davis PJ, Lin HY. Oestrogen inhibits resveratrol-induced post-translational modification of p53 and apoptosis in breast cancer cells. *Br J Cancer.* 2004; 91:178–85. [PubMed: 15188005]
324. Serrero G, Lu R. Effect of resveratrol on the expression of autocrine growth modulators in human breast cancer cells. *Antioxid Redox Signal.* 2001; 3:969–79. [PubMed: 11813992]

325. Lu R, Serrero G. Resveratrol, a natural product derived from grape, exhibits antiestrogenic activity and inhibits the growth of human breast cancer cells. *J Cell Physiol.* 1999; 179:297–304. [PubMed: 10228948]
326. Sakamoto T, Horiguchi H, Oguma E, Kayama F. Effects of diverse dietary phytoestrogens on cell growth, cell cycle and apoptosis in estrogen-receptor-positive breast cancer cells. *J Nutr Biochem.* 2010; 21:856–64. [PubMed: 19800779]
327. Verma SP, Salamone E, Goldin B. Curcumin and genistein, plant natural products, show synergistic inhibitory effects on the growth of human breast cancer MCF-7 cells induced by estrogenic pesticides. *Biochem Biophys Res Commun.* 1997; 233:692–6. [PubMed: 9168916]
328. Shao ZM, Shen ZZ, Liu CH, Sartippour MR, Go VL, Heber D, et al. Curcumin exerts multiple suppressive effects on human breast carcinoma cells. *Int J Cancer.* 2002; 98:234–40. [PubMed: 11857414]
329. Schmitt E, Stopper H. Estrogenic activity of naturally occurring anthocyanidins. *Nutr Cancer.* 2001; 41:145–9. [PubMed: 12094617]
330. Ashok BT, Chen YG, Liu X, Garikapaty VP, Sepowitz R, Tschorn J, et al. Multiple molecular targets of indole-3-carbinol, a chemopreventive anti-estrogen in breast cancer. *Eur J Cancer Prev.* 2002; 11(Suppl 2):S86–93. [PubMed: 12570340]
331. Ashok BT, Chen Y, Liu X, Bradlow HL, Mittelman A, Tiwari RK. Abrogation of estrogen-mediated cellular and biochemical effects by indole-3-carbinol. *Nutr Cancer.* 2001; 41:180–7. [PubMed: 12094623]
332. Meng Q, Yuan F, Goldberg ID, Rosen EM, Auborn K, Fan S. Indole-3-carbinol is a negative regulator of estrogen receptor- α signaling in human tumor cells. *J Nutr.* 2000; 130:2927–31. [PubMed: 11110848]
333. Fan S, Meng Q, Auborn K, Carter T, Rosen EM. BRCA1 and BRCA2 as molecular targets for phytochemicals indole-3-carbinol and genistein in breast and prostate cancer cells. *Br J Cancer.* 2006; 94:407–26. [PubMed: 16434996]
334. Riby JE, Chang GH, Firestone GL, Bjeldanes LF. Ligand-independent activation of estrogen receptor function by 3, 3'-diindolylmethane in human breast cancer cells. *Biochem Pharmacol.* 2000; 60:167–77. [PubMed: 10825461]
335. Sreeja S, Santhosh Kumar TR, Lakshmi BS. Pomegranate extract demonstrate a selective estrogen receptor modulator profile in human tumor cell lines and in vivo models of estrogen deprivation. *J Nutr Biochem.* 2012; 23:725–32. [PubMed: 21839626]
336. Hirsch K, Atzmon A, Danilenko M, Levy J, Sharoni Y. Lycopene and other carotenoids inhibit estrogenic activity of 17 β -estradiol and genistein in cancer cells. *Breast Cancer Res Treat.* 2007; 104:221–30. [PubMed: 17051425]
337. Bonofiglio D, Gabriele S, Aquila S, Catalano S, Gentile M, Middea E, et al. Estrogen receptor α binds to peroxisome proliferator-activated receptor response element and negatively interferes with peroxisome proliferator-activated receptor γ signaling in breast cancer cells. *Clin Cancer Res.* 2005; 11:6139–47. [PubMed: 16144913]
338. Wiggins AK, Mason JK, Thompson LU. Growth and gene expression differ over time in α -linolenic acid treated breast cancer cells. *Exp Cell Res.* 2015; 333:147–54. [PubMed: 25743093]
339. Bayet-Robert M, Kwiatkowski F, Leheurteur M, Gachon F, Planchat E, Abrial C, et al. Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. *Cancer Biol Ther.* 2010; 9:8–14. [PubMed: 19901561]
340. Pop EA, Fischer LM, Coan AD, Gitzinger M, Nakamura J, Zeisel SH. Effects of a high daily dose of soy isoflavones on DNA damage, apoptosis, and estrogenic outcomes in healthy postmenopausal women: a phase I clinical trial. *Menopause.* 2008; 15:684–92. [PubMed: 18446090]
341. Shike M, Doane AS, Russo L, Cabal R, Reis-Filho JS, Gerald W, et al. The effects of soy supplementation on gene expression in breast cancer: a randomized placebo-controlled study. *J Natl Cancer Inst.* 2014:106.
342. Reed GA, Peterson KS, Smith HJ, Gray JC, Sullivan DK, Mayo MS, et al. A phase I study of indole-3-carbinol in women: tolerability and effects. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:1953–60. [PubMed: 16103443]

343. Voskuil DW, Vrieling A, Korse CM, Beijnen JH, Bonfrer JM, van Doorn J, et al. Effects of lycopene on the insulin-like growth factor (IGF) system in premenopausal breast cancer survivors and women at high familial breast cancer risk. *Nutr Cancer*. 2008; 60:342–53. [PubMed: 18444168]
344. Nesaretnam K, Selvaduray KR, Abdul Razak G, Veerasenan SD, Gomez PA. Effectiveness of tocotrienol-rich fraction combined with tamoxifen in the management of women with early breast cancer: a pilot clinical trial. *Breast Cancer Res*. 2010; 12:R81. [PubMed: 20929592]
345. Yu B, Khan G, Foxworth A, Huang K, Hilakivi-Clarke L. Maternal dietary exposure to fiber during pregnancy and mammary tumorigenesis among rat offspring. *Int J Cancer*. 2006; 119:2279–86. [PubMed: 16921499]
346. Chen J, Tan KP, Ward WE, Thompson LU. Exposure to flaxseed or its purified lignan during suckling inhibits chemically induced rat mammary tumorigenesis. *Exp Biol Med (Maywood)*. 2003; 228:951–8. [PubMed: 12968067]
347. Bishayee A, Mandal A, Bhattacharyya P, Bhatia D. Pomegranate exerts chemoprevention of experimentally induced mammary tumorigenesis by suppression of cell proliferation and induction of apoptosis. *Nutr Cancer*. 2015:1–11.
348. Stroheker T, Picard K, Lhuguenot JC, Canivenc-Lavier MC, Chagnon MC. Steroid activities comparison of natural and food wrap compounds in human breast cancer cell lines. *Food Chem Toxicol*. 2004; 42:887–97. [PubMed: 15110097]
349. Fokialakis N, Alexi X, Aligiannis N, Siriani D, Meligova AK, Pratsinis H, et al. Ester and carbamate ester derivatives of Biochanin A: synthesis and in vitro evaluation of estrogenic and antiproliferative activities. *Bioorg Med Chem*. 2012; 20:2962–70. [PubMed: 22464681]
350. Tu SH, Ku CY, Ho CT, Chen CS, Huang CS, Lee CH, et al. Tea polyphenol (–)-epigallocatechin-3-gallate inhibits nicotine- and estrogen-induced alpha9-nicotinic acetylcholine receptor upregulation in human breast cancer cells. *Mol Nutr Food Res*. 2011; 55:455–66. [PubMed: 21370452]
351. Stromeier S, Peterleit F, Nahrstedt A. Phenolic esters from the rhizomes of *Cimicifuga racemosa* do not cause proliferation effects in MCF-7 cells. *Planta Med*. 2005; 71:495–500. [PubMed: 15971118]
352. Hu XJ, Xie MY, Kluxen FM, Diel P. Genistein modulates the anti-tumor activity of cisplatin in MCF-7 breast and HT-29 colon cancer cells. *Arch Toxicol*. 2014; 88:625–35. [PubMed: 24504162]
353. Schmidt S, Michna H, Diel P. Combinatory effects of phytoestrogens and 17beta-estradiol on proliferation and apoptosis in MCF-7 breast cancer cells. *J Steroid Biochem Mol Biol*. 2005; 94:445–9. [PubMed: 15876409]

Figure 1.

Diagrammatic representation of the pathways involved in the effects of estrogen on breast cancer development. The diagram is based on information from references [2, 43–46].

Table 1Effects of bioactive natural products against ER-positive breast cancer *in vivo*

Natural compounds	Experimental model of breast cancer	Effects	Ref
Allyl isothiocyanate	DMBA-treated SD rats	↓ Tumor incidence, tumor volume ↓ TBARS, LOOH, CYP450, TC, TG, PL, FFA, LDL, VLDL ↑ SOD, CAT, GPx, GSH, GST, GR, HDL activities	[80]
Apigenin	MPA-accelerated DMBA-induced SD rats	↓ Tumor incidence, VEGF, VEGF receptor-2 expression	[81, 88]
	BT-474 xenograft	↓ Tumor size, ↓ Her2/neu, Ki-67, VEGF, ↑ Apoptotic cells	[87]
Berries	E2 pellet-implanted ACI rats	↓ Tumor incidence, volume, multiplicity ↓ CYP1A1, 17βHSD7, COMT expression	[92]
	E2 pellet-implanted ACI rats	↓ Tumor volume, tumor multiplicity	[93]
	E2-treated ACI rats	↓ 8-OH-dG, P-1, P-2, PL-1 levels	[94]
	E2 pellet-implanted ACI rats	↓ Tumor volume, tumor multiplicity ↓ CYP1A1, ERα, Cyclin D1, PCNA expression ↓ miR18a, miR20a, miR25, miR34c expression	[95]
	E2 pellet-implanted ACI rats	↓ Tumor volume, tumor multiplicity ↓ Serum estradiol, prolactin level ↓ CYP1A1, ERα, PCNA expression	[96]
Biochanin A	NMU-treated CD/Crj rats	↓ Tumor incidence, multiplicity, ↓ PCNA labeling index	[102]
	DMBA-treated SD rats	↓ Tumor burden, ↑ Necrosis ↑ SOD, CAT, GPx, GST, DTD activities, ↓ MDA activity	[104]
	MCF-7 xenograft	↓ Tumor growth, tumor incidence	[103]
Caffeine	DES-treated ACI rats	↓ Total tumor number	[111]
	DMBA-treated SD rats	↓ Tumor incidence	[112, 113]
	PhIP-treated SD rats	↓ Tumor incidence, multiplicity, tumor size	[114]
Coumarin	DMBA-treated SENCAR mice	↓ Cytochrome P450 1A1/1B1 and DNA adduct formation ↓ Tumor size, multiplicity and tumor occurrence	[119]
	DMBA-treated Wistar rats	↓ Tumor size, multiplicity and tumor occurrence ↓ Hepatic drug metabolizing activity ↑ Serum prolactin level	[120]
Curcumin	E2 pellet-implanted ACI rats	↓ Tumor multiplicity, tumor volume ↑ Hepatic CYP1A and CYP1B1 level	[130]
	DMBA-treated SD rats	↓ Tumor incidence, multiplicity ↓ VEGF induction in hyperplastic lesions	[127]
	DMBA-treated SENCAR mice	↓ Tumor growth ↑ Pro-apoptotic protein, maspin ↓ Anti-apoptotic protein, survivin	[128]
	MCF-7 xenograft	↓ Tumor growth ↓ Cyclin D1, cyclin E, cyclin A, CDK2, CDK4, p38 ↑ p21, p27	[129]
Diallyl sulfide	DES-treated ACI rats	↓ nDNA adduct formation	[133]

Natural compounds	Experimental model of breast cancer	Effects	Ref
Diosgenin	MCF-7 xenograft	↑ CYP1A1, CYP1B1, GST, SOD expression	[134]
		↑ p53, Gadd45a, PCNA, DNA polymerase δ expression	[135]
	NMU-treated SD rats	↓ DES-induced LOOH and ROS production	[136]
		↓ Tumor growth	[132]
		↑ Antioxidant enzyme activities	[139]
		↓ Peroxidation reaction	
		↓ Tumor growth	[137]
		↓ Tumor volume, tumor multiplicity	[93]
		↓ Tumor incidence, volume, multiplicity	[92]
		↓ 17β-hydroxysteroid dehydrogenase, COMT expression	
		↓ Tumor incidence, burden, multiplicity	[143]
		↓ Plasma prolactin and PCNA levels	
Ellagic acid	MCF-7 xenograft	↓ Tumor growth	[137]
		↓ Tumor volume, tumor multiplicity	[93]
	E2-treated ACI rats	↓ Tumor incidence, volume, multiplicity	[92]
		↓ 17β-hydroxysteroid dehydrogenase, COMT expression	
		↓ Tumor incidence, burden, multiplicity	[143]
		↓ Plasma prolactin and PCNA levels	
		↓ Tumor volume, multiplicity	[96]
		↓ Serum E2 level, CYP1A1 expression	
		↓ ERα, Bcl-w, CCND1, CCNG1, RASD	[144]
		↑ FOXO1, FOXO3a	
		↑ Uterine peroxidase activity	[161]
		↓ Tumor growth, tumor size	[160]
Ferulic acid	DMBA-treated SD rats	↓ Tumor volume, tumor burden	[165]
		↓ p53, bcl-2 expression and TBARS activity	
	NMU-treated SD rats	↑ GST, GR, DTD, SOD, CAT and GPx activities	
		↓ Tumor multiplicity	[172]
		↓ Tumor invasiveness, tumor grade	
		↓ Tumor incidence, tumor multiplicity	[345]
		↓ Cell proliferation ↑ Apoptosis	
		↑ BRCA1, p53 expression	
		↓ 8-OH-dG levels	
		↓ Tumor incidence, size, number, weight	[346]
		↓ Tumor growth, tumor size	[168–170]
		↓ Cell proliferation ↑ Apoptosis	
Flaxseed	DMBA-treated SD rats	↓ ERα, PR, IGF-1 expression	
		↓ Tumor volume	[178]
	MCF-7 xenograft	↓ NFκB p65, pAkt, pPI3K, hypoxia inducible factor 1α, VEGF expression	
		↓ Bcl-2/Bax ratio	[187]
		↓ Tumor incidence	[185]
		↓ AIB1, erbB2, PCNA expression and PTK activity	
		↓ Plasma vascular endothelial growth factor	
		↓ Tumor weight, multiplicity, tumor incidence rates	[186]
		↑ Plasma endostatin levels	
		↓ Tumor weight, volume	[190]
Gallic acid	E2-treated SD rats	↓ Bcl-2/Bax ratio	[187]
		↓ Tumor incidence	[185]
	DMBA-treated SD rats	↓ AIB1, erbB2, PCNA expression and PTK activity	
		↓ Plasma vascular endothelial growth factor	
		↓ Tumor weight, multiplicity, tumor incidence rates	[186]
		↑ Plasma endostatin levels	
		↓ Tumor weight, volume	[190]
Genistein	E2-treated SD rats	↓ Bcl-2/Bax ratio	[187]
		↓ Tumor incidence	[185]
	DMBA-treated SD rats	↓ AIB1, erbB2, PCNA expression and PTK activity	
		↓ Plasma vascular endothelial growth factor	
		↓ Tumor weight, multiplicity, tumor incidence rates	[186]
		↑ Plasma endostatin levels	
		↓ Tumor weight, volume	[190]

Natural compounds	Experimental model of breast cancer	Effects	Ref
		↓ Smo, Gli1 expression, ALDH staining, Hedgehog-Gli pathway expression	
Hesperetin	MCF-7 xenograft	↑ Tumor incidence in long-term genistein exposure	[189]
Indole-3-carbinol	DMBA-treated SD rats	↓ Tumor growth, volume	[205]
	E2-treated SD rats	↑ CYP1A1, 1A2, 3A, 2B activities, ↑ E1 and E2 metabolism	[206]
	MMTV-induced mice	↓ Tumor growth	[188]
	MCF-7 xenograft	↓ Tumor growth	[204]
Luteolin	DMBA-treated Wistar rats	↓ Tumor incidence, volume	[213]
		↑ SOD, CAT, GPx activities	
		↓ Lipid peroxidation levels	
		↓ Cell numbers	[214]
	T47D xenograft	↓ Tumor volume, tumor incidence rate	[55]
		↓ VEGF expression, blood-vessel density	
Lycopene	DMBA-treated SD rats	↓ MDA and NO levels	[220]
		↑ SOD, CAT, GPx activities	
	DMBA-treated ACI rats	↓ Tumor incidence	[221]
		↑ SOD, CAT, GPx activities	
		↓ Bcl-2 expression and serum MDA, NO, 8-OH-dG levels	
	DMBA-treated Wistar rats	↓ Tumor incidence, tumor weight, tumor volume	[222]
		↑ Bax, caspase-3 and caspase-9 expression	
Morin	DMBA-treated SD rats	↓ Tumor weight, incidence, size, volume	[228]
		↓ TBARS and hydroperoxides, AFP, CEA, CA-15-3, PCNA	
		↑ SOD, CAT, GPx, GST, GR, GSH, G6PD, Vit C, Vit E	
Myricetin	DMBA-treated Wistar rats	↓ Plasma TBARS levels, ↑ SOD levels	[233]
Phenylethyl isothiocyanate	DMBA-treated SD rats	↓ Tumor multiplicity, tumor volume	[234]
	NMU-treated SD rats	↓ Tumor incidence, multiplicity	[235]
		↓ Angiogenesis and invasive tumors	
	PyMT transgenic mice	↓ Tumor growth	[237]
		↓ ERα, FOXA1 expression	
Pomegranate	DMBA-treated SD rats	↓ ERα, ERβ expression, ERα: ERβ ratio	[244]
		↓ β-catenin expression, nuclear translocation	
		↓ Cyclin D1 expression	
	DMBA-treated SD rats	↓ Tumor incidence, total tumor burden	[347]
		↓ Cell proliferation ↑ Apoptosis	
		↑ Bax, Bad, caspase-3, caspase-7, caspase-9, cytochrome C expression	
		↓ Bcl-2 expression	
	BT474 xenograft	↓ Tumor volume, tumor weight	[249]
		↑ Apoptotic lesions	
		↓ Sp1, Sp3, Sp4, VEGF, p65, miR-27a, SHIP-1, pAKT, pPI3K expression	
		↑ ZBTB10 expression	
Quercetin	DMBA-treated Wistar albino rats	↓ Tumor volume	[257]

Natural compounds	Experimental model of breast cancer	Effects	Ref
Resveratrol	E2-treated ACI rats	↓ CEA, ACP, cathepsin D levels	[258]
		No chemopreventive effects	
		↓ COMT activity, tumor latency	
	C3(1)SV40Tag mice	↓ Tumor number, volume	[256]
	MCF-7 xenograft	↓ Tumor size	[103, 251]
	DMBA-treated SD rats	↓ Tumor growth ↑ miR-146a expression	[268]
	DMBA-treated SD rats	↓ Tumor incidence, tumor multiplicity	[269]
		↓ NFκB, COX-2, MMP-9 expression	
	NMU-treated SD rats	↓ Tumor incidence, tumor multiplicity	[270]
	E2-treated ACI rats	↓ Tumor multiplicity	[271]
Sesamin	DMBA-treated SD rats	↓ Cell proliferation in mammary terminal ductal structures	[275]
		↑ Nrf2-mediated protective pathways	
		↓ Nrf2 promoter methylation	
		↓ Cumulative number of palpable mammary cancer	
		↓ Lipid peroxide, fatty acid, tumor phosphatidylcholine, prostaglandin E2	
Sulforaphane	MCF-7 xenograft	↑ PBMC activity	[276]
		↓ Tumor size, tumor proliferation ↑ Apoptosis	
	BCSC in NOD/SCID mice	↓ Tumor growth	
	KPL-1 xenograft	↓ Tumor volume, tumor weight, tumor growth	
Tangeretin	DMBA-treated SD rats	↑ Apoptosis	[284]
		↓ Tumor growth, total tumor weight, tumor volume	
		↓ NO, LOOH, CEA levels	
		↑ SOD, CAT, GPx, GST, GSH, Vit-C, Vit-E levels	
		↓ Tumor weight	
Thymoquinone	DMBA-treated Wistar rats	↓ Prolactin, estradiol, TSA, LSA, protein carbonyl, NO levels, PCNA, COX-2, Ki-67, cyclin D1, cyclinE, CDK4, CDK2, MMP2, MMP9, VEGF expression	[288, 290]
		↑ Progesterone level and p53, p21, TIMP2 expression	
		↓ Tumor weight	
		↓ AST, ALT, ALP, ACP, 5'-ND, GGT, LDH, CytP450, Cytb5, EROD, MROD, PROD, TBARS, CD, AFP, CEA, CA15-3 activities and ER, PR, Her2/neu expression	
		↑ GST, QR, SOD, CAT, GPx activities	
γ-TmT	DMBA-treated albino rats	↓ BRCA, BRCA2, Id-1, p53 expression and MDA, LDH, ALP, AST levels	[296]
		↓ Tumor burden, multiplicity	
γ-TmT	NMU-treated SD rats	↓ Bcl-2, XIAP, ERα, PCNA, PKC, p-Akt, Cyclin D1, CDK4, CDK6, Keap1 expression	[302]
		↑ Bax, cleaved-caspase 3, cleaved-caspase 9, cleaved-PARP, PPARγ, PTEN, p53, p21, p27, Nrf2, GCLm, GSTm1, NQO1, TXN, GPx, HO-1 expression	
		↓ Tumor volume, multiplicity	
		↓ Serum estrogen, 8-OH-dG levels and PCNA expression	
		↑ CYP1A1, CYP1B1, Nrf2, NQO1, GCLm, HO-1, PPARγ, PTEN and p27 expression	
	E2 pellet-implanted ACI rats		[301]

Natural compounds	Experimental model of breast cancer	Effects	Ref
γ -Tocopherol δ -Tocopherol	NMU-treated SD rats	↓ Serum E2 level, PCNA, ER α , ER β , COX-2 expression and nitrotyrosine, 8-OH-dG levels	[305]
		↑ Cleaved-caspase3, PPAR γ , Nrf2, NQO1, UGT, HO-1, GST, GSTm1, GCIm levels	
		↓ Nitrotyrosine, 8-OH-dG, 8-isoprostane levels	[306]
		↑ Nrf2, SOD1, GPx, CAT expression	
		↓ Tumor incidence, multiplicity	[302–304]
		↑ PTEN, p53, p21, p27, NQO1, PPAR γ , Nrf2 and phase II detoxifying/antioxidant enzyme expression	[302]
		↓ PCNA, PKC, c-Myc, p-Akt, cyclin D1, ER α expression and nitrotyrosine, 8-OH-dG levels	
		↑ p21, p27, PPAR γ , cleaved PARP, cleaved caspase-3 expression, ↓ ER α , p-Akt expression	[303]
		↓ PCNA expression	[304]
		↓ Tumor growth, ↓ Ki67, PCNA expression	[307]
Xanthohumol	KPL-3C xenograft	↓ Endogenous BIG3-PHB2 complex	
		↓ Tumor weight	[315]
	MCF-7 xenograft	↑ Cell apoptosis in tumor tissues	
		↓ Endothelial marker VIII expression and NF κ B p65, I κ B, IL-1 β activities	

Abbreviations: AIB1: amplified in breast cancer 1; BCSC: breast cancer stem cells; CA-15-3: cancer antigen 15-3; EROD: ethoxyresorufin O-decarboxylase; GCIm: glutamate cysteine ligase modifier subunit; GSTm1: glutathione s-transferase mu 1; G6PD: glucose-6-phosphate dehydrogenase; HDL: high-density lipoprotein; HIF: hypoxia-inducible factor; HO-1: heme oxygenase 1; Id-1: inhibitor of DNA binding 1; IL-1 β : interleukin 1 β ; MROD: methoxyresorufin O-decarboxylase; PAH: polycyclic aromatic hydrocarbons; PKC: protein kinase C; PROD: pentoxyresorufin O-decarboxylase; RASD1: RAS dexamethasone-induced 1; Smo: smoothened; TIMP: tissue inhibitor of metalloproteinase; UGT: UDP-glucuronosyltransferase; XIAP: x-linked inhibitor of apoptosis

Table 2

Bioactive natural products targeting estrogen-mediated mechanisms

Natural compounds	Dose of estrogen used	Effects	Ref
Apigenin	100 pM	↓ Cell proliferation	[348]
Biochanin A	100 pM	↓ Cell proliferation	[349]
Curcumin	1 nM	↓ Cell proliferation	[328]
		↓ pS2/TFF1, ER, TGF- β expression	
		↓ ERE activities	
EGCG	10 nM	↓ Cell proliferation	[350]
Ferulic acid	10 pM	↓ Cell proliferation	[351]
Flaxseed	1 nM	↓ Cell proliferation	[338]
		↓ ABCG2, GATA3, KRT8, MAPK1, SNAI2, SRC, BRCA1, FOXA1 expression	
Genistein	100 pM - 50 nM	↓ Cell proliferation, DNA synthesis	[317–322]
		↑ Apoptosis	[97, 187, 319, 320, 326, 352, 353]
		↓ TERT, Myc, ras, Bcl-2, human complement 3 expression	[97]
		↓ FADD, cytochrome C, truncated Bid, caspase-9, caspase-3 expression	[319]
		↑ CCNB1, p21, p53 expression	[187]
		↓ ERE-dependent transcriptional activity	[326]
		↓ ER α expression	[97]
Indole-3-carbinol	1 nM	↓ Cell proliferation	[331]
		↓ ER and E2 metabolites	[331–333]
		↓ pS2/TFF1, cathepsin-D expression	[332]
Lycopene	100 pM	↓ ERE transactivation	[336]
Pomegranate	10 nM	↓ Cell proliferation	[335]
		↓ ERE-dependent transcriptional activity	
		↓ ER α , pS2/TFF1, PR expression	
Quercetin	10 nM	↑ PCNA, PI3K, p-Akt, ER α expression	[319]
		↓ FADD, cytochrome C, truncated Bid, caspase-9, caspase-3 and ER β expression	
Resveratrol	1nM, 10 nM	↓ Cell proliferation	[323–326]
		↑ Apoptosis	[319, 323, 326]
		↓ p53, p21 expression	[323]

Natural compounds	Dose of estrogen used	Effects	Ref
		↓ FADD, cytochrome C, truncated Bid, caspase-9, caspase-3 expression	[326]
		↓ NFκB activation	
		↓ PR, pS2/TFF1 expression	[270, 324, 325]
		↓ ERβ expression	[319]
		↓ ERE-dependent transcriptional activity	[324, 326]
Sesamin	1 nM	↓ ERE activity	[274]
γ-Tocopherol	10 pM	↓ Cell proliferation, ERα expression	[303]
δ-Tocopherol		↑ PPARγ transcription activity	
Xanthohumol	10 nM	↓ BIG3-PHB2 complex	[307]
		↓ ERα, ERE transcriptional activity	
		↓ Akt, p42/44 MAPK, ERα, pS2/TFF1, CCND1 expression	

Abbreviations: ABCG: ATP-binding cassette, subfamily G member; FADD: FAS-associated death domain; KRT 8: keratin 8; SNAI2: snail homolog 2; SRC: v-src sarcoma viral oncogene homolog; TERT: telomerase reverse transcriptase

Table 3

Clinical trials of bioactive natural products in breast cancer

Compounds	Subject number	Intervention	Trial phase	Current status	Numbers of clinical trial/Ref
Curcumin	30	2 g of curcumin three times per day orally for 4–7 weeks	Phase 2	Completed	NCT01042938
	695	2g of curcumin three times daily orally throughout course of radiation treatment plus one week	Phase 2/3	Completed	NCT01246973
	14	500 mg of curcumin orally daily for seven consecutive day	Phase 1	Completed	[339]
EGCG	40	Green tea extract daily for 6 months in the absence of disease progression or unacceptable toxicity	Phase 1	Completed	NCT00516243
	1084	800 mg of Epigallocatechin-3 gallate two times per day for 12 months	Phase 2	Completed	NCT00917735
	20	3 tea capsules daily orally for 3 weeks	Phase 1	Ongoing	NCT00949923
Flaxseed	32	25 g of flaxseed-containing muffin daily for 39 days	Unknown	Completed	[166]
Genistein	30	Genistein two times per day for 84 days	Phase 1	Completed	NCT00099008
	19	100 mg of genistein (Novasoy) two times per day for 7 and 21 days	Phase 2	Completed	[340] NCT00244933
	18	Indole-3-carbinol two times per day for 12 and 16 weeks	Phase 1	Completed	[341] NCT00033345
Lycopene	17	400 mg and 800 mg of indole-3-carbinol daily orally for 4 weeks	Phase 1	Completed	[342]
	60	30 mg of lycopene daily for 2 months	Unknown	Completed	[343]
Sulforaphane	54	Sulforaphane supplement three times per week for 2–8 weeks	Phase 2	Completed	NCT00843167
	34	Broccoli sprout extract daily for 14 days	Phase 2	Completed	NCT00982319
	32	Sulforaphane topical application three times a week for 5 weeks	Phase 2	Ongoing	NCT00894712
Tocotrienol	240	200 mg tocotrienol Rich Fraction daily for five years	Unknown	Completed	NCT01157026