Review Article
Phytotherapy and Nutritional Supplements on Breast Cancer

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Breast cancer is the most frequent type of nonskin malignancy among women worldwide. In general, conventional cancer treatment options (i.e., surgery, radiotherapy, chemotherapy, biological therapy, and hormone therapy) are not completely effective. Recurrence and other pathologic situations are still an issue in breast cancer patients due to side effects, toxicity of drugs in normal cells, and aggressive behaviour of the tumours. From this point of view, breast cancer therapy and adjuvant methods represent a promising and challenging field for researchers. In the last few years, the use of some types of complementary medicines by women with a history of breast cancer has significantly increased such as phytherapeutic products and nutritional supplements. Despite this, the use of such approaches in oncologic processes may be problematic and patient’s health risks can arise such as interference with the efficacy of standard cancer treatment. The present review gives an overview of the most usual phytherapeutic products and nutritional supplements with application in breast cancer patients as adjuvant approach. Regardless of the contradictory results of scientific evidence, we demonstrated the need to perform additional investigation, mainly well-designed clinical trials in order to establish correlations and allow for further validated outcomes concerning the efficacy, safety, and clinical evidence-based recommendation of these products.

1. Introduction

Breast cancer is a significant public health problem in both developed and developing countries [1, 2]. Despite superior diagnostic skills and valuable advances in its treatment during the last decades, breast cancer persists in representing one of the most commonly diagnosed occurring cancers and leading cause of cancer deaths among women worldwide [3]. According to World Health Organization (WHO) it is estimated that worldwide over 508,000 women died in 2011 due to breast cancer [4]. The epidemiologic parameters (e.g., incidence, mortality, and survival rates) related to breast cancer diverge significantly between countries and regions [1, 5] which could be attributed to various factors such as health habits, lifestyle changes (e.g., dietary changes), exposure to radiation, family history, related alterations in menstrual cycle patterns, early detection, and access to the current knowledge concerning breast cancer [3, 5].

The stage of diagnosis influences both the prognostic and the treatment strategies for breast cancer. Currently, standard treatment protocol combines a multidisciplinary approach involving different therapies such as surgery, radiation, and medical oncology (i.e., chemotherapy, immunotherapy, and hormonal therapy) to obtain a local (i.e., remove or destroy cancer in the breast) or systemic (i.e., destroy or control cancer cells throughout the body) effect [3].

Despite the high incidence, breast cancer survivors, which used Complementary and Alternative Medicines (CAM), associated with standard cancer therapy, namely, chemotherapy and radiotherapy, are increasing [6, 7]. The use of CAM is growing among the public, up to 65% of the European population uses this modality of medicine, and it is commonly practiced among cancer patients [8]. Some studies associated the increased CAM use with sociodemographic issues such as female gender, higher levels of education, higher income, and health insurance [9–12] that explains its advance in many developed countries.

CAM is defined as a group of different modalities, including diverse medical and healthcare systems, products,
and practices, which are not usually considered part of standard medical treatments [13]. This type of medicine could be used together with and thereby complement conventional medicine which is referred to as complementary medicine (e.g., using acupuncture to assist the side effects of conventional cancer treatment) or in place of conventional medicine (e.g., using a special diet to treat cancer instead of a conventional cancer treatment) [13, 14]. Despite alternative medicine being based on functional hypotheses often conflicting with conventional medicine, the complementary one uses the scientific approach of evidence-based medicine to support the conventional medicine. Currently an additional and promising term is emerging in this area, the “integrative medicine” which is based on the integration of conventional and complementary approaches together in a coordinated way that have been confirmed to be safe and effective [13, 15]. In CAM perspective, the patients are evaluated as a whole with all their complexities and connections instead of focusing on isolated pathological processes [15].

There are different classifications of CAM therapies which vary mainly with time and institutional approaches. In accordance with the National Centre for Complementary and Integrative Health, a reference USA Federal Agency, CAM therapies can be divided into three broad categories [13]:

(i) Natural products which include dietary supplements (e.g., vitamins, minerals, and probiotics) and phytotherapeutic products.

(ii) Mind and body practices and manipulations which include different procedures or techniques such as yoga, chiropractic and osteopathic manipulation, meditation, massage therapy, acupuncture, relaxation techniques, tai chi, healing touch, qi gong, hypnotherapy, and movement therapies.

(iii) Other complementary health approaches which include some approaches that may not neatly fit into either of the previous group, for example, traditional healers, Ayurvedic Medicine, Traditional Chinese Medicine, Homeopathy, and Naturopathy.

In the oncology field, the patient survival rates have increased in recent years, so the practice of integrative care, termed integrative oncology [16] (Figure 1), makes the acceptance of the holistic approach to cancer care by medical professionals feasible, once CAM modalities can meet various needs of the patients that go beyond the simple alleviation of severe side effects of conventional cancer treatments. This fact explains the use of CAM approaches by a great proportion of cancer patients [17, 18] and, among these patients, women with breast cancer remain the most likely users of some form of CAM modalities [12, 19–21] with an estimated rate as high as 75% [22]. Dobos et al. reported the practice of the concept of integrative oncology for breast cancer patients by German cancer centres such as the Department of Internal and Integrative Medicine, Kliniken Essen-Mitte, academic teaching hospital of the University of Duisburg-Essen, and the Breast Centre at Kliniken Essen-Mitte [16].

The reasons reported by breast cancer patients for the widespread use of CAM diverge and include [12, 19] activating the immune system, curing cancer, alleviating symptoms
associated with the side effects of conventional cancer treatments, enhancing quality of life, increasing the perception of disease control, and preventing relapse and prolonging survival. Consequentially, the patients attempt to be active and gain autonomy [23].

However, the use of certain CAM methods in oncologic processes (i.e., a life-threatening disease) may become problematic and several partly substantial risks for the health of patient can arise, particularly when, as commonly happening, patients use them arbitrarily and do not report this information to their oncologists [19, 24–26]. This is true mainly for CAM recommendations or treatments that interfere/interact with chemotherapy or endocrine/hormonal treatment approaches, such as phytotherapeutic products and dietary supplements, or have intrinsic toxicity or other negative effects. Despite such interactions possibly being beneficial, in some situations, the concomitant use of CAM and conventional medicines approaches could compromise or be in conflict and enhance the drug toxicity or reduce the effectiveness [27]. A well-known example is phytoestrogens that might neutralize endocrine therapies. So, there are some CAM modalities that require a temporary adjustment of their use during periods of conventional treatment [28]. Additionally, among the CAM modalities, the consumer of these natural products is the most popular in breast cancer patients [19, 24] probably due to the assumption that “natural” products are less toxic than conventional prescribed medicines [29]. Therefore, attending the proactive role that nowadays the patients have in relation to their health, it is crucial to have reports in integrative medicine to guide and support clinicians and patients. The aim is to improve clinical/healthcare outcomes in combining CAM and conventional care and prevent misuse of CAM methods and preparations. The purpose is also to prevent harmful interactions and to enrich personal control over disease.

Based on the intensive investigation of nutritional supplements and phytochemicals as breast cancer therapeutics, the aim of this study is to compile and to explore the available scientific information regarding the most common phytotherapeutic and nutritional supplement products used in breast cancer patients. Therefore, recent scientific evidence studies (e.g., systemic reviews and clinical investigation studies) are consulted and the clinical relevant and validated outcomes concerning efficacy, safety, and limitations of the clinical data are reported.

2. Methodology

To elaborate this review, PubMed (indexed for MEDLINE) and ISI Web of Science were searched using the following key words: breast cancer; phytotherapy; supplements; CAM; integrative medicine; Echinacea; Tabebuia impetiginosa; Salvia; Uncaria; Allium sativum L., Linum usitatissimum; Curcuma; Camellia sinensis; Ginseng; Cimicifuga racemosa; Viscum album; vitamins; antioxidants; vitamin A; β-carotene; vitamin C; vitamin E; vitamin D; selenium, calcium; B complex; omega 3. For plants, both Latin designations and common trivial names were considered for search strategy. Additionally, text books were explored and reference lists from pertinent reviews were scrutinized. The literature search was confined to the period between 2000 to March of 2017. Systematic reviews, meta-analyses, and in vivo and relevant cell line studies were considered for this review.

3. Phytotherapy

Among CAM used in cancer patients, herbal preparations or phytotherapy is the most commonly and the oldest used group of treatment [30]. Most of time, patients use plant products for self-medication. It uses products derived from all or parts of plants and is a common practice in all civilizations around the world including Asia, Africa, Europe, and America. Herbal preparations may have superior risk of adverse effects and therapy interactions than other complementary therapies due to the potential active ingredients of various plants. Despite this, phytotherapeutic products are not tested with the scientific rigor required of conventional drugs nor are controlled by any purity and potency certificate [3].

The recognition of medicinal plants as effective and inexpensive sources of synthetic novel chemotherapeutic compounds is increasing in the last decades and many researchers focus their research on this promising area [31]. In the cancer domain, the biological effects of herbal medicinal products could be diverse such as [7] defence from malignancy by increasing detoxification or cleaning, modification of the action of some hormones and enzymes, reduction in side effects and complications of chemotherapy and radiotherapy, and improvement of the function of the body’s immune cells (i.e., stimulates the production of cytokines including interleukin, interferon, tumour necrosis factor, and colony stimulating factor).

The reasons for using phytotherapeutic products include [3] to lessen symptoms of disease and to prevent disease (e.g., garlic contains high levels of organosulfur compounds that have been experimentally proven to prevent cancer in animals [32]).

In a prospective study using an exploratory analysis, the authors found that some evidence that phytotherapeutic products use among long-term breast cancer survivors (for at least 10 years) was associated with inferior survival rates and a poorer physical component score [30]. The most frequent phytotherapeutic products used among long-term (at least 10 years) breast cancer survivors who participated in this study were Echinacea, herbal teas, and ginkgo biloba. Authors reported limitations in the study such as few deaths for mortality analysis and lack of information on when phytotherapeutics use was initiated, duration, or application. In another study, McLay et al. [33] reported that 38% of treated breast cancer patients (in a total of 360 questionnaires) use herbal preparations (Echinacea, pomegranate, peppermint, chamomile, grapefruit, garlic, and ginseng) that have the potential to interact with adjuvant endocrine therapies (e.g., tamoxifen, anastrozole, letrozole, and exemestane). Garlic, gingko, and Echinacea were the most frequently phytotherapeutic products among African Americans (Black Women’s Health Study) [34].
3.1. Echinacea. Echinacea, a member of the family Asteraceae, has a long history of medicinal use. It is endemic to eastern and central North America and is also cultivated in Europe. Three different species of Echinacea can be used as phytotherapeutic products: Echinacea purpurea, Echinacea angustifolia, and Echinacea pallida [3].

Some authors justified the potential use of Echinacea as an anticancer agent based on its rich content in flavonoids that act as an immune-stimulant by promoting the activity of lymphocytes thus increasing phagocytosis and the activity of natural killer cells and inducing interferon production [35].

Although studies indicated the use of Echinacea among breast cancer patients [30, 33, 34], there are not many studies, even in vitro, that demonstrated its effects in this type of cancer. Driggins et al. verified that despite Echinacea pallida decreasing the growth rate of BT-549 mammalian breast cancer cells, its effect was significantly lower as compared to Echinacea purpurea [36]. Huntimer and collaborators used Echinacea angustifolia roots and evaluated their activity when combined with doxorubicin (i.e., cytotoxic agent) in MCF-7 human breast cancer cell line [37]. This study showed that different constituents of Echinacea could have a different effect on MCF-7 cell proliferation and could interfere with cells treated with anticancer drug, affecting cell proliferation despite the presence of doxorubicin (i.e., counteracting the cell-killing activity of doxorubicin). Based on this effect, the authors suggest that herbal medicines need to be examined more closely for interactions with other chemotherapeutic agents. Echinacea induce cytochrome P450 3A4 isoenzyme system both in vitro and in humans [38, 39]. This enzyme system participates in the metabolism of many chemotherapeutic agents. Goey et al. demonstrated that the recommended dose and schedule of a commercially available Echinacea purpurea extract (A. Vogel Echinaforce®, Biohorma BV, Elburg, Netherlands) did not interact with docetaxel pharmacokinetice and this combination can be used safely [40]. Among other therapeutic indications, docetaxel is approved for the treatment of locally advanced or metastatic breast cancer. The benefits of the use of Echinacea to reduce unwanted effects of radiotherapy (e.g., leukopenia) are unclear [41]. Therefore, more clinical evidence is important to support or refute the recommendations for Echinacea in relation to cancer management.

Even though Echinacea seems to be relatively safe, it may cause liver damage or suppress the immune system if used for a prolonged period without a break (i.e., more than 8 weeks) [42]. Therefore, a patient with liver disturbance or taking drugs that potentially cause liver toxicity (e.g., some chemotherapy agents) should avoid Echinacea use.

3.2. Lapacho. Lapacho tree or pau d’arco is the common name of Tabebuia impetiginosa Martius ex DC species, the family of Bignoniaceae. It is a tree indigenous to the Amazonian rainforest and other regions of South America and Latin America. Pau d’arco has been used in traditional medicine for many centuries due to its different physiological effects such as fungicide, antibacterial, antiviral, anti-inflammation, and anticancer [43]. Above all, special attention has been given to the antitumour activity of 6-β-lapachone (i.e., a constituent of lapacho) against many in vitro cancer cell lines, including breast cancer [44, 45] due to its action on reinforcing the immune system.

The clinical evidence of the health benefits of lapacho is restricted to studies related to its potential anticancer effects in phase I and II clinical trials [46]. However, this effect was not borne out by clinical trials [43]. The Food and Drug Administration (FDA) registered it as a dietary supplement with the following recommendation “to alleviate conditions and symptoms of cancer.”

Despite the underlying mechanism being under investigation [47], the cytotoxic effects to some cancer cells, including breast cancer cell lines, are confirmed [45, 48, 49]. 6-β-Lapachone also sensitizes the response of different cancer cell lines to ionizing radiation [50, 51], interacting synergistically with this conventional cancer therapy. Bey and collaborators showed that the combination of 6-β-lapachone and radiation exert synergistic effects against human mammary epithelial cells (MCF1585), in which 6-β-lapachone sensitizes cells to radiation by inhibiting DNA repair, and radiation sensitizes cells to 6-β-lapachone by increasing oxidoreductase enzyme, which reduces 6-β-lapachone to an unstable semiquinone level, in tumour cells [51].

Concerning the toxicity issues of lapacho, limited data are available and more clinical trials are required to evaluate the toxicity of 6-β-lapachone toward normal human tissue and to establish the best dosage range [52]. Tabebuia impetiginosa tea emerges as generally safe and has a FDA regulatory classification of “generally recognized as safe” (GRAS) status. Recently, Lemos et al. [53] demonstrated genotoxiceffects in rats at a comparatively high dose range. The most important interaction of this botanical product refers to the interference in the biological cycle of vitamin K [46]. It is also important to attend the variable quality and composition of the herbal products commercially available.

3.3. Salvia. Salvia is the largest and the most important genus of the family Labiatae [89]. This genus includes wild growing and cultivated medicinally valuable species (e.g., Salvia bracteata and Salvia rubifolia) as well as ornamentals. Salvia species present a high diversity in their secondary metabolites (e.g., flavonoids, diterpenoids, volatile oils, and tannins) which justify the multiple pharmacological effects reported in the literature [90].

In breast cancer, different species were investigated for their in vitro antiproliferative activity. Abu-Dahab et al. [90] demonstrated that the ethanol extract of three species, namely, S. syrica, S. fruticosa, and S. horminum, presented selective antiproliferative activity against oestrogen receptor (ER) positive breast cancer cell lines with minimum toxicity against normal human periodontal fibroblasts. Based on their safe and selective effects, the authors suggested the use of these Salvia species as promising plant-originated anticancer agents. Other species also showed promising results. S. triloba and S. dominica ethanol extracts showed antiproliferative effects on adenocarcinoma of breast cell line (MCF7, oestrogen receptor-positive) and human ductal breast epithelial tumour cell line (T47D) via proapoptotic cytotoxic mechanisms [91]. S. miltiorrhiza (i.e., Danshen
which is widely used in traditional Chinese medicine) exhibited a strong inhibitory effect on the proliferation of MCF-7 breast cell line and induced cell cycle delay in the G1 phase via modulation of Akt phosphorylation and p27 level [92]. Authors also used MCF-7 HER2 cell line which over expresses HER2. HER2 (i.e., human epidermal growth factor receptor type 2) is a receptor tyrosine kinase and is involved in signal transduction pathways leading to tumour cell proliferation. HER2 is overexpressed in a high percentage of breast cancer (25–30%) and its overexpression is associated with aggressive tumours, a high rate of metastasis and relapse, poor prognosis, and limitation in treatment (in most cases it became resistant to endocrine therapy such as tamoxifen) [93, 94]. The MCF-7 HER2 cells were more resistant to the Danshen actions.

Danshen extracts contain diterpene quinone and phenolic acid derivatives such as tanshinone (I, IIA, and IIB), cryptotanshinone, isocryptotanshinone, miltirone, tanshinol, nolic acid derivatives such as tanshinone (I, IIA, and IIB), and salvio[95]. These compounds are antioxidant agents and protect against lipid peroxidation. Some of these compounds have been isolated from Danshen, sometimes synthesized, and their in vitro cytotoxic activity tested against diverse cancer cell lines, including breast cancer [96–99]. Besides the in vitro inhibition of ER-positive human cancer cells lines, Wang and collaborators also proved that neotanshinlactone was more potent and more selective than tamoxifen citrate [96]. In this area, only one in vivo study has reported antitumor activity on mice bearing human breast infiltrating duct carcinoma orthotopically [95], where the compound tanshinone II A strongly inhibited the proliferation of ER-positive breast cancer cells and inhibited in vivo growth of ER-negative breast cancer. The inhibition of proliferation and apoptosis induction of cancer cells through upregulation and downregulation of multiple genes involved in cell cycle regulation, cell proliferation, apoptosis, signal transduction, transcriptional regulation, angiogenesis, invasive potential, and metastatic potential of cancer cells could explain in part the anticancer effect of this compound. Chemotherapy resistance is a significant problem in breast cancer therapy. Cai et al. reported the reversal mechanism of salvianolic acid A (i.e., a phenolic active compound extract from Salvia miltiorrhiza) in human breast cancer paclitaxel resistance cell line, facilitating the sensitivity of chemotherapeutic agents [100]. In another study, the authors demonstrated that tanshinone II A ameliorated hypoxia-induced chemotherapy resistance to doxorubicin and epithelial-mesenchymal transition in breast cancer cell lines via downregulation of hypoxia-induced factor 1 expression [101]. However, in vivo studies are required to support these achievements.

Wong et al. performed a clinical trial and concluded that the coadministration of Coriolus versicolor (Yunzhi, 50 mg/kg body weight, 100% polysaccharopeptide) and Salvia miltiorrhiza (Danshen, 20 mg/Kg body weight) could be a promising approach to improve immunological function in posttreatment breast cancer patients [54]. Patients supplemented for 6 months presented significantly elevated values of absolute counts of T-helper lymphocytes, the ratio of T-helper/T suppressor and cytotoxic lymphocytes, and the percentage and absolute counts of B-lymphocytes and decreased values of plasma sIL-2R concentration. In other clinical study, the intravenous administration of Salvia miltiorrhiza extract was able to reduce ischemia and necrosis of skin flaps after mastectomy as well as anisodamine administration but with no adverse effects [55].

3.4. Uncaria. Two species of Uncaria, commonly known as cat’s claw, Uncaria guianensis and Uncaria tomentosa, found in northern regions of South America and belonging to Rubiaceae family, have also promising medicinal outcomes, including in breast cancer patients, due to their immune-stimulant and antioxidant properties [102]. This botanical product contains a complex combination of phytochemicals, including glycosides, tannins, flavonoids, and sterol fractions that could be complementary and/or synergic in their pharmacological actions [3]. Some of these constituents can present selectively cytostatic/cytotoxic to some cancer cells such as pentacyclic oxindole alkaloids [103].

Although some studies revealed the in vitro efficacy of cat’s claw in breast cell lines [102, 249] no clinical trials investigating Uncaria species as an anticancer agent are available. It is fundamental that more research is performed in animal models and mainly in humans before any conclusions can be drawn in this topic.

Utilising Uncaria tomentosa appears to be a beneficial approach to minimize the adverse effects associated with traditional cancer therapies, namely, in the case of chemotherapy. The use of this Uncaria species can stimulate DNA restoration [250], preventing mutations and cell damage caused by chemotherapy agents [251], and myelopoesis [252, 253]. Aqueous extracts of U. tomentosa also proved to improve leukocyte counts during a period of eight weeks in healthy animals [254] and after ten days of doxorubicin-induced neutropenia [251]. In addition, extracts or fractions of cat’s claw modulate the activity of the immune system [254, 255]. These preclinical data were proved in a randomized clinical trial. Santos Araujo Mdo et al. used 300 mg per day of U. tomentosa dried ethanolic extract, in patients diagnosed with Invasive Ductal Carcinoma Stage II, who underwent a treatment regimen known as FAC (Fluorouracil, Doxorubicin, and Cyclophosphamide) [56]. This adjuvant treatment for breast cancer patients was safe and effective in the recovery from neutropenia induced by cancer chemotherapy. The dose used in this trial was empiric and was based on the dose administrated in other (not cancer-related) clinical trials where the authors used different solvent extracts and, consequently, different phytochemicals. So, more clinical trials should identify the best dosage range for using cat’s claw as an adjuvant chemotherapy agent.

Budán et al. indicated that the combination of different phytotherapeutic (e.g., Clae of Dragon tea containing the bark of Uncaria guianensis, Uncaria tomentosa, and Tabebuia avellanedae) in a long-term experimental animal model acted as chemopreventive agent [256].

Concerning their safety, clinical trials with human volunteers reported no toxicity associated with the use of a commercially available aqueous extract of U. tomentosa named C-Med-100. The dose of Uncaria was different in the
trials, using 250 mg or 350 mg/day over 8 weeks and 2 × 350 mg daily for 2 months [250, 257].

Cat's claw could provoke adverse effects including diarrhoea or loose stools and lower blood pressure, which tend to diminish with continued usage. However, some literature reported that cat's claw can interact with medications intended to suppress the immune system (e.g., cyclosporine) or other medications prescribed following an organ transplant; this information still needs to be proven scientifically. In vivo rat studies demonstrated that cat's claw may protect against gastrointestinal injury attributed to nonsteroidal anti-inflammatory drugs (NSAIDs) and can diminish the platelet aggregation and may increase the effect of anticoagulants [103].

3.5. Allium sativum L. Allium sativum, commonly known as garlic, presents different biologically useful secondary metabolites with high sulphur content, such as S-allylcysteine, diallyl disulphide, diallyl trisulphide, and methyl allyl trisulphide [258]. Garlic also contains other beneficial compounds such as arginine, oligosaccharides, flavonoids, and selenium (i.e., cellular antioxidants) [259]. The main active ingredients of garlic, organic sulphur compounds, have attracted great attention as cancer prevention and treatment agents in breast cancer [260–263]. Among these constituents derived from garlic, the oil-soluble compounds are more effective than water-soluble compounds in suppressing breast cancer [264]. The mechanisms involved in the anticancer effect of garlic-containing compounds include activation of metabolizing enzymes that detoxify chemical carcinogens, inhibition of DNA adduct formation, suppression of reactive oxygen species production, induction of apoptosis, and regulation of cell cycle progression and signal transduction modification [264]. All referred to studies used experimental breast cancer cell lines, other studies extended their anticancer evidences to in vivo models [265, 266], and no clinical trials are available in literature. For example, Liu et al. [260] demonstrated that diallyl trisulphide, a natural organosulphur compound with most sulphur atoms found in garlic, suppressed the migration and invasion of breast cancer cell lines (MDA-MB-231 cells and HS 578t cells) and suggested that the inhibitory effects are associated with downregulation of the transcriptional activities of nuclear factor-kappa (NF-κB, a transcription factor that regulates the expression of antiapoptotic proteins) and ERK/MAPK (i.e., major kinases involved in cell survival) signalling pathways. In many malignant tumours, constitutive NF-activation occurs and consequently inflammation, proliferation, resistant to apoptosis, invasion, and so forth [267]. These authors reported that a concentration of diallyl trisulphide equal to 10 μM should be achieved in vivo for preventing or treating breast cancer. Chandra-Kuntal and collaborators established the critical role for reactive oxygen species in the anticancer effects of diallyl trisulphide compound using human breast cancer cells (MCF-7 and MDA-MB-231). Using an oestrogen receptor-negative human breast cancer cell line (MDA-MB-231), Nakagawa et al. [266] reported that diallyl disulphide synergizes the effect of eicosapentaenoic acid, a breast cancer suppressor, and antagonizes the effect of linoleic acid, a potent breast cancer stimulator. Diallyl trisulphide inhibits the expression of ADAM10 and ADAM17 (proteases with a role on metabolism of abnormal cells and whose high expression is associated with a lower disease-free survival in breast cancer patients) in estrogen-independent MDA-MB-231 and estrogen-dependent MCF-7 breast cancer cells and seems to promote growth inhibition of breast cancer cells [268].

In terms of the cancer prevention, Wargovich et al. demonstrated robust chemopreventive action of constituents of garlic against experimentally induced cancer, including the mammary gland [32].

Despite garlic affecting cytochrome P450 3A4 activity, Cox et al. showed that garlic supplementation does not significantly affect the disposition of docetaxel but it can decrease the clearance of docetaxel in patients carrying a CYP3A5*1A allele (present in all African American) [58].

A case-control study performed in northwest Iran aimed to find the association between dietary Allium consumption and risk of breast cancer. The study included 285 women (25–65 years old) diagnosed with histopathologically confirmed breast cancer (grade II or III or clinical stage II or III) which completed a food-frequency validated questionnaire. A reduced risk of breast cancer associated with higher consumption of garlic and leek and an increased risk associated with high consumption of cooked onion was found [57]. No interactions are reported. Theoretically, garlic can increase bleeding with anticoagulants, aspirin, and antiplatelet drugs [269].

3.6. Linum usitatissimum. Linum usitatissimum (flaxseed) is known for its phytoestrogen lignans content, namely, secoisolariciresinol diglucoside, which are converted into mammalian lignans (enterolactone and enterodiol) by bacterial fermentation in the colon [270]. This bacterial conversion beneficially influences the anticancer effects of flaxseed [271]. Based on their structural similarity to estrogens, mammalian lignan metabolites can attach to oestrogen receptors and inhibit the growth of estrogen-stimulated breast cancer [3]. Flaxseed can modulate the estrogen metabolism and oestrogen receptor and epidermal growth factor receptor signalling pathways [272]. Flaxseed also contains up to 40% oil which is mainly rich in α-linolenic acid-rich oil (i.e., n-3 polyunsaturated fatty acid).

However, some questions remain and are discussed, such as if flaxseed and its compounds are effective in reducing the breast cancer risk, present antiproliferative properties, and can interact beneficially with conventional cancer therapy. In 2013, a Canadian study revealed that flaxseed intake alone is associated with a prevention of breast cancer [59].

In vitro studies showed that flaxseed induces apoptosis and inhibits human breast cancer cells proliferation [273–276]. Animal models have shown that flaxseed, secoisolariciresinol diglucoside, and flaxseed oil can reduce the growth of breast cancer [277–279]. Additionally, experimental studies using rodents demonstrated that flaxseed dietary inclusion has antiproliferative effect in different heterotransplanted mammary carcinomas in mice [280–282]. For example, Chen et al. proved that flaxseed diet on a mouse model has a dose-dependent inhibition of breast tumour growth.
In addition, flaxseed also contributed to decreased metastasis and tumour angiogenesis [60, 279, 284].

Even though numerous experimental studies using animal models being available in literature, there are a few studies concerning the influence of flaxseed on breast carcinomas in humans and more clinical trials are required to assess whether flaxseed has anticancer properties in humans. No study reveals that flaxseed has a negative effect. For example, in a double-blinded, randomized controlled clinical trial, the dietary flaxseed demonstrated remarkable protection with a reduction in tumour growth and alteration of tumour biological markers in postmenopausal breast cancer patients [285]. Buck and collaborators [63, 286] also reported the beneficial effect of flaxseed ingestion and high serum lignan levels in the survival rate of postmenopausal patients with breast cancer.

Taking into consideration the interaction of flaxseed in chemotherapy, Chen et al. demonstrated that n-3 fatty acid-rich cotyledon fraction of flaxseed reduced the growth of ER-positive human breast tumours, alone and in combination with tamoxifen, increasing the effectiveness of this chemotherapeutic agent [280]. Some studies reported the decreased tumour angiogenesis with the association of flaxseed and tamoxifen [60, 61] and the tumour cell apoptosis with flaxseed and doxorubicin [287]. In a recent study, Manson et al. reported that dietary flaxseed presented minimal tumour-reducing outcome did not interfere with trastuzumab action (a recombinant human monoclonal antibody used as the first-line therapy in HER2-overexpression breast cancer) but enhanced survival in athymic mice with established HER2-overexpressing human breast tumours [288]. However, the use of flaxseed oil combined with trastuzumab increased the effectiveness of low doses of this monoclonal antibody, that is, reduced tumour size and cell proliferation and increased apoptosis on HER2-overexpressing breast tumours (BT-474) in athymic mice compared to trastuzumab alone [289]. The author suggests the potential use of flaxseed oil as a complementary treatment for premenopausal women undergoing trastuzumab treatment, reducing the dose, and, therefore, lowering the side effects and potentially increasing survival rates. However, these recommendations should be confirmed through clinical trials. The use of flaxseed and aromatase inhibitor (using anastrozole as model drug) was also studied by MaCann and collaborators using biopsy and resection samples from postmenopausal women with oestrogen receptor-positive breast cancer [62]. Nevertheless, the results did not support strong effects on aromatase inhibitor activity but suggested that anastrozole might reduce the beneficial effects of flaxseed.

Additionally, Chen et al. verified that flaxseed components (secoisolariciresinol diglucoside and oil) did not attenuate the positive effects on bone health induced by tamoxifen (i.e., increase bone mineral content and density) in breast cancer patients [290].

Based on the current evidence, the flaxseed and its components are safe and effective in reduction risk and treatment of breast cancer. Despite this, the use of flaxseed is associated with bowel obstruction and bleeding disorder [3].
and a superior response rate in comparison to docetaxel in monotherapy. The recommended dose of curcumin is 6.0 g/day for seven consecutive days every 3 weeks in combination with a standard dose of docetaxel which proved its feasibility, safety, and tolerability. However, some scientific evidence demonstrated that dietary curcumin can inhibit chemotherapy-induced apoptosis in models of human breast cancer lines (MCF-7, MDA-MB-231, and BT-474) [314]. The chemotherapeutic agents evaluated were camptothecin, mechloroethamine, and doxorubicin-induced apoptosis. In conclusion, additional clinical studies are required to demonstrate the avoidance of curcumin (in both supplements and intake foods containing curcuma) in breast cancer patients undergoing chemotherapy.

In addition, this phytotherapeutic agent is well tolerated in human subjects. Therefore, curcumin could be considered an alternative nontoxic agent in the treatment of one of the most aggressive breast cancer, that is, triple negative breast cancer (ER-negative, PR-negative, and HER2/neu not over expressed) [303]. This breast cancer remains the most challenging factor in cancer treatment.

3.8. Green Tea. Green tea extract is prepared from the steamed and dried leaves of Camellia sinensis and contains flavonoids, a large group of polyphenolic compounds with antioxidants properties [269]. Epigallocatechin-3-gallate (EGCG) is the most abundant polyphenol in green tea and has been the focus of preclinical and clinical research on health beneficial effects [3]. However, the main mechanism by which green tea might help to prevent cancer has not been recognized.

In vitro and animal studies demonstrated that tea polyphenols can inhibit tumour cell proliferation and induce apoptosis [315, 316]. Additionally, tea catechins have revealed the ability to inhibit angiogenesis and tumour cell invasiveness as well as modulate the immune system function [317]. The chemopreventive potential of green tea contrasts with the consistent results from animal models. Evidence of green tea consumption on breast cancer prevention and development is not supported by epidemiologic studies and the role of green tea consumption in breast cancer remains unclear. The results of antiproliferative effect of green tea extracts or its polyphenols from human studies are inconsistent and depend on the type of cancer [318]. A systematic review and meta-analysis of prospective observational studies, 57 relevant articles, concluded that tea consumption has no significant effect on the risk of common malignancies including breast cancer [65]. A prospective cohort study performed in Japan found no association between green tea drinking and risk of breast cancer [66]. However, in a case-control study conducted by Zhang and colleagues in Southeast Chine between 2004 and 2005, despite the fact that the authors concluded that regular consumption of green tea can protect against breast cancer, they also suggested more research to closely examine the relationship between tea consumption and breast cancer risk [67].

In a follow-up study, despite prevention recurrence of stage I and II breast cancer being observed with an increase green tea intake, no improvements were confirmed in patients with stage III breast cancer. A potential prevention of green tea consumption in breast cancer recurrence in early-stage (I and II) cancer was also reported by Seely et al. [77]. In order to better evaluate the in vivo exposure to specific tea catechins, two studies incorporated prediagnostic biomarkers of green tea intake and metabolism on risk of breast cancer [68, 69]. In a prospective cohort in China, urinary tea catechins and their metabolites were measured in 353 cases and 701 controls and no association was found between urinary concentrations of biomarkers measured and risk of breast cancer [69]. Similar results were achieved in a prospective cohort Chinese study in which tea catechins biomarkers concentrations were measured in plasma [68]. In both studies, the detectable rates of some biomarkers were as low as 20–30%, which increased concern about the sensitivity of the assays, because ~50% of study participants reported drinking at least one cup of green tea daily. Crew et al. conducted a study using archived blood/urine from a phase IB randomized, placebo-controlled dose escalation trial of an oral green tea extract, polyphenon E (Poly E), in breast cancer patients [70]. The results suggested that the consumption of EGCG can have a preventive effect in breast cancer by influencing the growth factor signalling, angiogenesis, and lipid metabolism mechanisms.

In a cross-sectional study, including 3315 Asian women, daily green tea consumption demonstrated a significantly lower mammographic density percentage compared to nontea drinkers [319]. Mammographic density is a well-established breast cancer risk factor. The difference in mammographic density was observed mainly among postmenopausal women. The authors suggest that long-term exposure to green tea may act as a protective approach in breast cancer.

In addition, genetic factors may have an important role in the influence of green tea on breast cancer, namely, genetic polymorphism in angiotensin-converting enzyme gene and in the catechol-O-methyltransferase gene, probably due to the interindividual differences in the metabolism and elimination of tea polyphenols [71, 72]. In the specific case of catechol-O-methyltransferase gene, studies have inconsistent findings. Wu et al. [73] conducted a population-based case-control study in Asians in Los Angeles County and reported that consumption of green tea was associated with significant reduced risk of breast cancer in women carrying at least one copy of the low-activity catechol-O-methyltransferase allele relative to nondrinkers. In women carrying both high-activity catechol-O-methyltransferase alleles no association was found. In the Chinese population, the catechol-O-methyltransferase genotype did not present any modifying effect on the association between tea consumption and breast cancer risk.

Green tea has also demonstrated a promising role as adjuvant of chemo/radiotherapy due to both additive or synergistic effects and amelioration of cancer therapy side effects [320]. However, further clinical research is required to ascertain the effectiveness of these actions. EGCG can modify the pharmacokinetics of tamoxifen and induce chemosenstization in tamoxifen-resistant breast cancer cells [321]. In another study, the cotreatment of EGCG and tamoxifen...
increased apoptosis and reduced tumour growth in breast cancer cells using a murine model of breast carcinoma, enhancing the cytotoxicity of paclitaxel [322]. EGCG also has antiproliferation activity against estrogen-induced breast cancer cells (e.g., sunitinib) [323] and sensitizes hormone responsive tumours to drugs that act in steroid receptors (e.g., tamoxifen) [321, 324]. Li et al. reported chemosensitization and synergistic anticancer effects with the coadministration of EGCG and histone deacetylase inhibitor trichostatin A in oestrogen receptor-negative breast cancer cells [325]. Zhang et al. conducted a clinical trial in breast cancer patients undergoing radiotherapy and supplemented with EGCG. The results showed that EGCG and its metabolites could potentiate the effects of radiotherapy [74]. Green tea also seems to protect the body against the harmful effects of radiation and chemotherapy [7, 320].

In the Minnesota Green Tea Trial, 1075 postmenopausal women at high risk of breast cancer due to dense breast tissue randomly consumed green tea extract (845 mg EGCG) or placebo, daily for one year. The safety of green tea was also tested. The main conclusion was that there were no statistically significant differences between groups in frequencies adverse events or serious adverse events, but EGCG consumption leads to a higher incidence of nausea, dermatologic events, and alanine aminotransferase elevation [75].

La3zeroniet al. [76] studied the EGCG tissue distribution and evaluated its effect on cell proliferation in breast cancer patients. The consumption of 300 g of tea catechin extract phytosomes (equivalent to 44.9 mg of EGCG) increased the bioavailability of EGCG, which was detectable in breast tumour tissue and is associated with a decrease in the tumour circulating biomarker revealing antiproliferative effects on breast cancer tissue.

Based on the current data, large randomized intervention trials focusing on the efficacy of green tea polyphenols are required before a recommendation as preventive-cancer should be made.

No known contradictions are reported. Green tea has been consumed safely over thousands of years; recently a liver toxicity has been reported. However, this is probably related to the presence of contaminants in the plant.

3.9. Ginseng. The generic term ginseng encloses several species of plants belonging to the genus Panax such as Panax ginseng and Panax japonicus (i.e., Asian ginseng) and Panax quinquefolius L. (American ginseng) [269]. In recent years, ginseng has gained popularity in Western countries and is included in the Pharmacopoeias of Germany, Austria, and United Kingdom [326]; in the United States, ginseng is the second top-selling herbal supplement but it is not a drug approved by the Food and Drug Administration [327–329]. Ginseng presents a complex mixture of various active compounds but the main pharmacologically active ingredients are triterpene saponins known as ginsenosides, which are found in the roots. Therefore, the dried roots are used in traditional medicines due to the variety of beneficial effects, including in breast cancer [330, 331]. However, its clinical significance in breast cancer patients has not been fully investigated and some divergences are reported.

Despite several in vitro studies having proved the promising use of ginseng extract or its active components as anticancer agent in breast cancer [332, 333], no animal studies have been found in literature. The mechanisms by which components of ginseng or metabolites performed their antiproliferative effect are reported in several research studies and resumed in a recent review paper [334]. These compounds can modulate signalling pathways associated with inflammation, oxidative stress, angiogenesis, metastasis, and stem/progenitor-like properties of cancer cells. For example, ginsenoside Rp 1 inhibits the insulin-like growth factor 1 receptor (IGF-1R)/Akt pathway in breast cancer cells [332]. In addition, ginsenoside Rp 1 was also demonstrated to induce cycle arrest and apoptosis. Kwak et al. studied the inhibitory effect of ginseng sapogenins and their derivatives on the proliferation of MDA-MB-231 human breast cancer cells (a model of triple negative breast cancer) [333]. 20(S)-Protopanaxadiol exhibited IC50 (i.e., half maximal inhibitory concentration) comparable to the taxol (chemotherapeutic agent) and acts by stimulating caspase-dependent apoptosis in breast cancer cells. The ability of ginsenoside Rg 3, one of the major active compounds of heat-processed ginseng, to induce apoptosis in MDA-MB 231 cells by blocking NF-κB signalling was also verified [335, 336].

A specific effect of ginseng in cancer is increasing the sensitivity of breast cancer cells to various chemical anticancer agents including gemcitabine (an antimetabolite), cisplatin (an alkylating agent), paclitaxel (a taxane agent belonging to a plant alkaloid), and epirubicin (an antibiotic) through downregulation of them RNA level of MDR-1 [337].

Despite popular use of ginseng in cancer patients, only a few clinical studies have been conducted on ginseng-chemotherapeutic agent association. A clinical phase II study using no ginseng alone but in Shengmai formula (i.e., a traditional Chinese ginseng preparation that contains red ginseng, lilyturf root, and magnolia vine fruit) reported immunologic improvements among breast cancer patients [78].

Some beneficial effects related to the use of ginseng in human include maintenance of natural energy, improvements of physical, chemical, and biological performance and enhancement mood and general vitality and immune function [326, 338]. Despite these positive outcomes which are attributed to its “adaptogen” characteristic, findings on the effects of ginseng in breast cancer patients are mixed. Bao et al. [79] conducted the Shanghai Breast Cancer Survival Study to detect some association between quality of life and postdiagnosis ginseng use among breast cancer survivors. The authors did not find any improvements. In another study, Cui and collaborators reported that the use of ginseng had positive quality of life scores, namely, in the psychological and social domains [80]. The authors explained the variability in response to the design of study and the different doses of ginseng use among breast cancer survivors.

Nevertheless, evidence of efficacy is sparse. Well-designed clinical trials are required to provide information for scientists and healthcare consumers. Furthermore, treatment of symptoms and side effects is crucial for people with cancer because of the longevity associated with successful cancer...
Black cohosh is one of the most controversial natural therapies used among breast cancer patients due to its ambiguous estrogenic or antiestrogenic activities with many studies in literature exploring considerable debate over the safety of its uses [349]. Under conditions of excessive estrogen, the active ingredients of this plant may behave as estrogen antagonists by a mechanism of competitive inhibition of the ER. However, in the presence of low estrogen, actives may act as weak agonists [350–352]. If black cohosh exhibits estrogenic activity, it may result in potentially negative outcomes on breast cancer risk or recurrence, mainly in women undergoing antiestrogen therapy [353]. However, Fritz and collaborators carried out a systematic review about the use of black cohosh in breast cancer and found that evidence is conflicting in all analysed aspects [81]. The authors concluded that current evidence does not sustain an association between black cohosh and increased risk of breast cancer (results from observational studies) and reduce evidence that supports the efficacy of black cohosh for reduction of hot flashes in breast cancer patients (results from observational studies and clinical trials). Some limitations of studies include subjective outcomes, different risk of bias, namely, lack of binding and inadequate reporting of withdrawals (for clinical trials); variation of dose and duration schedules of black cohosh, different products and methods of extraction, and lack of information and criteria included in the retrospective design (for observational studies). In addition, black cohosh seems to have limited and no classic estrogenic activity as seen by its effect on bone metabolism.

Different conclusions have also been reported concerning the potential for interactions with antiproliferative effects of different classes of chemotherapy agents. A cohort study suggested that taking black cohosh can reduce risk of recurrence in patients taking tamoxifen [82]. No risk of recurrent and no consistent serious adverse events related to the combination of black cohosh and tamoxifen were reported in clinical trials [354, 355]. No interaction on the forestamene- (i.e., an aromatase inhibitor-) induced tumour reduction was observed with the coadministration of black cohosh extract in a chemically induced rat model for mammary carcinoma [356]. In humans, different findings were reported [357, 358].

The Clinical Practice Guideline of the Canadian Society of Obstetricians and Gynaecologists list black cohosh interactions with some drugs including anesthetics, antihypertensives, and sedatives [359]. Despite this, Walji et al. conducted a systematic review and suggested that black cohosh has a high safety profile in cancer patients; however, the authors did not include recent evidence [360]. In another study based on animal studies, Freudenstein and colleagues suggested that *Cimicifuga racemosa* extract is safe for treatment of menopausal symptoms in breast cancer survivors in whom hormone-replacement therapy is contraindicated [361]. Case reports of hepatotoxicity have been reported but confounding factors such as “poor case data quality, uncertain of black cohosh product, quality, and insufficient adverse event definition” could justify this adverse effect [362].

The outcome of black cohosh uses in women with or without a history of breast cancer is unclear and its use must be discouraged.
3.11. Mistletoe. Mistletoe (Viscum album from the Visceaceae family), as part of anthroposophical medicine, is potentially effective against cancer and is used frequently in breast cancer due to its minimal side effects and the fact that these side effects are not life threatening [363]. The mistletoe contains different types of biological active ingredients, but the main constituents responsible for anticancer and immunomodulatory effects are lectins (ML-I, ML-II, and ML-III) [364, 365].

Experiments in cell cultures, animal models, and clinical data propose that cytotoxic and antitumour activities of mistletoe may be mediated by different mechanisms: apoptosis induction and necrosis, cell cycle inhibition [366, 367], and activation of specific and nonspecific immune system [368, 369].

Different in vitro studies demonstrated the antiproliferative effect of mistletoe extract against breast cancer cell lines [370, 371]. Kelter et al. proved that mistletoe extracts have cytotoxic activity on different human breast cancer cell lines and suggested that no growth stimulation of these cell occurred [370]. Using human breast carcinoma cell lines HCC 1937 and HCC 1143, Weissenstein and collaborators suggested that no herb-drug interactions occurred from the exposition of cancer cells simultaneously with doxorubicin (i.e., a chemotherapeutic) and Viscum album extract [371]. Additionally, at higher concentrations of mistletoe extract an additive in vitro inhibitory effect was observed. When Viscum album extract was associated with trastuzumab in an in vitro SK-BR-3 cells test, the results suggested no herb-drug interaction and exhibited a complementary anticancer effect [347]. A similar synergistic anticancer effect was observed in inhibition in the growth of both breast cancer cell lines (i.e., MCF-7—oestrogen receptor-positive—and MDA-MB 231-oestrogen receptor-negative) when the authors combined doxorubicin and lectin from Korean mistletoe [372]. Furthermore, in vivo investigations using different animal models were also presented in literature. For example, Beuth et al. reported the dose-dependent anticancer activity of mistletoe using a BALB/c mouse/BT474 ductal breast carcinoma model [373].

Several studies on breast cancer patients receiving chemotherapy report an efficacy on survival rate, tumour reduction and remission, and better quality of life with reduction of adverse reaction of standard chemotherapy when additionally treated with mistletoe products [84–87]. Safety and efficacy were set as the endpoints in a multicentric and comparative clinical trial conducted by Beuth et al. among women with primary breast cancer who received mistletoe extract [88]. In clinical trials, some limitations should also be pointed out such as limited sample size, lack of control, exclusion and inclusion criteria of the clinical trial, quality rating, and mistletoe preparations.

Twelve patients were selected by the presence of histological confirmed breast cancer tumour (≥2 cm in diameter) and included in a study to investigate the mistletoe effect in tumour regression of breast cancer. After six months, the mistletoe extract therapy demonstrated being highly effective [83].

Despite the promising results for the use of mistletoe in addition to chemotherapy, the discussion on the reduction of side effects and improvement of quality of life in breast cancer patients remains open and is still a controversial topic.

4. Nutritional Supplements

In cancer topic, three different phases could be passive intervention with nutritional supplements: prevention, during conventional treatments after diagnosis and survival period.

Although studies have not established a specific role for vitamins and selenium in the prevention of breast cancer, some anticancer activities have been demonstrated using tumour cell lines (i.e., in vitro) [374–376].

Some notable institutions in cancer research, such as the American Cancer Society, the World Cancer Research Fund, and American Institute for Cancer Research, advise against the use of nutritional supplements for cancer survivors [377, 378]. Nevertheless, the supplementation with multivitamins and minerals is frequent after a breast cancer diagnosis and in survivors who recognize them as anticancer and antioxidant agents [26, 34, 113, 379]. Despite this, the evidence base for nutritional supplementation in cancer patients during treatment remains inconsistent and ambiguous and the results obtained in some studies have been contradictory. For example, some observational studies performed in breast patients have not reported improvements in breast cancer prognostic [152, 380]; others showed beneficial effects [112, 123, 381] and some showed harmful events [123].

The information obtained with the studies that examine the association between supplementation use and cancer-related outcomes must be interpreted with care due to the methodological limitations of most study designs such as lack of complete prospective data on supplement uses, specifically around the time of prediagnosis, diagnosis, and treatment and lack of data collection on changes in supplement use over time. Greenlee et al. [379] published a prospective cohort study (the Pathways study) with methodological improvements over previous studies in which the authors provided specific detailed information on changes in supplementation use following diagnosis in a multiethnic population. In this study, most women used vitamin/mineral supplements before (84%) and after (82%) diagnosis. The most commonly initiated supplements were calcium and vitamin D; the most commonly discontinued supplements were multivitamins, vitamin C and vitamin E. In another study, the Intergroup Phase III Breast Cancer Chemotherapy trial (S0221), the authors collected data between 2003 and 2010 and reported that 48% of patients were taking multivitamins; 20% were taking vitamins C and D and omega 3 fatty acids in fish oils; 15% were taking vitamins E and B6 and folic acid; and 34% were taking calcium. In this study, the advice of clinicians related to the nutritional supplementation was diverse [382]. This review refers only to the most commonly used nutritional supplements among the breast cancer patients.

After reviewing the available scientific literature [157], at this moment no consensual recommendation for cancer patients is available even among the clinicians and a greater understanding of processes involved in the regulation of tumour growth is desirable.
4.1. Multivitamins. Generally, cancer patients have an augmented requirement for essential nutrients (e.g., vitamins, trace elements, and minerals) adequate levels of which are achieved with the supplementation products. This is particularly true before or during cancer destructive therapies for supporting their side effects better.

However, multivitamin supplements are usually a heterogeneous group of products with no standard composition that depends on the manufacturer, year of production, and batches [104, 106]. In the Swedish Mammography prospective cohort study, Larsson and collaborators highlighted an increase in the risk of developing breast cancer both for high frequency of consumption (19%) and for long duration of multivitamin supplementation (22%) [105].

Until now, no randomized trials have evaluated the outcomes of multivitamin supplementation on the toxicity or survival rate after breast cancer diagnostic [383]. However, Kwan and collaborators conducted an observational study in which 72% of women with early-stage breast cancer were self-prescribing multivitamins and reported neither beneficial nor harmful effects of these supplements on toxicity or survival [113]. Similar conclusions were found by Wassertheil-Smoller and collaborators in US postmenopausal women with invasive breast cancer [111]. However, other authors did not find any association of consumption of multivitamins and breast cancer risk [106, 107].

4.2. Antioxidant Vitamins and Minerals. There is scientific documentation that relates the high intake of antioxidant with both a lower risk of developing breast cancer [104, 110] and a positive impact in the mortality rates of cancer. In accordance with the American Cancer Society and Cancer Research UK, although the studies of nutritional supplements to reduce cancer risk have not all been disappointing, until now there is no consistent evidence that any type of nutritional supplement can help to prevent cancer, in contrast with the nutrients (including antioxidant) obtained in a healthy and balanced diet with abundance of fruits and vegetables [108, 384, 385]. Therefore, according to the American Cancer Society, the best advice is to get antioxidants through food sources rather than supplements.

The use of antioxidant agents in patients with cancer seems to be an intelligent idea based on their biologic mechanism, first because of their potential anti-cancer properties—that is, diminished oxidative damage; reduced proliferation and angiogenesis; increased apoptosis [386]—and second because they may reduce the oxidative damage from conventional cancer treatments involving chemo- and radiotherapy and therefore limited the toxicity of these therapies [383].

Despite the potential improvement outcomes, the supplementation with antioxidant agents (e.g., vitamin A, vitamin E, vitamin C, and selenium) during cancer treatment is discussed controversially mainly due to the probable interaction with or modification in the effects of conventional cancer treatments [386, 387]. Since radiotherapy and several chemotherapy agents (e.g., alkylating agents, anthracyclines, podophyllin derivatives, platinum complexes, and camptothecins) exert their anticancer properties through production of reactive oxygen species (ROS) and promoting apoptosis, the antioxidant agents may reduce the efficacy of radio- and chemotherapy-related cytotoxicity and consequently act as potential cancer-promoting. Antioxidant supplements appear to successfully block otherwise effective prooxidant therapies and protect both normal and tumour cells from the oxidative damage [106]. In this context, some studies highlight the adverse effects of antioxidant supplementation on overall mortality for patients with cancer [388, 389]. However, other studies proved the benefits of antioxidant supplementation in a specific treatment (e.g., chemotherapy [112]; radiotherapy [390]; and both [381]). Based on these restricted outcomes of the observational studies and clinical trials, there does not appear to be obvious evidence concerning the effect of antioxidant supplementation and its use during chemo and radiation treatments. Therefore, high-quality placebo-controlled trials are needed.

4.2.1. Vitamin A and Carotenoids. Vitamin A refers to a group of compounds named retinoids which cooperate in a large variety of physiological processes such as in vision, bone growth, reproduction, cell division, and differentiation [391, 392]. Two forms of vitamin A can be ingested via diet: preformed vitamin A, found in foods derived from animal sources (e.g., liver, whole milk) and absorbed as retinol, and provitamin A carotenoids, derived from fruits and green leafy vegetables and converted into retinol once ingested. Most of the supplements contain the preformed vitamin A [391]. It is stored in the liver. Synthetic retinoids are also available such as bexarotene and fenretinide.

Various longitudinal cohort studies, performed in different ethnic groups and geographic locations worldwide, evaluated the intake of carotenoid and endogenous retinol levels with the risk for developing breast cancer [115–118]. The type of beneficial carotenoids is controversial [115–121]. For example, in the postmenopausal women population, some studies did not correlate the retinol levels with breast cancer risk [115, 117]. Other studies demonstrated different effects between the lycopene levels (i.e., a carotenoid substance that does not convert into vitamin A) and the risk of breast cancer, that is, an increased risk [116, 119] or a protective effect among ER-positive and progesterone receptor-positive breast cancer [120].

The European Prospective Investigation into Cancer and Nutrition cohort studied 1502 female incident breast cancer cases (premenopausal (n = 582) and oestrogen receptor-negative cases (n = 462)). Carotenoids, tocopherols, vitamin C, and retinol plasma levels were determined to find an association with risk of breast cancer. The results showed that a higher concentration of plasma β-carotene and α-carotene is associated with lower breast cancer risk of oestrogen receptor-negative tumours and higher risk of breast cancer was found for retinol in relation to oestrogen receptor-negative/progesterone receptor-negative tumours. There was no statistical difference for the other studied compounds [121].

A positive relationship between a high plasma carotenoids and breast cancer survivals was reported by Rock et al. in the Women's Healthy Eating and Living study [122].
Higher biological exposure to carotenoids, when assessed over the period of the study, was associated with greater likelihood of breast cancer-free survival regardless of study group assignment.

4.2.2. Vitamin C. Vitamin C, or ascorbic acid, is an essential water-soluble vitamin that acts as antioxidant and has important biological roles such as in protein metabolism, including the biosynthesis of collagen, neurotransmitters, and L-carnitine; in immune function and in absorption of iron from plant-derived foods [391]. This vitamin, which is crucial for the structural integrity of intercellular matrix, is produced by the most animals but not by humans who must get it from the diet or as supplement.

There is restricted evidence of using vitamin C supplementation in the primary prevention or delay of total cancer incidence, including breast cancer [115, 393]. One of the largest studies in women, followed up for 9.4 years, reported that the supplementation with 500 mg daily of vitamin C had no effect on the occurrence of breast cancer [393]. However, in a cohort study including postmenopausal women, Cui and colleagues found a significant increased risk of breast cancer with high dose of vitamin C supplementation [120].

The safety of oral vitamin C supplements subsequent of the cancer diagnosis is not obvious [386]. The attention given to vitamin C is increasing since the publication of the in vitro study by Chen and collaborators [394] which verified the selective apoptosis of cancer cells induced by high concentrations of vitamin C. This effect was also supported by Ullah et al. [395]. Additionally, vitamin C enhances immunity and presents antioxidant properties including the neutralization of free radicals which may interfere with cancer progression [396]. The important issue is if these beneficial outcomes can be effective in vivo (i.e., in human body) considering the solubility of this vitamin and some parameters should be clarified, namely, the dose of vitamin C, the timing of supplementation, the side effects of high concentration of vitamin C (e.g., for kidneys), and its effect in combination with pharmacological and conventional cancer therapies (e.g., chemo- and radiotherapy). These properties are controversial and seem to be dependent on the dose, the source of vitamin C intake (i.e., derived from food or supplementation), and the timing and duration of intake [125, 397]. For example, some studies associated the dietary vitamin C intake with reduced risk of breast cancer mortality [125, 398] and no relationship demonstrated in other studies [26]. Additionally, the results also varied in the case of vitamin C supplementation. Studies reported inverse association between vitamin C supplementation, most of them referred to postdiagnosis breast cancer supplementation and mortality or recurrence [123, 126, 381], and no association was reported by Harris et al. [125]; however, this study presented a limited power analysis. These differences are probably related to the limitations of each study (i.e., small population with no confidence intervals or statistical analysis; details of concurrent treatment, heterogeneity across included studies). The relationship between vitamin C supplement intake and breast cancer risk was evaluated in an epidemiologic study with 57,403 postmenopausal women via food-frequency and supplement questionnaires. Vitamin C supplement was not associated with breast cancer risk overall but was associated with increased postmenopausal breast cancer risk in women with high vitamin C intake from foods [124].

Concerning the use of antioxidant supplements, including vitamin C, during conventional treatment of cancer, the evidence from experimental studies and observational or clinical trials is also controversial. Jacobs et al., since there is no high-quality evidence to confirm the benefits of vitamin supplementation in cancer patients (either increases the antitumour effects of chemotherapy or reduces its toxicity), do not recommend the use of this vitamin until double-blind placebo-controlled trials are completed [399]. Moreover, Subramani and collaborators verified that the pretreatment of MCF-7 breast cancer cells with vitamin C, in a dose-dependent reply, protected them against lipid peroxidation caused by tamoxifen treatment [400]. However, Hubner and Hanf suggested that the vitamin C from dietary sources does not have negative effects not only in chemo- and radiotherapy but also for targeted drugs [397]. Vitamin C (500 mg daily) supplementation in combination with vitamin E (400 mg daily) and tamoxifen therapy, for the period of 3 months, in postmenopausal women with breast cancer reduced the tamoxifen effect in plasma lipid and lipoprotein levels [127]. The tamoxifen therapy may enhance the synthesis of VLDL and diminish the activity of lipoprotein lipase which hydrolyses triglycerides [391]. A retrospective study showed fewer side effects of chemotherapy in breast cancer patients supplemented with low-dose infusion of vitamin C [401]; nonetheless this study did not refer to recurrence and survival data and conclusions about its safety could not be assessed. In a randomized 5-month study, Suhail and collaborators concluded that the supplementation of vitamin C (500 mg daily) and vitamin E (400 mg daily) restores antioxidant status, lowered by the breast cancer and chemotherapy, and reduces the DNA damage [128]. The authors also suggested that this regimen of supplementation should be helpful in protecting against the side effects associated with the cycles of chemotherapy treatments. Other studies reported similar conclusions after intravenous vitamin C administration [129, 130]. For example, Vollbracht et al. conducted a retrospective, multicentre, epidemiological cohort study which proved that the intravenous vitamin C administration improves quality of life in breast cancer patients during chemo/radiotherapy and aftercare [130]. In this context, the route (oral versus intravenous) used for vitamin C supplementation should also be considered when evaluating the efficacy and safety among cancer patients. Pharmacokinetic studies suggest that much higher levels of plasmatic vitamin C can be achieved by bypassing the oral route [402].

The dose of vitamin C supplementation varied in the breast cancer patients from 400 mg or less per day (in the Shanghai Breast Cancer Survival Study [381]) to higher than 1 g [403]. Development validated randomized trials are warranted to define if these higher amounts are safe and which dosage is required to reach the experimental concentrations described by Chen et al. [394]. Different levels of intake (from both dietary and supplementation) may influence the safety and efficacy in cancer patients [386]. Hoffer et al., in
a dose-finding phase I study, demonstrated that the intravenous administration of ascorbic acid in a low-dose had inferior outcomes compared to patients supplemented with higher doses [404].

Ascorbic acid is a critical nutrient for the synthesis and integrity of collagen and for the optimal stability of the extracellular matrix which are essential factors for controlling cancer. Based on the presumption that cancer patients have low reserves of ascorbic acid [405], Cha and colleagues showed that the supplementation of ascorbate in ascorbate-restricted mice injected with breast cancer cells reduced tumour growth and enhanced encapsulation of tumours [406]. Additionally, it modulated inflammatory cytokine secretion. These results support the proposed approach of using vitamin C to treat the cancer [407]. The administration of intratumoural vitamin C delayed tumour growth in murine solid tumour models and synergistic antitumour effects were observed with cisplatin [408]. However, this study was performed on animals. So, the use of vitamin C as anticancer therapy is not recommended in cancer patients.

4.2.3. Vitamin E. Vitamin E is a liposoluble vitamin that exhibits different pharmacological properties such as antioxidant, anti-inflammatory, and inhibition of protein kinase C [391]. It can be acquired from some dietary sources (e.g., nuts, seeds, vegetable oils, green leafy vegetables, and fortified cereals) or as a supplement. Among its different chemical forms, the alpha-tocopherol is the main and most active form achieved in human plasma and studied in clinical trials.

The supplementation with vitamin E in breast cancer patients has also different outcomes. Some of the effects of vitamin E in breast cancer have been explored previously with the coadministration of other antioxidant vitamins (e.g., vitamin C). Other studies have shown that long-term uptake of vitamin E could have a negative effect on breast cancer patients [114, 131]. The HOPE-TOO trial revealed no effects of long-term vitamin E supplementation (71 years) on individual rates of breast cancer [409]. Nagel and collaborators did not find any association between long-term dietary intake vitamin E (8.8 years) and risk of breast cancer development [109]. Alpha-tocopherol acetate (400 mg) supplementation increased biomarkers of estrogen-stimulation in 5 out of 7 breast cancer patients while taking tamoxifen suggesting that vitamin E supplements may decrease the antiproliferative effect of tamoxifen [132].

Tam et al. verified that alpha-tocopheryl succinate, a synthetic derivative of alpha-tocopherol, improved the cells’ sensitivity to doxorubicin (anticancer agent) which reduced the cell viability in cancerous breast tissue samples [410]. This combination, using vitamin E or its analogue in a supplementation regimen, is promising for the treatment of cancer. Random placebo-controlled trials showed that the association of pentoxifylline and vitamin E after radiotherapy in breast cancer women may be used to prevent radiation-induced side effects [133, 134].

In another study, the intracardiac injection of Trolox inhibited osteolysis bone metastasis caused by breast cancer in an experimental metastasis model [411]. Despite this, vitamin E analogue did not have any effect in the mammary fat pad model; it suppressed breast cancer cell-induced osteoclast differentiation and the invasive behaviour of cancer cells via prostaglandin E2- (PGE2-) dependent and PGE2-independent mechanisms.

4.2.4. Selenium. Selenium is an antioxidant mineral that activates enzymes (e.g., glutathione peroxidase) which participate in the metabolism of oxidants and drugs [412]. However, this activation is dependent on the physiological selenium concentrations which should be between 70 and 90 mcg/L [413]. In humans, physiological selenium concentrations depend on the intake of food products containing high levels of selenium (e.g., grains, cereals, organ meats, and seafood, with lower amounts in dairy products, fruits, and vegetables), the selenium content in soil of each geographic region, and the supplementation [397]. However different organic nutritional forms of selenium are available for cancer prevention; sodium selenite is the favourite form of selenium for therapeutic purposes [414].

Selenium appears to be a crucial trace element recognized in some types of cancers as cancer-protective agent [415]. Adequate selenium levels should be maintained to provide therapeutic benefits such as preventive activity in breast cancer [416]. In a meta-analysis, prospective studies demonstrated the protective effect in cancer incidence when patients were supplemented with selenium in the case of deficiency in physiological levels [417]. Nevertheless, the results from studies are again unclear. In another meta-analysis study, the authors evaluated the association between selenium exposure/supplement and cancer risk and did not find a protective efficacy of selenium supplement [418]. Additionally, different effects (i.e., decreased or not associated effect) on specific types of cancer were reported; namely, it decreased the risk of breast cancer. In a review paper related to the prevention of cancer by selenium, the authors reported that positive evidence was only achieved from epidemiological data and not from randomized studies [415]. From this perspective, before the supplementation of cancer patients with selenium (e.g., sodium selenite), the individual selenium status should be measured (e.g., selenium in whole blood) [419] to avoid overdosing and side effects such as higher incidence of serum lipids, hypertension, and diabetes [391].

To investigate the input of selenium and other trace elements in the etiology of breast cancer, Adeoti and collaborators determined the serum concentration of these elements in breast cancer patients [420]. An inverse relationship between the concentration of zinc and selenium in the venous blood was verified while that of the control reported a direct relationship. The authors demonstrated the association between the serum concentration of trace elements, including selenium, and breast cancer.

In addition, selenium seems to reduce the side effects of radiotherapy and does not affect the efficacy of conventional treatments [421]. In this study, diarrhoea was significantly reduced in the group supplemented with selenium.

4.2.5. Vitamin D and Calcium. Vitamin D is a liposoluble vitamin mainly acquired through endogenous synthesis via sun exposure of the skin (ultraviolet B rays); a daily sunlight
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exposure can generate the equivalent of a 10,000 IU oral dose of vitamin D3 [188]. It can also be obtained from dietary sources (e.g., fatty fish and fortified food products, cereal, milk and dairy products, beef, and liver) or as a nutritional supplement (ergocalciferol (D2) or cholecalciferol (D3)) [422]. Either of these forms needs to be metabolized via hydroxylation in the liver and kidney to the active form known as calcitriol. Our levels of vitamin D are mainly affected by the limited sun exposure (darker skin, use of sunscreen, season, latitude, and time of day) and limited physical activity. However, daily recommended intake (DRI) values generally consider vitamin D levels in persons with limited sun exposure as adequate to restore levels. Several other biological systems (e.g., heart, brain, muscle, immune, pancreas, and control cell cycle) present vitamin D receptors. Physiologically, appropriate levels of vitamin D are essential in skeletal mineralization, regulation of parathyroid hormone production, and maintenance of calcium and phosphorous plasmatic concentrations [423]. Vitamin D regulates intestinal calcium absorption and bone and renal calcium resorption [422]. Regarding the topic of cancer, it presents promising actions [424]: regulating the expression of genes that are involved in development and progression of cancer; being able to stimulate cell differentiation and apoptosis; inhibiting proliferation, angiogenesis, invasion, inflammation, and metastatic potential; suppressing aromatase activity leading to reduce estrogen levels and reduced breast cancer risk. Blood levels of 25-hydroxy-vitamin D can be measured to determine a deficiency of vitamin D [423].

Vitamin D deficiency is common among cancer patients, namely, in breast cancer cases [135, 154, 160, 167, 170, 425]. Some authors found no association between breast cancer risk and vitamin D/calcium intake [136, 138–140, 142] or serum levels [145–147]. Studies about intake or serum vitamin D and/or calcium levels found controversial results: dietary vitamin D or serum levels were associated with a decrease of breast cancer risk in several countries such as Pakistan [154], Iran [161], Korea [162], USA [163, 164], Europe [165], Australia [156], France [150], Italy [153], and Germany [166]; dietary calcium and vitamin D had no association with breast cancer risk in a large cohort study performed in Europe [141] but other authors found a significant evidence of the inverse relationship between vitamin D and calcium intake and breast cancer risk, related or not to menopausal status [157, 158], a U-shape association between plasma vitamin D levels and breast cancer risk while an inverse association was observed with serum calcium levels [171–173]. Serum calcium levels were inversely associated with breast cancer in premenopausal women and the opposite occurred in overweight postmenopausal women [169]. However, in Asian population calcium serum levels and breast cancer were not related [148]. The risk of breast cancer also appears to vary with menopausal status. While no relation between vitamin D serum levels was found in premenopausal women, an inverse association seems to be evident in postmenopause with threshold serum values of 27 ng/ml [168]. Lee et al. found that vitamin D has a protective effect on premenopausal women [155]. Despite the fact that age may be a risk factor, Mohr et al. showed no relationship between vitamin D levels and breast cancer in young military women [137], and results in postmenopausal women revealed no association either [136, 145]. Until now there is no agreement about the optimal dietary vitamin D and calcium intake to diminish breast cancer risk. However, based in existing studies, some authors suggested that daily intake of 600 mg calcium + 400 IU vitamin D and a target of 30–50 ng/ml of serum vitamin D may achieve the lowest risk of breast cancer in women [153, 166, 426].

Discordant data about the dietary source of those nutrients have been also discussed. Dietary but not vitamin D supplement was positively associated with increased breast cancer risk [176]. Other studies found no association with dairy products consume and breast cancer risk [149, 151, 427]. Sun exposure is also a relevant source of vitamin D and it seems to be an important protective factor when combined with dietary vitamin D, especially in postmenopausal women at northern latitudes with poor UV light [152].

Nonetheless, there are no adequate clinical trials that support the promising outcomes of supplementation breast cancer patients, in the case of a shortfall, with vitamin D. Most of the studies referred to the fact that the results required cautious interpretations. In accordance with Goodwin et al. [181], vitamin D deficiency in these patients is a negative prognostic factor. Women with aggressive subtypes of breast cancer have lower serum vitamin D levels which can be an indicator of poor prognostic [177, 183, 184]. For example, in a multiethnic cohort, Villaseñor and collaborators revealed that higher serum of 25-hydroxy vitamin D may be associated with improved survival, but the results were not statistically significant, referring to the need of including additional endpoints in future larger studies [182]. Calcium serum levels were positively related to breast cancer aggressiveness in premenopausal women with or without overweight [185]. The calcium/magnesium ratio appears to be also important since they have antagonist effects on absorption-resorption cycle. Magnesium intake has been related to an improved breast cancer survival and this effect is potentiated with higher calcium/magnesium ratios [180].

Vitamin D intake was not related to breast cancer recurrence independently of menopausal status [179].

Some studies related the lower risk of breast cancer and vitamin D to the inhibition of cell proliferation via nuclear vitamin D receptor (VDR). Polymorphism of VDR may be determinant in the breast cancer risk and may also explain the controversial data from different epidemiologic studies [176, 178, 428]. However, despite contradictory results reported in different studies, polymorphism of this receptor has been pointed as responsible for individual sensitivity to vitamin D [174, 429]. This relation might be also dependent on breast cancer subtype and menopausal status [175].

As with other nutritional supplements, in vitro and in vivo studies using vitamin D in breast cancer patients demonstrated contradictory results. Because a high concentration of calcitriol induces the hormone transcriptional targets and presents antiproliferative effects in culture breast cancer lineages, Urata et al. evaluated the outcomes of calcitriol supplementation in postmenopausal breast cancer specimens
results between studies [159]. On breast cancer risk, which can be the reason for discrepant results. Alcohol consumption may modify the effect of vitamin D supplementation in women undergoing breast cancer therapy. Evaluate the safety and efficacy of these regimens of supplementation with the enhanced risk of cardiovascular disease, so future validated trials should be considered to improve the condition of people with breast cancer. Sometimes, even with the supplementation of 500–1,000 UI women present a vitamin D deficit [186, 431]. Khan et al. [190] successfully supplemented patients with high doses of vitamin D (50,000 IU per week) for several weeks to control joint pain and fatigue associated with letrozole (i.e., an aromatase inhibitor). Other authors achieve similar improvement with calcium and/or vitamin D supplementation [187, 192, 432].

Amir and colleagues [188] explored the effects of high dose vitamin D3 (10,000 IU/day for 4 months) in breast cancer patients with bone metastases. In this phase 2 trial, the authors suggested the safety of supplementation but neither significant palliative benefit nor significant change in bone resorption occurred.

In breast cancer patients, whose bone density can be affected by chemotherapy-induce menopause and aromatase inhibitor, clinical practices guidelines recommend the supplementation not only with vitamin D but also with calcium [189]. Calcium is the most prevalent mineral in the body. Chung et al. reported no benefits for bone density or risk of fractures in breast cancer patients supplemented only with vitamin D and limited benefits for combination higher doses of vitamin D (>10 μg/day) with calcium (>1,000 mg) in noninstitutionalized individuals [433]. In a systematic review, results from trials point to insufficient calcium and vitamin D supplementation doses (i.e., 500–1,500 mg for calcium and 200–1,000 IU vitamin D) to prevent bone mineral density loss [189]. Vitamin D supplementation was associated with an improvement in bone loss if target serum levels of 30 ng/ml were achieved [194], but some negative results are also reported. Doses of 500–1,500 mg calcium and 200–1,000 IU vitamin D were not sufficient to prevent bone mineral loss [189]. Some of the studies reported associated calcium supplementation with the enhanced risk of cardiovascular disease, so future validated trials should be considered to evaluate the safety and efficacy of these regimens of supplementation in women undergoing breast cancer therapy. Another aspect to consider is the confounding factor in human trials. Deschaux et al. found that body mass index and alcohol consumption may modify the effect of vitamin D on breast cancer risk, which can be the reason for discrepant results between studies [159].

There are very few randomized placebo-controlled trials that proved the efficacy, safety, and optimum dosage of vitamin D and calcium supplementation for cancer patients. Rohan et al. found no benefit in the administration of daily use of 1000 mg of calcium carbonate and 400 IU of vitamin D3 for 7 years, in postmenopausal women and the risk of benign proliferative breast disease [143]. The same study concluded that daily doses used were not associated with a protective effect related to breast cancer risk [144].

Vitamin D deficiency has also been linked with increased toxicity from bisphosphonate therapy, which can provoke hypocalcaemia [434]. Currently, researchers investigate the need to supplement vitamin D and calcium simultaneously with bisphosphonate therapy [435]. In a double-blind, randomized, placebo-controlled study, Rhee et al. proved the efficacy of combined alendronate (5 mg) and calcitriol (0.5 μg) to prevent bone loss due to aromatase inhibitor in Korean postmenopausal women with early breast cancer.

Despite the huge data from experimental and observational studies, a better understanding of the biologic effect of vitamin D in breast tissue and a more careful clinical design will be useful for making recommendations for vitamin D supplementation among breast cancer prevention or treatment.

4.2.6. B Complex Vitamins. B complex vitamins include eight water-soluble vitamins: vitamin B1 (thiamine), vitamin B2 (riboflavin), vitamin B3 (niacin or niacinamide), vitamin B5 (pantothenic acid), vitamin B6 (pyridoxine), vitamin B7 (biotin), vitamin B9 (folic acid), and vitamin B12 (cobalamin; cyanocobalamin) [391]. Each B complex vitamin presents a specific function in the human organs. Some of them can be found naturally in unprocessed food (e.g., beans, meat, poultry, fish, eggs, milk, peas, select fruits, and vegetables) or fortified products (e.g., fortified cereals). Additionally, supplementation with complex B vitamins is also considered as an approach in the case of breast cancer patients or survivors, namely, folic acid [436]. These authors concluded that folic acid supplementation may promote the progression of established breast tumours.

Different conclusions were also reported in the literature related to the effect of B complex vitamins and the risk for breast cancer development [195–199, 201–203, 205–218, 437]. In different clinical studies, despite the fact that several authors verified that some vitamins of B complex (e.g., folate, vitamin B6, and vitamin B12) did not reduce the risk of developing breast cancer [202, 216, 437] even when stratified by hormone receptor status, other ones reported an association [195, 199, 208–213, 217]. For example, using data from the European Prospective Investigation into Cancer and Nutrition (EPIC), that is, a large prospective cohort study including 23 centres in 10 European countries [203], the plasma folate and vitamin B12 levels were not associated with the risk of breast cancer or by hormone receptor status [437]. Kim and colleagues indicated that high folate plasma concentrations may be associated with increased breast cancer risk among women with a BRCA1/2 mutation (i.e., tumour suppressor genes) [195]. In contrast with these results, a higher dietary folate intake may diminish breast cancer risk and
this association may differ by menopausal and sex hormone receptor status [213, 214]. In another based EPIC cohort study, the main conclusions were as follows: high vitamin B\textsubscript{12} plasma concentrations may reduce the breast cancer risk, particularly of estrogen receptor (+) breast cancer; high riboflavin plasma levels may reduce the breast cancer risk in premenopausal but not in postmenopausal women; and homocysteine and the other B vitamins do not seem to influence breast cancer risk [218]. In a large randomized, controlled trials, combined B vitamins daily supplementation (vitamin B\textsubscript{6}, 50 mg; vitamin B12, 1 mg; folate, 2.5 mg), administrated over a period of 7.3 years, had no significant effect on the cancer breast risk [196]. In different meta-analysis studies concerning folate plasmatic levels or folate (from diet and/or supplementation), the authors reported no association between folate intake and risk for developing breast cancer [215], and this did not vary by menopausal status or hormonal receptor status [197, 198]. In addition, some of these studies suggested that adequate ingestion of folate may have protective effects against breast cancer risk in women with moderate to high alcohol consumption level [215]. Zhang et al. also achieved similar conclusions; that is, folate intake had little or no effect on the risk of breast cancer; moreover, a dose-response meta-analysis suggested an association between folate intake and breast cancer risk; daily folate intake of 200–320 µg appeared to associate with a lower risk and a daily folate intake > 400 µg/d with an increased risk [205]. In a systematic review of clinical studies, Castillo and collaborators suggest a caution in women exposed to high folate intake during the folic acid fortification era, once some studies demonstrated a higher risk of this population for development breast cancer [201]. A weak relationship between the dietary vitamin B\textsubscript{2} intake and the reduction of breast cancer risk was also shown in another systematic review and meta-analysis study [207].

Some vitamins of the B complex can interact with one-carbon metabolizing genes which can have an important role in the breast cancer development [219–224]. For example, some case-control studies assessed the association between MTHFR (5,10-methylenetetrahydrofolate reductase) and MTR (methionine synthase) genotypes and breast cancer risk [219–224]. These enzymes are involved in the metabolism of folate and homocysteine and their deficiencies could explain some alterations during breast carcinogenesis. The results proved that some MTHFR (e.g., C667T and 2756GG genotypes) and MTR polymorphisms (e.g., 2756GG genotype) are associated with risk of development breast cancer in different populations [219, 221–224]. Despite the fact that several studies reported an influence of dietary specific B complex vitamins (e.g., folate, vitamin B6, and vitamin B12) intakes on these associations [221–224], some authors stated no association [219, 220, 223, 224]. Dietary methyl group donors such as some B complex vitamins could influence the hypermethylation status of certain genes. Pirouzpanah and colleagues showed that individual B vitamins can present different effects on promoter hypermethylation and methylation-related expression of retinoic acid receptor-beta (RARB) and breast cancer-1 (BRCA1) genes in Iranian patients with breast cancer [225]. Hypermethylation at promoters of RARB and BRCA1 is associated with reduced transcript levels of the respective gene in primary breast cancer tissue samples.

The folate also plays an important role in the regenerating methionine, the methyl donor for methylation, and in the DNA synthesis and repair and, consequently, in carcinogenesis process [438]. In a case-control study involving patients at a tertiary hospital in Uganda, the red blood cell folate levels were not associated with breast cancer risk [204].

Concerning the influence of folate in survival, a prospective cohort study reported that folate supplementation is unlikely to have a significant adverse effect on breast cancer survival among women treated with chemotherapy [200]. In another case-control study, the authors verified that higher dietary vitamins B\textsubscript{1} and B\textsubscript{2} intake as well as specific polymorphisms of one-carbon metabolizing genes were associated with improved breast cancer survival [226].

Some chemotheraphy often originates cutaneous side effects, namely, dry, itchy, and irritable skin due to nonspecific inhibition of the proliferative activity of keratinocytes. Based on the skin barrier stabilizing effect of vitamin B\textsubscript{3} (niacinamide), Wohlrab et al. [227] conducted a multicentre prospective randomized reference-controlled crossover study and proved the superiority of topical preparation containing niacinamide compared to standard care. The authors demonstrated the cytoprotective and barrier stabilizing effect of vitamin B3 and its prophylactic application for controlling the cutaneous symptoms and maintaining quality of life in breast cancer patients while undergoing cytostatic therapy.

4.3. Omega 3 Polyunsaturated Fatty Acids (PUFA). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are long-chain (n-3) polyunsaturated and highly peroxidizable fatty acids which are obtained mainly from marine sources. These supplements have important anti-inflammatory properties. Based on the results of preclinical and clinical studies, supplementation with omega 3 PUFA seems to be a promising approach among breast cancer patients. Food sources may be used with similar results [228]. Due to their nature, safety should not be a critical issue.

In a long-term prospective study, Brasky et al. showed an inverse association between the supplementation with omega-3 fatty acid and breast cancer risk [235]. This association depends on the type of fatty acids. For example, Pouchieu and colleagues [229] proved that specific plasma saturated, monounsaturated, and polyunsaturated fatty acids were differently associated with breast cancer risk. These authors reported that the total PUFAs were correlated with breast cancer risk only in the placebo group. Additionally, a modulation role of antioxidant agents in these associations via neutralizing the potential effects of these fatty acids on carcinogenesis was also suggested.

Different meta-analysis of epidemiological studies suggested that fish consumption and dietary fatty acids might be not associated with breast cancer risk [231–234]. Some authors proposed conducting well-designed prospective studies to explore the role of fish consumption/dietary fatty acids in relation to breast cancer risk [233]. However, Zheng et al. found an inverse relationship between dietary marine n-3 PUFA and breast cancer risk. The increment of dietary...
n-3 PUFA of 0.1 g/day may reduce breast cancer risk in 5% [238]. So, dietary oil fish intake or supplementation had a protective effect in breast cancer patients [236]. More pronounced preventive effects were found between omega 3 and postmenopausal women at risk [236, 237]. The populations who consume high levels of omega 3 and low levels of omega 6 showed a breast cancer risk reduction. In contrast to omega 3, omega 6 induces inflammation reactions [241]. In a meta-analysis, Yang et al. also demonstrated the negative association between the higher omega 3:omega 6 ratio intake and breast cancer risk [239]. Similar results were achieved by Murff and collaborators [240].

The protective effect of omega-3 fatty acids was put to the test in a pilot study of 35 postmenopausal women with cytological evidence of hyperplasia, with an intake of 1860 mg EPA + 1500 mg DHA ethyl esters daily for 6 months. A favourable decrease in several breast cancer biomarkers has indicated the need of further placebo-controlled clinical trials [243].

Patterson and collaborators did not associate EPA and DHA intake from fish oil supplements with breast cancer outcomes [230]. Sandhu et al. found an increased effect of protective omega-3 fatty acid supplementation in higher body mass index women [244].

To determine the dose of omega-3 fatty acids that reach the maximal target tissue effects in women at high risk of breast cancer, Yee et al. [242] suggested that doses up to 7.56 g of DHA and EPA (per day) were well tolerated with optimal compliance. A combination of omega 3 (4 g) and raloxifene (30 mg)—a breast cancer chemopreventive agent—was successful in reduction insulin-like growth factor (IGF-1) levels and omega 3 added the additional effects of improving serum lipids, antioxidant, and anti-inflammatory activities [245, 246].

EPA and DHA can increase the production of ROS in cancer cells, so they are being investigated as promising adjuvants of cancer treatment (e.g., chemotherapy; radiotherapy) to maximize the sensitivity of residual tumour cells to the therapy and maintain or (preferably) decrease the sensitivity on nontumour cells without any additional side effects [383, 439]. A phase II trial has proved the safety and feasibility benefits of omega 3 PUFA when supplemented together with chemotherapy. Bougnoux et al. [247] supplemented with DHA (1.8 g/day) metastatic breast cancer patients that were receiving anthracycline-based chemotherapy. Despite the limited number of patients (i.e., n = 25), the authors reported an increase disease-free survival and a longer time to progression in patients with high DHA incorporation into plasma phospholipids.

Considering the effects of EPA and DHA on cellular processes of bone turnover, these fatty oils may compensate aromatase inhibitors effects to bone and seems to be a promising approach in this clinical situation. Hutchins-Wiese et al. [248] supplemented postmenopausal breast cancer survivors with aromatase inhibitors with a high dose of DHA and EPA (4 g/daily for 3 months) and demonstrated that PUFA supplements can reduce bone resorption. Considering the short-term effects of fish oil supplementation, long-term studies are required.

5. Conclusions and Perspectives

Breast cancer is one of the most leading causes of cancer death among women. Women with a breast cancer history often resort to alternative and complementary therapies, mainly phytotherapeutic products and nutritional supplements, for the management of the typical symptoms and adverse effects of conventional cancer treatments. Although extensively used, these products are poorly regulated and can have either positive (e.g., synergetic effects) or negative (e.g., metabolic and drug interactions, diminishing the therapeutic benefits of conventional cancer treatments). There is a lack of high-quality scientific evidence for many of the most phytotherapeutic products and nutritional supplements and more clinical scientific evidences concerning the safety and efficacy are mandatory. Additionally, pharmacovigilance practices for these natural products are crucial to understanding the benefit, limitations, dosage regimen, and potential effects and how these modalities need to be modified during some periods.

Tables 1 and 2 summarize the main effects in the consulted clinical studies. Clinical studies were gathered accordingly to disease phase and main action. The ratio of trials versus nontrials included all the interventional clinical trials versus total of clinical studies.

Based on clinical study data, the following supplements can be used in the different phases of breast cancer history:

(i) Preventive Effects

Phytotherapeutic products: flaxseed; green tea.

Nutritional supplements: omega 3 polyunsaturated fatty acids (minimum daily dose of 2.5 g in women at high breast cancer risk).

(ii) During Conventional Treatments after Diagnosis

Phytotherapeutic products: U. tomentosa as an adjuvant treatment of FAC (Fluourouracil, Doxorubicin, and Cyclophosphamide) regimen in Invasive Ductal Carcinoma Stage II; Curcuma longa as coadjuvant in docetaxel therapy; green tea as adjuvant of radiotherapy; Viscum album in side effects, recurrence, and antitumour activity.

Nutritional supplements: vitamin C 500 mg + vitamin E 400 mg in side effects chemotherapy, vitamin D (necessary doses to target 30–50 ng/ml serum levels) + calcium, and vitamin D as adjuvant of aromatase inhibitor therapy; DHA as adjuvant in chemotherapy and side effects.

(iii) Posttreatment (i.e., Survival Period)

Phytotherapeutic products: Salvia sp. associated with Coriolus versicolor improves immunologic function.

Based on the current literature we concluded that well-designed clinical studies are needed to obtain high level of evidence to accomplish recommendation guidelines.
**Table 1:** The main clinical effects of the most common phytotherapeutic products used in breast cancer.

| Nutritional supplements | Disease phases | Trials versus nontrial | Main effects from clinical studies | Type of clinical study | Ref. |
|-------------------------|----------------|------------------------|-----------------------------------|-----------------------|------|
| **Echinacea spp.** | Risk | 0/1 | (i) Consumption not associated with increased risk for breast cancer | Prospective cohort | [30] |
| Treatment | 0/1 | (i) Consumption not induced pharmacokinetic parameters alterations of docetaxel | Case control | [40] |
| Prognostic | 0/2 | (i) Consumption associated with breast cancer survivors | Prospective cohort | [33, 34] |
| **Tabebuia impetiginosa** | | | | | |
| **Salvia spp.** | Prognostic | 1/1 | (i) Administration of *Salvia* extract (20 mg/Kg) and *Coriolus versicolor* (polysaccharopeptide 50 mg/Kg) promoted the immune function in posttreatment of breast cancer patients | Nonrandom clinical trial | [54] |
| Side effects | 1/1 | (i) Administration of *Salvia* extract (IV) reduced skin ischemia and necrosis after mastectomy with less side effects when compared to anisodamine drug | Random clinical trial | [55] |
| **Uncaria spp.** | Side effects | 1/1 | (i) Uncaria extract (300 mg/day) reduced the neutropenia caused by chemotherapy and restored cell DNA damage in patients with Invasive Ductal Carcinoma Stage II | Random clinical trial | [56] |
| **Allium sativum** | Risk | 0/1 | (i) High consumption of *Allium* may reduce the risk of breast cancer | Case control | [57] |
| Treatment | 1/1 | (i) Consumption does not affect the distribution of docetaxel. However, it can decrease docetaxel clearance in patients carrying a CYP3A5*1A allele | Nonrandom pilot clinical trial | [58] |
| **Linum usitatissimum** | Risk | 0/1 | (i) Dietary consumption associated with a reduction in breast cancer risk | Case control | [59] |
| Treatment | 3/3 | (ii) Dietary consumption of flaxseed (25 g) to healthy volunteers during one menstrual cycle does not affect the angiogenin and VEGF levels in normal breast tissue but increase the endostatin levels similar to tamoxifen | Random clinical trial | [60] |
| Prognostic | 0/1 | (iii) Flaxseed consumption does not affect the aromatase inhibitors activity | Random pilot clinical trial | [61] |
| **Curcuma longa** | | | (i) High consumption of enterolignans (sunflower, pumpkinseeds, sesame, and flaxseeds origin) may have a better impact in postmenopausal breast cancer patient survival | Cohort | [62] |
| | 1/1 | (i) Dose of 6 g/day of curcumin in combination with docetaxel (standard dose) demonstrated safe profile has a superior antitumour activity compared to docetaxel monotherapy | Nonrandom open-label clinical trial phase I | [63] |
| Nutritional supplements | Disease phases | Trials versus nontrial | Main effects from clinical studies | Type of clinical study | Ref. |
|-------------------------|----------------|------------------------|-----------------------------------|------------------------|-----|
| **Camellia sinensis**   | Risk          | 1/6                    | (i) High tea consumption had no significant effect on the risk of several cancers, including breast cancer (ii) Green tea consumption was not associated with breast cancer risk in Japanese women (iii) Regular green tea consumption can protect against breast cancer (iv) No association between plasma tea polyphenols and the risk of breast cancer in Japanese women (v) High epicatechin may be related to a reduced risk of breast cancer (vi) ECGC can prevent breast cancer by influencing the growth factor signalling, angiogenesis, and lipid metabolism mechanisms | Meta-analysis of prospective observational studies | [65] |
|                         | Polymorphism  | 0/3                    | (i) Genetic polymorphism can influence polyphenols green tea metabolism and excretion (ii) Men carrying low-activity associated COMT genotype may retain more tea polyphenols (iii) Green tea appeared to reduce breast cancer risk in Asian-American women with low-activity COMT alleles (iv) ECGC potentiated efficacy of radiotherapy in breast cancer patients | Nested case control | [71] |
|                         | Treatment     | 3/3                    | (i) Daily consumption of green tea (843 mg ECGC) is well tolerated by Caucasian postmenopausal women (ii) Green tea extract phytosomes increased ECGC bioavailability and decreased tumour circulating biomarker revealing antiproliferative effects on breast cancer tissue (iii) Consumption of 5 or more cups of green tea a day may prevent breast cancer recurrence in early-stage (I and II) cancers | Random double-blind placebo-controlled clinical trial | [75] |
|                         | Prognostic    | 0/1                    | (i) Consumption of ginseng among breast cancer survivors was not associated with quality of life improvement (ii) Regular consumption of ginseng 1.3 g/day may improve both overall and disease-free survival and enhance the quality life of Chinese women breast cancer survivors | Meta-analysis of observational studies | [77] |
| **Ginseng**             | Treatment     | 1/1                    | (i) Chinese herb formula including ginseng showed immunological improvement in breast cancer patients (ii) Consumption of ginseng among breast cancer survivors was not associated with quality of life improvement (iii) Regular consumption of ginseng 1.3 g/day may improve both overall and disease-free survival and enhance the quality life of Chinese women breast cancer survivors | Random clinical trial | [78] |
|                         | Prognostic    | 0/2                    | (i) Consumption of ginseng among breast cancer survivors was not associated with quality of life improvement (ii) Regular consumption of ginseng 1.3 g/day may improve both overall and disease-free survival and enhance the quality life of Chinese women breast cancer survivors | Cohort | [79] |
| Nutritional supplements | Disease phases | Trials versus nontrial | Main effects from clinical studies | Type of clinical study                                                                 | Ref.    |
|-------------------------|----------------|------------------------|-----------------------------------|---------------------------------------------------------------------------------------|---------|
| *Cimicifuga racemosa*   | Risk           | 0/1                    | (i) No relationship was found between black cohosh consumption and increased risk of breast cancer | Meta-analysis of interventional and observational studies                               | [81]    |
|                         | Prognostic     | 0/1                    | (i) Consumption can reduce risk of recurrence in patients taking tamoxifen             | Retrospective cohort study                                                            | [82]    |
| *Viscum album*          | Treatment      | 1/1                    | (i) Mistletoe extract was highly effective in the tumour regression of breast cancer   | Nonrandom pilot clinical trial                                                       | [83]    |
|                         |                |                        | (i) Mistletoe therapy associated with CAF (Cyclophosphamide, Doxorubicin, and 5-Fluorouracil) chemotherapy resulted in clinical improvements of life quality in breast cancer patients | Random open-label pilot clinical trial                                                | [84]    |
|                         |                |                        | (ii) *Viscum album* therapy during chemotherapy in the early-stage breast cancer patients increased the life quality, may prevent neutropenia, and did not influence the frequency of relapse or metastasis within 5 years | Prospective noninterventional follow-up study of a clinical trial                      | [85]    |
|                         | Side effects   | 2/5                    | (iii) Standardized aqueous mistletoe extracts therapy was well tolerated and reduced the side effects of chemotherapy, resulting in a significant stabilization of Health Related Quality of Life | Prospective cohort                                                                    | [86]    |
|                         |                |                        | (iv) Mistletoe intravenous administration (1 and 5 mg) during chemotherapy had no significant effect on granulocyte function but reduced chemotherapy-related side effects | Random clinical trial phase II                                                       | [87]    |
|                         |                |                        | (v) Standardized mistletoe extract therapy improved quality of life and significantly reduced side effects of the disease/treatment | Prospective cohort                                                                    | [88]    |

COMT: catechol-O-methyltransferase; VEGF: vascular endothelial growth factor.
Table 2: The main clinical effects of the most common nutritional supplements used in breast cancer.

| Nutritional supplements | Disease phases | Trials versus nontrials | Main effects from clinical studies                                                                 | Type of clinical study          | Ref. |
|-------------------------|----------------|------------------------|-----------------------------------------------------------------------------------------------------|--------------------------------|------|
| Multivitamins and antioxidants | Risk | 0/7 | (i) Supplementation of multivitamins and antioxidants in postmenopausal women may protect women from developing breast cancer  
(ii) High frequency and long duration multivitamins consumption was associated with an increase of breast cancer risk  
(iii) Multivitamins consumption was not associated with breast cancer risk  
(iv) Little inverse association between the use of multivitamins among white women and no evidence of reduced breast cancer risk among black women were reported  
(v) No association was verified between dietary intake of antioxidant vitamins and breast cancer risk  
(vi) Dietary intake of beta-carotene, vitamin C, and vitamin E was not related to breast cancer risk in pre- or postmenopausal women  
(vii) Dietary antioxidant was associated with a lower risk of breast cancer and reduced mortality rate  
(i) Use of multivitamins by postmenopausal women with invasive breast cancer had lower breast cancer mortality than nonusers  
(ii) Posttreatment use of antioxidant supplements was associated with an improved survival in breast cancer patients from the United States and China  
(iii) Consumption of multivitamins improved outcomes related to breast cancer recurrence and survival after two years after diagnosis  
(iv) Breast cancer survival was not improved by multivitamin treatment in nonmetastatic breast cancer diagnosed women | Case control  
Prospective cohort  
Prospective cohort  
Prospective cohort  
Prospective cohort  
Prospective cohort  
Meta-analysis of cohort studies  
Cohort  
Cohort | [104]  
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| Vitamin A and carotenoids | Risk | 0/7 | (i) No significant association was established between plasma retinol and vitamin A and breast cancer risk  
(ii) Plasma beta-carotene was inverse associated with overall cancer risk, including breast cancer  
(iii) High carotenoids consumption may reduce breast cancer risk in premenopausal but not in postmenopausal  
(iv) Dietary intake of lycopene, beta-carotene, and beta-cryptoxanthin was associated with a lower breast cancer risk among Chinese women. No association was found for alpha-carotene and lutein/zeaxanthin  
(v) Serum alpha-carotene and beta-carotene were inversely associated with breast cancer risk  
(vi) Dietary intake of alpha-carotene, beta-carotene, and lycopene are inversely associated with invasive breast cancers risk. No association was observed with the intake of lutein + zeaxanthin and beta-cryptoxanthin  
(vii) Higher concentrations of plasma beta-carotene and alpha-carotene were associated with a lower breast cancer risk | Meta-analysis of case-control studies  
Case control  
Case control  
Case control  
Prospective cohort  
Prospective cohort  
Nest case control  
Cohort | [115]  
[116]  
[117]  
[118]  
[119]  
[120]  
[121]  |
| Nutritional supplements | Disease phases | Trials versus nontrials | Main effects from clinical studies | Type of clinical study | Ref. |
|-------------------------|----------------|------------------------|----------------------------------|-----------------------|-----|
| Vitamin D and calcium   | Risk           | 2/41                   | (i) Vitamin D deficiency is highly prevalent in breast cancer patients | Cross-sectional analytical study | [135] |
|                         |                |                        | (ii) No association was observed between vitamin D supplementation and breast cancer risk in postmenopausal women | Meta-analysis of random clinical trials | [136] |
|                         |                |                        | (iii) No association was verified between vitamin D supplementation and breast cancer risk in young women | Case control | [137] |
|                         |                |                        | (iv) No association was established between vitamin D intake and breast cancer | Cohort | [138] |
|                         |                |                        | (v) Long-term calcium intake was not related to breast cancer risk | Case control | [139] |
|                         |                |                        | (vi) Calcium intake from several sources was not associated with breast cancer risk in Chinese women | Case control | [140] |
|                         |                |                        | (vii) No association was found between dietary intake of vitamin D and calcium and breast cancer risk | Case control | [141] |
|                         |                |                        | (viii) No association was reported between daily use of 1000 mg of calcium carbonate and 400 IU of vitamin D3 and benign proliferative breast disease risk | Placebo-controlled clinical trial | [142] |
|                         |                |                        | (ix) No association was verified between vitamin D3 serum levels and breast cancer | Cohort | [143] |
|                         |                |                        | (x) No association was established between vitamin D and calcium serum levels and breast cancer risk | Cohort | [144] |
|                         |                |                        | (xi) Serum calcium levels was not related to breast cancer in Asian population | Case control | [145] |
|                         |                |                        | (xii) Dairy products were not associated with breast cancer risk | Cohort | [146] |
|                         |                |                        | (xiii) UV light combined with dietary vitamin D intake was associated with a lower breast cancer risk in high latitudes | Case control | [147] |
|                         |                |                        | (xiv) Dietary vitamin D was associated with a decrease in breast cancer risk | Case control | [148] |
|                         |                |                        | (xv) Vitamin D supplements demonstrated a protective effect in breast cancer risk compared with nonuser Pakistani women | Meta-analysis of observational studies | [149] |
|                         |                |                        | (xvi) Vitamin D intake protects from breast cancer risk in premenopausal women | Case control | [150] |
|                         |                |                        | (xvii) Dietary vitamin D and calcium intakes were associated with a decrease in breast cancer risk | Case control | [151] |
|                         |                |                        | (xviii) Dietary vitamin D and calcium intakes were inversely related to breast cancer risk | Case control | [152] |
|                         |                |                        | (xix) Breast cancer risk presented an inverse relationship between vitamin D intake in premenopausal and calcium intake in postmenopausal women | Meta-analysis of observational studies | [153] |
|                         |                |                        | (xx) Higher plasma vitamin D3 was associated with a decreased breast cancer risk for women with a lower BMI; in higher alcohol intakes, lower levels of vitamin D3 are associated with an increase in breast cancer risk | Case control | [154] |
|                         |                |                        | (xxi) Serum vitamin D was associated with a decrease in breast cancer risk | Case control | [155] |
|                         |                |                        | (xxii) Daily intake of 600 mcg calcium + 400 IU vitamin D and 30 ng/ml of serum vitamin D adequate to lower breast cancer risk | Dose-response meta-analysis of observational studies | [156] |
|                         |                |                        | (xxiii) Higher plasma vitamin D and moderate physical activity are protective factor while family history and menopause are a risk factor | Case control | [157] |
|                         |                |                        | (xxiv) Serum vitamin D levels > 27 ng/ml may reduce breast cancer risk in postmenopausal women but not in premenopause | Dose-response meta-analysis of prospective studies | [158] |
|                         |                |                        | (xxv) Serum vitamin D levels may reduce breast cancer risk in premenopausal women and the opposite occurred in overweight postmenopausal women | Prospective cohort | [159] |
|                         |                |                        | (xxvi) Serum calcium and vitamin D3 levels were inversely associated with breast cancer risk | Meta-analysis of prospective studies | [160] |
|                         |                |                        | (xxvii) U-shape association between vitamin D plasma levels and breast cancer risk and inverse association with calcium serum levels were established | Case control | [161] |
|                         |                |                        | (xxviii) U-shape association was reported between vitamin D3 plasma levels and breast cancer risk and prognosis | Nested case control | [162] |
|                         |                |                        | (i) Presence of BB genotype of vitamin D receptor was associated with a significantly lower risk of advanced breast cancer | Case control | [163] |
|                         |                |                        | (ii) GC and vitamin D receptor gene polymorphism relationship with breast cancer may be altered by menopausal status and type of cancer | Case control | [164] |
|                         |                |                        | (iii) VDR polymorphism determines breast cancer risk | Case control | [165] |
| Nutritional supplements | Disease phases | Trials versus nontrials | Main effects from clinical studies | Type of clinical study | Ref. |
|-------------------------|---------------|------------------------|-----------------------------------|-----------------------|-----|
| Prognostic              |               |                        | (i) Vitamin D intake was not associated with breast cancer recurrence | Nested case control   | [179] |
|                         |               |                        | (ii) High calcium/magnesium ratio was related to an improved breast cancer survival | Cohort                | [180] |
|                         |               |                        | (iii) Breast cancer women with deficient vitamin D levels had an increased risk of recurrence and dead | Cohort                | [181] |
|                         |               |                        | (iv) Higher vitamin D serum levels may be associated with improved breast cancer survival but without statistical significance | Cohort                | [177] |
|                         |               |                        | (v) Lower serum vitamin D level was associated with aggressive subtypes of cancer | Case control          | [183] |
|                         |               |                        | (vi) Calcium serum levels was positively related to breast tumour aggressiveness | Prospective cohort    | [185] |
|                         |               |                        | (i) Daily dose 400 UI vitamin D for 1 year during and after chemotherapy was not sufficient to increase vitamin D deficiency in breast cancer | Random double-blind clinical trial phase III | [187] |
|                         |               |                        | (ii) No differences in aromatase inhibitors side effects were found between vitamin D3 daily doses of 600 UI and 4000 UI | Nonrandom clinical trial phase II | [188] |
|                         |               |                        | (iii) Daily 1000 IU of vitamin D3 and 1000 mg of calcium supplementation in breast cancer patients with bone metastasis reduced elevated parathyroid hormone levels but had no beneficial palliative or bone resorption | Systematic review of clinical trials | [189] |
|                         |               |                        | (iv) Doses of 500–1500 mg calcium and 200–1000 IU vitamin D were insufficient to prevent bone loss | Random placebo-controlled clinical trial | [190] |
|                         |               |                        | (v) Vitamin D supplementation (50,000 IU/week) may reduce side effects of aromatase inhibitors | | |
|                         |               |                        | (vi) Weekly dose of vitamin D reduced aromatase inhibitor side effects | | |
|                         |               |                        | (vii) Vitamin D3 and calcium supplementation (2000 IU/1000 mg and 4000 IU/1000 mg) increased serum vitamin D3 concentrations and improved arthralgia induced by aromatase inhibitors | Nonrandom clinical trial | [191] |
|                         |               |                        | (viii) Serum vitamin D3 target of 40 ng/ml reduced arthralgia related to aromatase inhibitors | Nonrandom clinical trial | [192] |
|                         |               |                        | (ix) Vitamin D supplementation may improve bone loss if target serum levels achieve 30 ng/ml | Nonrandom clinical trial | [193] |
|                         |               |                        | (x) Superior plasma folate levels may be associated with an increased breast cancer risk in women with a BRCA1/2 mutation | Propective Cohort Random, double-blind, placebo-controlled trial | [195] |
|                         |               |                        | (xi) Daily supplementation of folic acid (2.5 mg of folate), vitamin B₉ (50 mg), and vitamin B₁₂ (1 mg) had no effect on overall risk of total invasive cancer or breast cancer among women during the folic acid fortification era | Systematic review and meta-analysis of observational studies | [196] |
|                         |               |                        | (xii) Dietary folate intake has no significant effect on the breast cancer risk. Daily 220 µg increment in dietary folate intake was not associated with the risk of breast cancer | Meta-analysis of prospective and case-control studies | [197] |
|                         |               |                        | (xiii) Dietary folate intake and blood folate levels did not associate with breast cancer risk and this did not vary by menopausal status or hormonal receptor status | | |
|                         |               |                        | (xiv) Dietary folate intake and blood folate levels did not associate with breast cancer risk and this did not vary by menopausal status or hormonal receptor status | | |
|                         |               |                        | (xv) Weak evidence of an inverse relationship between breast cancer risk and riboflavin intake and a positive association with vitamin B₁₂ were established. No association varied by tumour hormone receptor status | Prospective cohort | [199] |
|                         |               |                        | (xvi) No evidence that high folate intakes (dietary and supplementation) before diagnosis adversely affect breast cancer survival after chemotherapy | Prospective cohort | [200] |
|                         |               |                        | (xvii) Scientific evidence does not support the hypothesis that higher dietary folate intakes reduce the risk for breast cancer | Systematic review of clinical studies | [201] |
|                         |               |                        | (xviii) Little or no association was reported between of plasma folate, pyridoxal 5-phosphate (i.e., the principal active form of vitamin B₆), and vitamin B₁₂ levels and breast cancer risk | Prospective cohort | [202] |
|                         |               |                        | (xix) Unclear association between plasma folate and vitamin B₁₂ levels and overall breast cancer risk | Propective cohort | [203] |
|                         |               |                        | (xx) The red blood cell folate levels were not associated with breast cancer risk | Case control | [204] |
|                         |               |                        | (xxi) Little or no association was shown between dietary folate intake and breast cancer risk; in addition, a dose-response meta-analysis suggested a J-shaped relationship between folate intake and breast cancer risk | Dose-response meta-analysis of prospective studies | [205] |
|                         |               |                        | (xxii) Dietary folate intake was not associated with breast cancer risk but may be inversely associated with ER-positive/PR-negative tumours in Swedish patients | Dose-response meta-analysis of prospective studies | [206] |
| Nutritional supplements | Disease phases | Trials versus nontrials | Main effects from clinical studies                                                                 | Type of clinical study                                                                 | Ref. |
|-------------------------|----------------|------------------------|---------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------|
|                         |                |                        | (xiii) Weak association was reported between dietary vitamin B<sub>2</sub> intake and reduced breast cancer risk | Systematic review and meta-analysis of epidemiologic studies                            | [207]|
|                         |                |                        | (xiv) Dietary folate and vitamin B<sub>6</sub> intakes were inversely associated with breast cancer risk by both ER and PR status in Chinese women | Case control                                                                        | [208]|
|                         |                |                        | (xv) High dietary vitamin B<sub>6</sub> intake is associated with a lower risk of developing ER-negative breast cancer in Taiwanese women | Case control                                                                        | [209]|
|                         |                |                        | (xvi) High dietary folate intake was associated with a lower incidence of postmenopausal breast cancer | Prospective cohort                                                                  | [210]|
|                         |                |                        | (xvii) High dietary folate intake was associated with a reduced breast cancer risk in French women. Vitamin B<sub>12</sub> intake may alter this association | Case control                                                                        | [211]|
|                         |                |                        | (xviii) Dietary folate intake was inversely associated with breast cancer risk. Dietary methionine, vitamin B<sub>12</sub>, and vitamin B<sub>6</sub> (i.e., folate cofactors) intakes were not independently related to risk of breast cancer; however, they may modify the effect of folate | Multicentered, population-based case control                                         | [212]|
|                         |                |                        | (xix) Higher dietary folate intake is slightly associated with a lower risk for ER-negative breast cancer, and high vitamin B<sub>12</sub> and methionine intakes are marginally associated with a lower risk of ER-positive breast cancer among Hispanic and non-Hispanic white women in the southwestern US | Case control                                                                        | [213]|
|                         |                |                        | (xx) High dietary folate intake may diminish breast cancer risk and this relationship may differ by menopausal and ER/PR status in Chinese patients | Nested case control                                                                 | [214]|
|                         |                |                        | (xxi) Adequate folate intake may reduce the increased breast cancer risk                              | Multicentered, population-based case control                                         | [215]|
|                         |                |                        | (xxii) Inverse association was verified between plasma folate levels and breast cancer risk was highly among women consuming at least 15 g/day of alcohol. Plasma vitamin B<sub>12</sub> levels were inversely associated with breast cancer risk among premenopausal women but not among postmenopausal women. Plasma homocysteine levels was not associated with breast cancer risk | Nested case control                                                                 | [216]|
|                         |                |                        | (xxiii) Serum pyridoxal 5-phosphate (i.e., the principal active form of vitamin B<sub>6</sub>) levels and dietary methionine intakes are associated with a reduced breast cancer risk, especially in postmenopausal women | Dose-response meta-analysis                                                           | [217]|
|                         |                |                        | (xxiv) High plasma vitamin B<sub>6</sub> levels may diminish the breast cancer risk, particularly of ER-positive breast cancer; high plasma riboflavin levels may decrease the risk of breast cancer in premenopausal but not postmenopausal women; and plasma homocysteine and the other B vitamins (e.g., folate and vitamin B<sub>12</sub>) levels do not appear to influence breast cancer risk | Nested case control                                                                 | [218]|
|                         |                |                        | (i) Association between MTHFR C667T polymorphism and breast cancer risk and no association between dietary folate intake and MTHFR T677TT polymorphisms were established | Case control                                                                        | [219]|
|                         |                |                        | (ii) Neither dietary folate and related B vitamins intakes nor MTHFR or MTR genotypes were overall associated with breast cancer risk in Japanese women. Associations of nutrients with breast cancer risk did not differ by hormone receptors status | Case control                                                                        | [220]|
|                         |                |                        | (iii) Association was observed between MTHFR C677T and MTR A2756G polymorphisms and breast cancer risk. Dietary folate, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub> intakes influence these associations | Case control                                                                        | [221]|
| Polymorphism            | 0/7            |                        | (iv) Significant association was observed between MTHFR C667T polymorphism, dietary folate, and vitamin B<sub>6</sub> intake and breast cancer risk and an interaction between MTHFR C667T polymorphism and folate intake on the breast cancer risk | Case control                                                                        | [222]|
|                         |                |                        | (v) Vitamin B<sub>12</sub> seems to reduce the risk of breast cancer, and MTHFR 667TT was associated with an increased breast cancer risk. Folate and vitamin B<sub>12</sub> intakes and MTHFR C677T and MTHFR A1298C polymorphisms showed no association with breast cancer risk. THFR C667T genotype and low vitamin B<sub>6</sub> intake are associated with an increased breast cancer risk among Chinese population | Case control                                                                        | [223]|
|                         |                |                        | (vi) Neither dietary folate, vitamin B<sub>6</sub>, or vitamin B<sub>12</sub> intakes nor MTHFR polymorphisms were independently associated with breast cancer risk. Increased breast cancer risk was observed in MTR 2756GG genotype and in premenopausal women with high folate intake among Brazilian women | Case control                                                                        | [224]|
|                         |                |                        | (vii) Dietary folate and cobalamin intakes are inversely associated with methylated retinoic acid receptor-beta (RARB) and breast cancer 1 (BRCA1) genes. High dietary riboflavin and pyridoxine intakes are associated with increased methylation in the RARB promoter in Iranian patients | Prospective cohort                                                                  | [225]|
| Prognostic              |                |                        | (i) Dietary vitamins B<sub>12</sub> and B<sub>6</sub> intake was associated with improved survival among women with breast cancer. MTHFR 677TT polymorphism reduced all-cause mortality and breast cancer specific mortality | Cohort                                                                              | [226]|
|                         |                |                        | (ii) Superior prophylactic effect of niacinamide compared to standard care for avoiding cutaneous symptoms and maintaining life quality of breast cancer patients while undergoing cytostatic treatment | Multicentre randomized crossover trial                                              | [227]|
| Nutritional supplements | Disease phases | Trials versus nontrials | Main effects from clinical studies                                                                                                                                                                                                 | Type of clinical study | Ref. |
|------------------------|---------------|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------|
| Omega 3 PUFAs          | Risk 4/16     |                        | (i) Comparable doses of marine ω-3 in dietary fish or in supplement provided increased plasma EPA and DHA in plasma, erythrocyte membranes, and breast adipose in women with a high risk of breast cancer. Increases in breast adipose EPA and DHA were the same for both groups.  
(ii) Total PUFAs were associated with increased overall breast cancer risk in the placebo group, whereas this relationship was not observed in the antioxidant-supplemented group (antioxidants preserve essential PUFAs from peroxidation).  
(iii) No association was observed between EPA and DHA intake from fish oil supplements and breast cancer outcomes. Marine fatty acids from food reduced risk of additional breast cancer events and all-cause mortality in breast cancer survivors.  
(iv) No association was established between dietary total fat and fatty acids, including ω-3 PUFAs and breast cancer risk.  
(v) No association was reported between total or individual marine n-3 PUFA in adipose tissue and breast cancer risk.  
(vi) No association was observed between fish consumption and breast cancer risk.  
(vii) Current use of fish oil may be inversely associated with ductal breast cancer risk in postmenopausal women.  
(viii) Fish oil consumption had a protective effect in breast cancer.  
(ix) Omega 3 PUFAs presented a preventive action in postmenopausal women.  
(x) Inverse relationship was established between dietary marine n-3 PUFA and breast cancer risk.  
(x) Higher omega 3:omega 6 ratio intake and breast cancer risk had an inverse association.  
(xii) Consumption of high levels of ω-3 and low levels of ω-6 had a reduced breast cancer risk, compared to women who consume low levels of ω-3 and high levels of ω-6 among Long Island, New York, residents.  
(xiii) A minimum daily dose of 2.52 g EPA + DHA is required to increase their concentrations in breast adipose tissue. Daily doses up to 7.56 g of DHA and EPA were well tolerated with optimal compliance. BMI and baseline fatty acid concentrations modulated the dose-response outcomes of ω-3 PUFAs supplements on serum EPA and DHA and breast adipose tissue DHA in women at high risk of breast cancer.  
(xiv) Primary prevention trial of high dose EPA and DHA ethyl esters at a daily dose of 3.36 g (1860 mg EPA +1500 mg DHA) resulted in a good uptake, excellent tolerability, and retention in postmenopausal women. Increase ω-3 PUFAs (EPA+DHA): ω-6 AA ratio in erythrocyte and benign breast tissue phospholipids provided a favourable modulation in several biomarkers of breast cancer risk and inflammatory process.  
(xv) Increase in plasma DHA was associated with a decrease in absolute breast density (i.e., a validated biomarker of breast cancer risk) but only in obese women (BMI > 29). | Random clinical trial | [228] |
|                        |               |                        | Nested case control | [229] |
|                        |               |                        | Cohort | [230] |
|                        |               |                        | Meta-analysis of prospective cohort studies | [231] |
|                        |               |                        | Case cohort | [232] |
|                        |               |                        | Meta-analysis of observational studies | [233] |
|                        |               |                        | Prospective cohort | [234] |
|                        |               |                        | Case control | [235] |
|                        |               |                        | Case control | [236] |
|                        |               |                        | Cohort | [237] |
|                        |               |                        | Meta-analysis and systematic review of prospective cohort studies | [238] |
|                        |               |                        | Meta-analysis of prospective studies | [239] |
|                        |               |                        | Prospective cohort | [240] |
|                        |               |                        | Case control | [241] |
|                        |               |                        | Random open-label dose-finding study | [242] |
|                        |               |                        | Phase II pilot study | [243] |
|                        |               |                        | Open-label random clinical trial | [244] |
Table 2: Continued.

| Nutritional supplements | Disease phases | Trials versus nontrials | Main effects from clinical studies | Type of clinical study | Ref. |
|-------------------------|----------------|-------------------------|------------------------------------|------------------------|------|
| Treatment 3/3           | (i) Combination of omega 3 (4 g) and raloxifene (30 mg) reduced IGF-1 levels and improved serum lipids, antioxidant, and anti-inflammatory activities | Random controlled placebo clinical trial | [245, 246] |
|                         | (ii) Combination of DHA to an ROS-generating chemotherapy regime was safe and retained significant antitumour activity in metastatic breast cancer patients with high plasma DHA incorporation | Pilot open-label single-arm phase II clinical trial | [247] |
|                         | (iii) High dose EPA and DHA supplementation (4 g/day) for 3 months increased serum EPA and DHA levels and total and long-chain ω-3 PUFAs and decreased arachidonic acid, total and long-chain ω-6 PUFAs, and the ω-6: ω-3 PUFAs ratio compared to placebo. This dose also reduced bone resorption | Random, double-blind, placebo-controlled pilot study | [248] |

AA: arachidonic acid; BMI: body mass index; BRCA1: breast cancer-1 gene; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; ER: oestrogen receptor; GC: gene encoding vitamin D binding protein; IGF-1: insulin-like growth factor; IV: intravenous; MTHFR: 5,10-methylenetetrahydrofolate reductase; MTR: methionine synthase; PR: progesterone receptor; PUFAs: polyunsaturated fatty acids; RARB: retinoic acid receptor-beta gene; VDR: vitamin D receptor.
Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

References

[1] P. M. Sowa, M. J. Downes, and L. G. Gordon, “RETRACTED ARTICLE: Cost-effectiveness of dual energy X-ray absorptiometry (DXA) plus anti-resorptive treatment in Australian women with breast cancer who receive aromatase inhibitors,” Journal of Bone and Mineral Metabolism, vol. 34, no. 2, p. 242, 2016.

[2] A. Soliman, S. Samadi, M. Banerjee, and Z. Aziz, “Brief Continuing Medical Education (CME) module raises knowledge of developing country physicians,” The International Electronic Journal of Health Education, vol. 9, pp. 31–41, 2006.

[3] R. E. Rossi, M. Pericleous, D. Mandaar, T. Whyand, and M. E. Caplin, “The role of dietary factors in prevention and progression of breast cancer,” Anticancer Research, vol. 34, no. 12, pp. 6861–6875, 2014.

[4] WHO, World Health Organization: Breast Cancer: Prevention and Control, 2017, http://www.who.int/cancer/detection/breast-cancer/en/index1.html.

[5] N. K. Lina, “Knowledge about breast cancer and negative influences affecting breast cancer screening among women in Jordan,” IJHSS, vol. 2, pp. 1–11, 2012.

[6] H. S. Boon, F. Olatunde, and S. M. Zick, “Trends in complementary/alternative medicine use by breast cancer survivors: Comparing survey data from 1998 and 2005,” BMC Women’s Health, vol. 7, article 4, 2007.

[7] T. Nagykalnai, L. Landherr, and A. C. Nagy, “Vitamin D and breast cancer,” Orvosi Hetilap, vol. 155, no. 28, pp. 1091–1096, 2014.

[8] C. Alliance, The Regulatory Status of Complementary and Alternative Medicine for Medical Doctors in Europe, 2015, http://www.camdoc.eu/Pdf/CAMDOCRegulatoryStatus8_10.pdf.

[9] L. T. Nguyen, R. B. Davis, T. J. Kapchuk, and R. S. Phillips, “Use of complementary and alternative medicine and self-rated health status: results from a national survey,” Journal of General Internal Medicine, vol. 26, no. 4, pp. 399–404, 2011.

[10] J. Saquib, L. Madlensky, S. Kealey et al., “Classification of CAM use and its correlates in patients with early-stage breast cancer,” Integrative Cancer Therapies, vol. 10, no. 2, pp. 138–147, 2011.

[11] J. A. Bennett, L. D. Cameron, L. C. Whitehead, and D. Porter, “Differences between older and younger cancer survivors in seeking cancer information and using complementary/alternative medicine,” Journal of General Internal Medicine, vol. 24, no. 10, pp. 1089–1094, 2009.

[12] A. Wanchai, J. M. Armer, and B. R. Stewart, “Complementary and alternative medicine use among women with breast cancer: a systematic review,” Clinical Journal of Oncology Nursing, vol. 14, no. 4, pp. E45–E55, 2010.

[13] National Center for Complementary and Integrative Medicine (NCCIM), Complementary, Alternative, or Integrative Health: What’s in a Name?, 2015, https://nccih.nih.gov/health/integrative-health.

[14] National Cancer Institute (NCI), Thinking about Complementary and Alternative Medicine: A Guide for People with Cancer, 2015, http://www.cancer.gov/publications/patient-education/367NCINewV2.pdf.

[15] G. Dobos and I. Tao, “The model of Western integrative medicine: the role of Chinese medicine,” Chinese Journal of Integrative Medicine, vol. 17, no. 1, pp. 11–20, 2011.

[16] G. J. Dobos, P. Voiss, I. Schwidde et al., “Integrative oncology for breast cancer patients: Introduction of an expert-based model,” BMC Cancer, vol. 12, article no. 539, 2012.

[17] M. Horneber, G. Bueschel, G. Dennert, D. Less, E. Ritter, and M. Zwhalen, “How many cancer patients use complementary and alternative medicine: a systematic review and metaanalysis,” Integrative Cancer Therapies, vol. 11, no. 3, pp. 187–203, 2012.

[18] O. Micke, F. Bruns, M. Glatzel et al., “Predictive factors for the use of complementary and alternative medicine (CAM) in radiation oncology,” European Journal Integrative Medicine, vol. 1, no. 1, pp. 19–25, 2009.

[19] M. Vidal, C. Carvalho, and R. Bispo, “Use of complementary and alternative medicine in a sample of women with breast cancer,” SAGE Open, pp. 1–4, 2013.

[20] T. Gansler, C. Kaw, C. Cramer, and T. Smith, “A population-based study of prevalence of complementary methods use by cancer survivors: A report from the American cancer society’s studies of cancer survivors,” Cancer, vol. 113, no. 5, pp. 1048–1057, 2008.

[21] V. S. Eschiti, “Lesson from comparison of CAM use by women with female-specific cancers to others: It’s time to focus on interaction risks with CAM therapies,” Integrative Cancer Therapies, vol. 6, no. 4, pp. 313–344, 2007.

[22] J. A. Astin, C. Reilly, C. Perkins, and W. L. Child, “Breast cancer patients’ perspectives on and use of complementary and alternative medicine: a study by the Susan G. Komen Breast Cancer Foundation,” Journal of the Society for Integrative Oncology, vol. 4, no. 4, pp. 157–169, 2006.

[23] N. Tung, “What is the optimal endocrine therapy for postmenopausal women with hormone receptor-positive early breast cancer?” Journal of Clinical Oncology, vol. 31, no. 11, pp. 1391–1397, 2013.

[24] A. Molassiotis, P. Fernandez-Ortega, D. Pud et al., “Use of complementary and alternative medicine in cancer patients: a European survey,” Annals of Oncology, vol. 16, no. 4, pp. 655–663, 2005.

[25] T. Kremser, A. Evans, A. Moore et al., “Use of complementary therapies by Australian women with breast cancer,” The Breast, vol. 17, no. 4, pp. 387–394, 2008.

[26] J. Saquib, C. L. Rock, L. Natarajan et al., “Dietary intake, supplement use, and survival among women diagnosed with early-stage breast cancer,” Nutrition and Cancer, vol. 63, no. 3, pp. 327–333, 2011.

[27] Z. Hu, X. Yang, P. C. L. Ho et al., “Herb-drug interactions: a literature review,” Drugs, vol. 65, no. 9, pp. 1239–1282, 2005.

[28] G. A. Saxe, L. Madlensky, S. Kealey, D. P. H. Wu, K. L. Freeman, and J. P. Pierce, “Disclosure to physicians of CAM use by breast cancer patients: Findings from the women’s healthy eating and living study,” Integrative Cancer Therapies, vol. 7, no. 3, pp. 122–129, 2008.

[29] A. Cassidy, “Are herbal remedies and dietary supplements safe and effective for breast cancer patients?” Breast Cancer Research, vol. 5, no. 6, pp. 300–302, 2003.

[30] H. Ma, C. L. Carpenter, J. Sullivan-Halley, and L. Bernstein, “The roles of herbal remedies in survival and quality of life among long-term breast cancer survivors - results of a prospective study,” BMC Cancer, vol. 11, article no. 222, 2011.
[31] Z. O. Omogbadegun, "Medicinal plants-based foods for breast cancer treatment: an ethnobotanical survey and digitization," *International Journal of Medicinal Plants and Alternative Medicine*, vol. 1, pp. 137–163, 2013.

[32] M. J. Wargovich, C. Woods, D. M. Hollis, and M. E. Zander, "Herbal, cancer prevention and health," *Journal of Nutrition*, vol. 131, no. 11, pp. 3034S–3036S, 2001.

[33] J. S. McClay, D. Stewart, J. George, C. Rore, and S. D. Heys, "Complementary and alternative medicines use by Scottish women with breast cancer: What, why and the potential for drug interactions?" *European Journal of Clinical Pharmacology*, vol. 68, no. 5, pp. S81–S89, 2012.

[34] A. K. L. Goey, I. Meijerman, H. Rosing et al., "Use of multivitamins, folic acid and herbal supplements among breast cancer survivors: The black women’s health study." *BMC Complementary and Alternative Medicine*, vol. 11, article no. 30, 2011.

[35] W. J. Craig, "Health-promoting properties of common herbs," *Am J Clin Nutr*, vol. 70, 3, pp. 491S–499S, 1999.

[36] S. N. Driggs, E. L. Myles, and T. Gary, "The anti-prolific effect of Echinacea Pallida on BT-549 cancer cell line," *Proc Amer Assoc Cancer Res*, vol. 45, 2004.

[37] E. D. Huntimer, F. T. Halaweh, and C. C. L. Chase, "Proliferative activity of Echinacea angustifolia root extracts on cancer cells: Interference with doxorubicin cytotoxicity," *Chemistry and Biodiversity*, vol. 3, no. 6, pp. 695–703, 2006.

[38] M. Modarai, I. Gertsch, A. Suter, M. Heinrich, and A. Kortenkamp, "Cytotoxicity of P450 inhibitory action of Echinacea preparations differs widely and co-varies with alkylamide content," *Journal of Pharmacy and Pharmacology*, vol. 59, no. 4, pp. 567–573, 2007.

[39] S. R. Penzak, S. M. Robertson, J. D. Hunt et al., "Echinacea purpurea significantly induces cytotoxic P450 3A activity but does not alter Lopinar-Ritonavir exposure in healthy subjects," *Pharmacotherapy*, vol. 30, no. 8, pp. 797–805, 2010.

[40] A. K. L. Goey, I. Meijerman, H. Rosing et al., "The effect of echinacea purpurea on the pharmacokinetics of docetaxel," *British Journal of Clinical Pharmacology*, vol. 76, no. 3, pp. 467–474, 2013.

[41] CAM-CANCER, *Echinacea spp*, 2015, http://www.cam-cancer.org/CAM-Summaries/Herbal-products/Echinacea-spp/Does-it-work.

[42] J. T. Giles, C. T. Palat III, S. H. Chien, Z. G. Chang, and D. T. Kennedy, "Evaluation of echinacea for treatment of the common cold," *Pharmacotherapy*, vol. 20, no. 6 1, pp. 690–697, 2000.

[43] S. E. Edwards, I. C. Rocha, E. M. Williamson, and M. Heinrich, *Phytopharmacy: An Evidence-Based Guide to Herbal Medicinal Products*, John Wiley & Sons, 2015.

[44] B. Mukherjee, N. Telang, and G. Y. C. Wong, "Growth inhibition of estrogen receptor positive human breast cancer cells by Taheebo from the inner bark of Tabebuia avellandae tree," *International Journal of Molecular Medicine*, vol. 24, no. 2, pp. 253–260, 2009.

[45] J. J. Pink, S. Wierzerberger-Davis, C. Tagliarino et al., "Activation of a cysteine protease in MCF-7 and T47D breast cancer cells during β-lapachone-mediated apoptosis," *Experimental Cell Research*, vol. 255, no. 2, pp. 144–155, 2000.

[46] J. R. Gómez Castellanos, J. M. Prieto, and M. Heinrich, "Red Lapacho (Tabebuia impetiginosa)—a global ethnopharmacological commodity?" *Journal of Ethnopharmacology*, vol. 121, no. 1, pp. 1–13, 2009.

[47] K. J. Ahn, H. S. Lee, S. K. Bai, and C. W. Song, "Enhancement of radiation effect using beta-lapachone and underlying mechanism," *Radiation Oncology Journal*, vol. 31, no. 2, pp. 57–65, 2013.

[48] C. Tagliarino, J. J. Pink, G. R. Dubyak, A.-L. Nieminenll, and D. A. Boothman, "Calcium Is a Key Signaling Molecule in β-Lapachone-mediated Cell Death," *Journal of Biological Chemistry*, vol. 276, no. 22, pp. 19150–19159, 2001.

[49] M.-T. Lin, C.-C. Chang, S.-T. Chen et al., "Cyr61 expression confers resistance to apoptosis in breast cancer MCF-7 cells by a mechanism of NF-κB-dependent XIAP up-regulation," *Journal of Biological Chemistry*, vol. 279, no. 23, pp. 24015–24023, 2004.

[50] H. J. Park, K.-J. Ahn, S.-D. Ahn et al., "Susceptibility of cancer cells to beta-lapachone is enhanced by ionizing radiation," *International Journal of Radiation Oncology*, *Biology, Physics*, vol. 61, no. 1, pp. 212–219, 2005.

[51] E. A. Bey, K. E. Reinicke, M. C. Srougi et al., "Catalase abrogates β-lapachone-induced PARP1 hyperactivation-directed programmed necrosis in NQO1-positive breast cancers," *Molecular Cancer Therapeutics*, vol. 12, no. 10, pp. 2110–2120, 2013.

[52] H. Kung, K. S. Lu, and Y. P. Chau, "The chemotherapeutic effects of lapacho tree extract: β-lapachone," *Chemotherapy*, vol. 3, no. 2, pp. 131–135, 2014.

[53] O. A. Lemos, J. C. M. Sanches, I. E. F. Silva et al., "Genotoxic effects of Tabebuia impetignosa (Mart. Ex DC.) Standl. (Lamiales, Bignoniaceae) extract in Wistar rats," *Genetics and Molecular Biology*, vol. 35, no. 2, pp. 498–502, 2012.

[54] C. K. Wong, Y. X. Bao, E. L. Wong, P. C. Leung, K. P. Fung, and C. W. Lam, "Immumomodulatory activities of Yunzhi and Danshen in post-treatment breastcancer patients," *The American Journal of Chinese Medicine*, vol. 33, no. 3, pp. 381–395, 2005.

[55] J. Chen, Q. Lv, M. Yu, X. Zhang, and J. Gou, "Randomized clinical trial of Chinese herbal medications to reduce wound complications after mastectomy for breast carcinoma," *British Journal of Surgery*, vol. 97, no. 12, pp. 1798–1804, 2010.

[56] C. Santos Araujo Mdo, I. L. Farias, J. Gutierres et al., "Uncaria tomentosa—adjuvant treatment for breast cancer: clinical trial," *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, Article ID 676984, 8 pages, 2012.

[57] A. Pourzand, A. Tajaddini, S. Pirouzpanah et al., "Associations between dietary alliumvegetables and risk of breast cancer: A hospital-based matched case-control study," *Journal of Breast Cancer*, vol. 19, no. 3, pp. 292–300, 2016.

[58] M. C. Cox, J. Low, J. Lee et al., "Influence of garlic (Allium sativum) on the pharmacokinetics of docetaxel," *Clinical Cancer Research*, vol. 12, no. 15, pp. 4636–4640, 2006.

[59] E. C. Lowcock, M. Cotterchio, and B. A. Boucher, "Consumption of flaxseed, a rich source of lignans, is associated with reduced breast cancer risk," *Cancer Causes and Control*, vol. 24, no. 4, pp. 813–816, 2013.

[60] G. Lindahl, N. Saarinen, A. Abrahamsson, and C. Dabrosin, "Tamoxifen, flaxseed, and the lignan enterolactone increase stroma- and cancer cell-derived IL-1Ra and decrease tumor angiogenesis in estrogen-dependent breast cancer," *Cancer Research*, vol. 71, no. 1, pp. 51–60, 2011.

[61] U. W. Nilsson˚Aberg, N. Saarinen, A. Abrahamsson, T. Nurmi, S. Engblom, and C. Dabrosin, "Tamoxifen and flaxseed alter angiogenesis regulators in normal human breast tissue in vivo," *PLoS ONE*, vol. 6, no. 9, Article ID e25720, 2011.

[62] S. E. McCann, S. B. Edge, D. G. Hicks et al., "A pilot study comparing the effect of flaxseed, aromatase inhibitor, and the combination on breast tumor biomarkers," *Nutrition and Cancer*, vol. 66, no. 4, pp. 566–575, 2014.
[92] W. Yang, J.-H. Ju, M. J. Jeon, X. Han, and I. Shin, "Danshen (Salvia miltiorrhiza) extract inhibits proliferation of breast cancer cells via modulation of akt activity and p27 level," *Phytotherapy Research*, vol. 24, no. 2, pp. 198–204, 2010.

[93] J. Baselga, E. A. Perez, T. Pienkowski, and R. Bell, "Adjuvant trastuzumab: A milestone in the treatment of HER-2-positive early breast cancer," *Oncologist*, vol. 11, no. 1, pp. 4–12, 2006.

[94] M. Dowsett, "Overexpression of HER-2 as a resistance mechanism to hormonal therapy for breast cancer," *Endocrine-Related Cancer*, vol. 8, no. 3, pp. 191–195, 2001.

[95] X. Wang, J. Cai, S. Chen, W. Zhang et al., "Salvianolic acid A reverses J. M. Meulepas, P. A. Newcomb, A. N. Burnett-Hartman, J. M. P. G. Moorman, M. F. Ricciuti, R. C. Millikan, and B. Newman, "Vitamin supplement use and breast cancer risk in a North Carolina population," *Public Health Nutrition*, vol. 4, no. 3, pp. 821–827, 2001.

[96] C. Wang, R. N. Baumgartner, D. Yang et al., "No evidence of association between breast cancer risk and dietary carotenoids, retinols, vitamin C and tocopherols in Southwestern Hispanic and non-hispanic white women," *Breast Cancer Research and Treatment*, vol. 114, no. 1, pp. 137–145, 2009.

[97] G. Nagel, J. Linseisen, C. H. van Gils et al., "Dietary beta-carotene, vitamin C and E intake and breast cancer risk in the European prospective investigation into cancer and nutrition (EPIC)," *Breast Cancer Research and Treatment*, vol. 119, pp. 753–765, 2010.

[98] A. Pantavos, R. Ruiter, E. F. Feskens et al., "Total dietary antioxidant capacity, individual antioxidant intake and breast cancer risk: The Rotterdam study," *International Journal of Cancer*, vol. 136, no. 9, pp. 2178–2186, 2015.

[99] S. Wassethiel-Smith, A. P. McGinn, N. Budrys et al., "Multivitamin and mineral use and breast cancer mortality in older women with invasive breast cancer in the women’s health initiative," *Breast Cancer Research and Treatment*, vol. 141, no. 3, pp. 495–505, 2013.

[100] E. M. Poole, X. Shu, B. J. Caan et al., "Postdiagnosis supplement use and breast cancer prognosis in the after Breast Cancer Pooling Project," *Breast Cancer Research and Treatment*, vol. 139, no. 2, pp. 529–537, 2013.

[101] M. L. Kwan, H. Greenlee, V. S. Lee et al., "Multivitamin use and breast cancer outcomes in women with early-stage breast cancer: The life after cancer epidemiology study," *Breast Cancer Research and Treatment*, vol. 130, no. 1, pp. 195–205, 2011.

[102] M. L. Lesperance, I. A. Olivotto, N. Forde et al., "Mega-dose vitamins and minerals in the treatment of non-metastatic breast cancer: an historical cohort study," *Breast Cancer Research and Treatment*, vol. 76, no. 2, pp. 137–143, 2002.

[103] F. Hu, Z. Wu, G. Li et al., "The plasma level of retinol, vitamins A, C, and β-carotene could reduce breast cancer risk? A meta-analysis and meta-regression," *Journal of Cancer Research and Clinical Oncology*, vol. 141, no. 4, pp. 601–614, 2015.

[104] C. Pouchieu, P. Galan, V. Ducros, P. Latino-Martel, S. Hercberg, and M. Touvier, "Plasma carotenoids and retinol and overall and breast cancer risk: a nested case-control study," *Nutrition and Cancer*, vol. 66, no. 6, pp. 980–988, 2014.

[105] L. I. Mignone, E. Giovannucci, P. A. Newcomb et al., "Dietary carotenoids and the risk of invasive breast cancer," *International Journal of Cancer*, vol. 124, no. 12, pp. 2929–2937, 2009.

[106] J. P. Huang, M. Jain, A. B. Miller, G. R. Howe, and T. E. Rohan, "Dietary carotenoids and risk of breast cancer in Chinese women," *Asia Pacific Journal of Clinical Nutrition*, vol. 16, pp. 437–442, 2007.

[107] G. C. Kabat, M. Kim, L. L. Adams-Campbell et al., "Longitudinal study of serum carotenoid, retinol, and tocopherol concentrations in relation to breast cancer risk among postmenopausal women," *American Journal of Clinical Nutrition*, vol. 90, no. 1, pp. 162–169, 2009.

[108] Y. Cui, J. M. Shikany, S. Liu, Y. Shagufa, and T. E. Rohan, "Selected antioxidants and risk of hormone receptor-defined invasive breast cancers among postmenopausal women in the women’s health initiative observational study," *The American Journal of Clinical Nutrition*, vol. 87, no. 4, pp. 1009–1018, 2008.

[109] M. F. Bakker, P. H. Peeters, V. M. Klaassen et al., "Plasma carotenoids, vitamin C, tocopherols, and retinol and the risk of breast cancer in the European prospective investigation into
cancer and nutrition cohort,” *The American Journal of Clinical Nutrition*, vol. 103, no. 2, pp. 454–464, 2016.

[122] C. L. Rock, L. Natarajan, M. Pu et al., “Longitudinal biological exposure to carotenoids is associated with breast cancer-free survival in the women’s healthy eating and living study,” *Cancer Epidemiology Biomarkers and Prevention*, vol. 18, no. 2, pp. 486–494, 2009.

[123] J. Hutchinson, V. J. Burley, D. C. Greenwood, J. D. Thomas, and J. E. Cade, “High-dose vitamin C supplement use is associated with self-reported histories of breast cancer and other illnesses in the UK Women’s Cohort Study,” *Public Health Nutrition*, vol. 14, no. 5, pp. 768–777, 2010.

[124] C. Cadeau, A. Fournier, S. Mesrine, F. Clavel-Chapelon, G. N. Suhail, N. Bilal, H. Y. Khan et al., “Effect of vitamins C and E on antioxidant status of breast-cancer patients undergoing chemotherapy,” *Zealand Medical Journal*, vol. 71, no. 9, pp. 611–621, 2013.

[125] H. R. Harris, L. Bergkvist, and A. Wolk, “Vitamin C intake and breast cancer mortality in a cohort of Swedish women,” *British Journal of Cancer*, vol. 109, no. 1, pp. 257–264, 2013.

[126] H. R. Harris, N. Oursini, and A. Wolk, “Vitamin C and survival among women with breast cancer: A Meta-analysis,” *European Journal of Cancer*, vol. 50, no. 7, pp. 1223–1231, 2014.

[127] J. Ramesh Babu, S. Sundaravel, G. Arumugam, R. Renuka, N. Deepa, and P. Sachadanandan, “Salubrious effect of vitamin C and vitamin E on tamoxifen-treated women in breast cancer with reference to plasma lipid and lipoprotein levels,” *Cancer Letters*, vol. 151, no. 1, pp. 1–5, 2000.

[128] N. Suhail, N. Bilal, H. Y. Khan et al., “Effect of vitamins C and e on antioxidant status of breast-cancer patients undergoing chemotherapy,” *Journal of Clinical Pharmacy and Therapeutics*, vol. 37, no. 1, pp. 22–26, 2012.

[129] A. C. Carr, M. C. Vissers, and J. Cook, “Relief from cancer chemotherapy side effects with pharmacologic vitamin C,” *New Zealand Medical Journal*, vol. 127, no. 1388, pp. 66–70, 2014.

[130] C. Vollbrach, B. Schneider, V. Leendert, G. Weiss, L. Auerbach, and J. Beuth, “Intravenous vitamin C administration improves quality of life in breast cancer patients during chemotherapy/radiotherapy and aftercare: results of a retrospective, multicentre, epidemiological cohort study in Germany,” *In Vivo*, vol. 25, no. 6, pp. 983–990, 2011.

[131] M. Saintot, H. Mathieu-Daude, C. Astre, J. Grenier, J. Simony-Lafontaine, and M. Gerber, “Oxidant-antioxidant status in relation to survival among breast cancer patients,” *International Journal of Cancer*, vol. 97, no. 5, pp. 574–579, 2002.

[132] E. A. Peralta, A. T. Brewer, S. Louis, and G. L. Dunnington, “Vitamin E Increases Biomarkers of Estrogen Stimulation When Taken With Tamoxifen,” *Journal of Surgical Research*, vol. 153, no. 1, pp. 143–147, 2009.

[133] M. Magnusson, P. Höglund, K. Johansson et al., “Pentoxifylline and vitamin E treatment for prevention of radiation-induced side-effects in women with breast cancer: A phase two, double-blind, placebo-controlled randomised clinical trial (PtX-5),” *European Journal of Cancer*, vol. 45, no. 14, pp. 2488–2495, 2009.

[134] S. Delanian, R. Porcher, S. Balra-Mekias, and J.-L. Lefax, “Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis,” *Journal of Clinical Oncology*, vol. 21, no. 13, pp. 2545–2550, 2003.

[135] L. Teleni, J. Baker, B. Koczwarz et al., “Clinical outcomes of vitamin D deficiency and supplementation in cancer patients,” *Nutrition Reviews*, vol. 71, no. 9, pp. 611–621, 2013.

[136] F. Sperati, P. Vici, M. Maugeri-Saccà et al., “Vitamin D Supplementation and Breast Cancer Prevention: A Systematic Review and Meta-Analysis of Randomized Clinical Trials,” *PLoS ONE*, vol. 8, no. 7, Article ID e69269, 2013.

[137] S. B. Mohr, E. D. Gorham, J. E. Alcaraz et al., “Serum 25-hydroxyvitamin D and breast cancer in the military: A case-control study utilizing pre-diagnostic serum,” *Cancer Causes and Control*, vol. 24, no. 3, pp. 495–504, 2013.

[138] K. Edvardsen, M. B. Veierød, M. Brustad, T. Braaten, O. Engelsen, and E. Lund, “Vitamin D-effective solar UV radiation, dietary vitamin D and breast cancer risk,” *International Journal of Cancer*, vol. 128, no. 6, pp. 1425–1433, 2011.

[139] S. C. Larsson, L. Bergkvist, and A. Wolk, “Long-term dietary calcium intake and breast cancer risk in a prospective cohort of women,” *American Journal of Clinical Nutrition*, vol. 89, no. 1, pp. 277–282, 2009.

[140] S. M. Boyapati, X. O. Shu, F. Jin et al., “Dietary calcium intake and breast cancer risk among Chinese women in Shanghai,” *Nutrition and Cancer*, vol. 46, no. 1, pp. 38–43, 2003.

[141] S. Abbas, J. Linseisen, S. Rohrmann et al., “Dietary Intake of Vitamin D and Calcium and Breast Cancer Risk in the European Prospective Investigation into Cancer and Nutrition,” *Nutrition and Cancer*, vol. 65, no. 2, pp. 178–187, 2013.

[142] L. N. Anderson, M. Cotterchio, R. Vieth, and J. A. Knight, “Vitamin D and calcium intakes and breast cancer risk in pre- and postmenopausal women,” *American Journal of Clinical Nutrition*, vol. 91, no. 6, pp. 1699–1707, 2010.

[143] T. E. Rohan, A. Negassa, R. T. Chlebowski et al., “A randomized controlled trial of calcium plus vitamin D supplementation and risk of benign proliferative breast disease,” *Breast Cancer Research and Treatment*, vol. 116, no. 2, pp. 339–350, 2009.

[144] R. T. Chlebowski, Johnson K. C., C. Kooperberg et al., “Calcium plus Vitamin D supplementation and the risk of breast cancer,” *Journal of the National Cancer Institute*, vol. 100, no. 22, pp. 1581–1591, 2008.

[145] S. Scarino, Y. Afanasyeva, P. Lenner et al., “Circulating levels of 25-hydroxyvitamin D and risk of breast cancer: A nested case-control study,” *Breast Cancer Research*, vol. 15, no. 1, article no. R15, 2013.

[146] A. H. Eliasson, D. Spiegelman, B. W. Hollis, R. L. Horst, W. C. Willett, and S. E. Hankinson, “Plasma 25-hydroxyvitamin D and risk of breast cancer in the Nurses’ Health Study II,” *Breast Cancer Research*, vol. 13, no. 3, article no. R50, 2011.

[147] B. L. Sprague, H. G. Skinner, A. Trenthmen-Dietz, K. E. Lee, B. E. K. Klein, and R. Klein, “Serum Calcium and Breast Cancer Risk in a Prospective Cohort Study,” *Annals of Epidemiology*, vol. 20, no. 1, pp. 82–85, 2010.

[148] J. Li, W.-P. Koh, A.-Z. Jin, J.-M. Yuan, M. C. Yu, and L. M. Butler, “Calcium intake is not related to breast cancer risk among Singapore Chinese women,” *International Journal of Cancer*, vol. 135, no. 3, pp. 680–686, 2013.

[149] C.-X. Zhang, S. C. Ho, J.-H. Fu, S.-Z. Cheng, Y.-M. Chen, and F.-Y. Lin, “Dairy products, calcium intake, and breast cancer risk: A case-control study in China,” *Nutrition and Cancer*, vol. 63, no. 1, pp. 12–20, 2011.

[150] P. Engel, G. Fagherazzi, A. Boutten et al., “Serum 25(OH) vitamin D and risk of breast cancer: A nested case-control study from the French E3N cohort,” *Cancer Epidemiology Biomarkers and Prevention*, vol. 19, no. 9, pp. 2341–2350, 2010.

[151] E. Kesse-Guyot, S. Bertrais, B. Duperray et al., “Dairy products, calcium and the risk of breast cancer: Results of the
French SUVI.MAX prospective study,” *Annals of Nutrition and Metabolism*, vol. 51, no. 2, pp. 139–145, 2007.

[152] P. Engel, G. Fagherazzi, S. Mesrine, M.-C. Bouthon-Ruault, and F. Clavel-Chapelon, “Joint effects of dietary vitamin d and sun exposure on breast cancer risk: Results from the French E3N cohort,” *Cancer Epidemiology Biomarkers and Prevention*, vol. 20, no. 1, pp. 187–195, 2011.

[153] M. Rossi, J. K. McLaughlin, P. Lagiou et al., “Vitamin D intake and breast cancer risk: a case-control study in Italy,” *Annals of Oncology*, vol. 20, no. 2, pp. 374–378, 2009.

[154] U. Shamsi, S. Khan, S. Usman, S. Soomro, and I. Azam, “A multicenter matched case control study of breast cancer risk factors among women in Karachi, Pakistan,” *Asian Pacific Journal of Cancer Prevention*, vol. 14, no. 1, pp. 183–188, 2013.

[155] M.-S. Lee, Y.-C. Huang, M. L. Wahliqvist et al., “Vitamin d decreases risk of breast cancer in premenopausal women of normal weight in subtropical Taiwan,” *Journal of Epidemiology*, vol. 21, no. 2, pp. 87–94, 2011.

[156] K. Blinski and J. Boyages, “Association between 25-hydroxyvitamin D concentration and breast cancer risk in an Australian population: an observational case-control study,” *Breast Cancer Research and Treatment*, vol. 137, no. 2, pp. 599–607, 2013.

[157] P. Chen, P. Hu, D. Xie, Y. Qin, F. Wang, and H. Wang, “Meta-analysis of vitamin D, calcium and the prevention of breast cancer,” *Breast Cancer Research and Treatment*, vol. 121, no. 2, pp. 469–477, 2010.

[158] T. Kawase, K. Matsuo, T. Suzuki et al., “Association between vitamin D and calcium intake and breast cancer risk according to menopausal status and receptor status in Japan,” *Cancer Science*, vol. 101, no. 5, pp. 1234–1240, 2010.

[159] M. Deschasaux, J.-C. Souberbielle, P. Latino-Martel et al., “Weight status and alcohol intake modify the association between vitamin D and breast cancer risk,” *Journal of Nutrition*, vol. 146, no. 3, pp. 576–585, 2016.

[160] A. H. Eliassen, E. T. Warner, B. Rosner et al., “Plasma 25-hydroxyvitamin D and risk of breast cancer in women followed over 20 years,” *Cancer Research*, vol. 76, no. 18, pp. 5423–5430, 2016.

[161] Y. Jamshidinaeini, M. E. Akbari, M. Abdollahi, M. Ajami, and S. H. Davoodi, “Vitamin D Status and Risk of Breast Cancer in Iranian Women: A Case–Control Study,” *Journal of the American College of Nutrition*, vol. 35, no. 7, pp. 639–646, 2016.

[162] S. Park, D. H. Lee, J. Y. Jeon et al., “Serum 25-hydroxyvitamin D deficiency and increased risk of breast cancer among Korean women: a case–control study,” *Breast Cancer Research and Treatment*, vol. 152, no. 1, pp. 147–154, 2015.

[163] Y. Kim, A. A. Franke, Y. B. Shvetsov et al., “Plasma 25-hydroxyvitamin D3 is associated with decreased risk of post-menopausal breast cancer in whites: A nested case-control study in the multiethnic cohort study,” *BMC Cancer*, vol. 14, no. 1, article no. 29, 2014.

[164] K. D. Crew, M. D. Gammon, S. E. Steck et al., “Association between plasma 25-hydroxyvitamin D and breast cancer risk,” *Cancer Prevention Research*, vol. 2, no. 6, pp. 598–604, 2009.

[165] T. Kuhn, R. Kaaks, S. Becker et al., “Plasma 25-hydroxyvitamin D and the risk of breast cancer in the European prospective investigation into cancer and nutrition: a nested case-control study,” *International Journal of Cancer*, vol. 133, no. 7, pp. 1689–1700, 2013.

[166] S. Abbas, J. Chang-Claude, and J. Linseisen, “Plasma 25-hydroxyvitamin D and premenopausal breast cancer risk in a German case-control study,” *International Journal of Cancer*, vol. 124, no. 1, pp. 250–255, 2009.

[167] C. M. N. Oliveira-Sediyama, M. M. Dos Santos Dias, M. C. Pessoa et al., ”Lifestyle and vitamin D dosage in women with breast cancer,” *Nutrition Hospitallaria*, vol. 33, no. 5, pp. 1179–1186, 2016.

[168] S. R. Bauer, S. E. Hankinson, E. R. Bertone-Johnson, and E. L. Ding, “Plasma vitamin d levels, menopause, and risk of breast cancer: dose-response meta-analysis of prospective studies,” *Medicine*, vol. 92, no. 3, pp. 123–131, 2013.

[169] M. Almqquist, J. Manjer, L. Bondeson, and A.-G. Bondeson, “Serum calcium and breast cancer risk: Results from a prospective cohort study of 7,847 women,” *Cancer Causes and Control*, vol. 18, no. 6, pp. 595–602, 2007.

[170] D. Wang, O. I. Vélez De-La-Paz, J.-X. Zhai, and D.-W. Liu, “Serum 25-hydroxyvitamin D and breast cancer risk: A meta-analysis of prospective studies,” *Tumor Biology*, vol. 34, no. 6, pp. 3509–3517, 2013.

[171] W. Wulangisih, H. K. Sagoo, M. Hamza et al., “Serum calcium and the risk of breast cancer: Findings from the Swedish AMORIS study and a meta-analysis of prospective studies,” *International Journal of Molecular Sciences*, vol. 17, no. 9, article no. 1487, 2016.

[172] L. Huss, S. Butt, S. Borgquist, M. Almqquist, J. Malm, and J. Manjer, “Serum levels of vitamin D, parathyroid hormone and calcium in relation to survival following breast cancer,” *Cancer Causes and Control*, vol. 25, no. 9, pp. 1131–1140, 2014.

[173] L. Shirazi, M. Almqquist, S. Borgquist, J. Malm, and J. Manjer, “Serum vitamin D (25OHD3) levels and the risk of different subtypes of breast cancer: A nested case-control study,” *Breast*, vol. 28, pp. 184–190, 2016.

[174] J. D. McKay, M. L. McCullough, R. G. Ziegler et al., “Vitamin D receptor polymorphisms and breast cancer risk: results from the national cancer institute breast and prostate cancer cohort consortium,” *Cancer Epidemiology, Biomarkers & Prevention*, vol. 18, no. 1, pp. 197–305, 2009.

[175] J. Shi, A. Grundy, H. Richardson et al., “Genetic variation in vitamin D-related genes and risk of breast cancer among women of European and East Asian descent,” *Tumor Biology*, vol. 37, no. 5, pp. 6379–6387, 2016.

[176] D. E. Rollison, A. L. Cole, K.-H. Tung et al., “Vitamin D intake, vitamin D receptor polymorphisms, and breast cancer risk among women living in the southwestern U.S.,” *Breast Cancer Research and Treatment*, vol. 132, no. 2, pp. 683–691, 2012.

[177] H. J. Kim, Y. M. Lee, B. S. Ko et al., “Vitamin D deficiency is correlated with poor outcomes in patients with luminal-type breast cancer,” *Annals of Surgical Oncology*, vol. 18, no. 7, pp. 1830–1836, 2011.

[178] B. Trabert, K. E. Malone, J. R. Daling et al., “Vitamin D receptor polymorphisms and breast cancer risk in a large population-based case-control study of Caucasian and African-American women,” *Breast Cancer Research*, vol. 9, no. 6, p. R84, 2007.

[179] E. T. Jacobs, C. A. Thomson, S. W. Flatt et al., “Vitamin D and breast cancer recurrence in the Women’s Healthy Eating and Living (WHEL) Study,” *American Journal of Clinical Nutrition*, vol. 93, no. 1, pp. 108–117, 2011.

[180] M. A. Tao, Q. Dai, A. E. Millen et al., “Associations of intakes of magnesium and calcium and survival among women with breast cancer: results from western New York exposures and breast cancer (WEB) study,” *Cancer Research*, vol. 6, no. 1, pp. 105–113, 2015.
[181] P. J. Goodwin, M. Ennis, K. I. Pritchard, J. Koo, and N. Hood, “Prognostic effects of 25-hydroxy vitamin D levels in early breast cancer,” Journal of Clinical Oncology, vol. 27, no. 23, pp. 3757–3763, 2009.

[182] A. Villaseñor, R. Ballard-Barbash, A. Ambs et al., “Associations of serum 25-hydroxyvitamin D with overall and breast cancer-specific mortality in a multiethnic cohort of breast cancer survivors,” Cancer Causes and Control, vol. 24, no. 4, pp. 759–767, 2013.

[183] L. J. Peppone, A. S. Rickles, M. C. Janelins, M. R. Insalaco, and K. A. Skinner, “The association between breast cancer prognostic indicators and serum 25-OH vitamin D levels,” Annals of Surgical Oncology, vol. 19, no. 8, pp. 2590–2599, 2012.

[184] S. Yao, L. E. Sucheston, A. E. Millen et al., “Pretreatment serum concentrations of 25-hydroxyvitamin D and breast cancer prognostic characteristics: A case-control and a case-series study,” PLoS ONE, vol. 6, no. 2, Article ID e17251, 2011.

[185] M. Almquist, L. Anagnostaki, L. Bondeson et al., “Serum calcium and tumour aggressiveness in breast cancer: A prospective study of 7847 women,” European Journal of Cancer Prevention, vol. 18, no. 5, pp. 354–360, 2009.

[186] K. D. Crew, E. Shane, S. Cremers, D. J. McMahon, D. Irani, and D. L. Hershman, “High prevalence of vitamin D deficiency despite supplementation in premenopausal women with breast cancer undergoing adjuvant chemotherapy,” Journal of Clinical Oncology, vol. 27, no. 13, pp. 2151–2156, 2009.

[187] A. C. Shapiro, S. A. Adlis, K. Robien et al., “Randomized, blinded trial of vitamin D3 for treating aromatase inhibitor-associated musculoskeletal symptoms (AIMSS),” Breast Cancer Research and Treatment, vol. 155, no. 3, pp. 501–512, 2016.

[188] E. Amir, C. E. Simmons, O. C. Freedman et al., “A phase 2 trial exploring the effects of high-dose (10,000 IU/day) vitamin D3 in breast cancer patients with bone metastases,” Cancer, vol. 116, no. 2, pp. 284–291, 2010.

[189] M. Datta and G. G. Schwartz, “Calcium and vitamin D supplementation and loss of bone mineral density in women undergoing breast cancer therapy,” Critical Reviews in Oncology/Hematology, vol. 88, no. 3, pp. 613–624, 2013.

[190] Q. J. Khan, P. S. Reddy, B. F. Kimler et al., “Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer,” Breast Cancer Research and Treatment, vol. 119, no. 1, pp. 111–118, 2010.

[191] A. L. Rastelli, M. E. Taylor, F. Gao et al., “Vitamin D and aromatase inhibitor-induced musculoskeletal symptoms (AIMSS): a phase II, double-blind, placebo-controlled, randomized trial,” Breast Cancer Research and Treatment, vol. 129, no. 1, pp. 107–116, 2011.

[192] S. Arul Vijaya Vani, P. H. Ananthanarayanan, D. Kadambari, K. T. Harichandrakumar, R. Niranjan, and H. Nandeesh, “Effects of vitamin D and calcium supplementation on side effects profile in patients of breast cancer treated with letrozole,” Clinica Chimica Acta, vol. 459, pp. 53–56, 2016.

[193] D. Prieto-Alhambra, M. K. Javaid, S. Servitja et al., “Vitamin D threshold to prevent aromatase inhibitor-induced arthalgia: A prospective cohort study,” Breast Cancer Research and Treatment, vol. 125, no. 3, pp. 869–878, 2011.

[194] D. Prieto-Alhambra, S. Servitja, M. K. Javaid et al., “Vitamin D threshold to prevent aromatase inhibitor-related bone loss: The B-ABLE prospective cohort study,” Breast Cancer Research and Treatment, vol. 133, no. 3, pp. 1159–1167, 2012.

[195] S. J. Kim, A. Zuchniak, K.-J. Sohn et al., “Plasma folate, Vitamin B-6, and Vitamin B-12 and breast cancer risk in BRCA1-And BRCA2-mutation carriers: A prospective study,” American Journal of Clinical Nutrition, vol. 104, no. 3, pp. 671–677, 2016.

[196] S. M. Zhang, N. R. Cook, C. M. Albert, J. M. Gaziano, J. E. Bur- ring, and J. E. Manson, “Effect of combined folic acid, vitamin B6, and vitamin B12 on cancer risk in women. A randomized trial,” The Journal of the American Medical Association, vol. 300, pp. 2012–2021, 2008.

[197] M. Liu, L. H. Cui, A.-G. Ma, N. Li, and J.-M. Piao, “Lack of effects of dietary folate intake on risk of breast cancer: An updated meta-analysis of prospective studies,” Asian Pacific Journal of Cancer Prevention, vol. 15, no. 5, pp. 2323–2328, 2014.

[198] M. Tio, J. Andrici, and G. D. Eslick, “Folate intake and the risk of breast cancer: A systematic review and meta-analysis,” Breast Cancer Research and Treatment, vol. 145, no. 2, pp. 513–524, 2014.

[199] J. K. Bassett, L. Baglietto, A. M. Hodge et al., “Dietary intake of B vitamins and methionine and breast cancer risk,” Cancer Causes and Control, vol. 24, no. 8, pp. 1555–1563, 2013.

[200] T. A. Sellers, S. R. Alberts, R. A. Vierkant et al., “High-folate diets and breast cancer survival in a prospective cohort study,” Nutrition and Cancer, vol. 44, no. 2, pp. 139–144, 2002.

[201] C. Castillo-L, J. A. Tur, and R. Uauy, “Folate and breast cancer risk. A systematic review,” Revista Medica de Chile, vol. 140, no. 2, pp. 251–260, 2012.

[202] J. Lin, I. M. Lee, Cook N. R. et al., “Plasma folate, vitamin B-6, vitamin B-12 and risk of breast cancer in women,” The American Journal of Clinical Nutrition, vol. 87, pp. 734–743, 2008.

[203] E. Riboli, K. J. Hunt, N. Slimani et al., “European prospective investigation into cancer and nutrition (EPIC): study populations and data collection,” Public Health Nutrition, vol. 5, no. 6, pp. 1113–1124, 2002.

[204] G. Rukundo, M. Galukande, P. Ongom, and J. O. Fualal, “Red blood cell folate as a risk factor for breast cancer among patients at a tertiary hospital in Uganda: A case control study,” World Journal of Surgical Oncology, vol. 12, no. 1, article no. 260, 2014.

[205] Y.-F. Zhang, W.-W. Shi, H.-F. Gao, L. Zhou, A.-J. Hou, and Y.-H. Zhou, “Folate intake and the risk of breast cancer: A dose-response meta-analysis of prospective studies,” PLoS ONE, vol. 9, no. 6, Article ID e100044, 2014.

[206] S. C. Larsson, L. Bergkvist, and A. Wolk, “Folate intake and risk of breast cancer by estrogen and progesterone receptor status in a Swedish cohort,” Cancer Epidemiology Biomarkers and Prevention, vol. 17, no. 12, pp. 3444–3449, 2008.

[207] L. Yu, Y. Tan, and L. Zhu, “ Dietary vitamin B2 intake and breast cancer risk: a systematic review and meta-analysis,” Archives of Gynecology and Obstetrics, vol. 295, no. 3, pp. 721–729, 2017.

[208] C.-X. Zhang, S. C. Ho, Y.-M. Chen, F.-Y. Lin, J.-H. Fu, and S.-Z. Cheng, “Dietary folate, vitamin B 6, vitamin B 12 and methionine intake and the risk of breast cancer by oestrogen and progesterone receptor status,” British Journal of Nutrition, vol. 106, no. 6, pp. 936–943, 2011.

[209] Y.-C. Chou, C.-H. Chu, M.-H. Wu et al., “Dietary intake of vitamin B6 and risk of breast cancer in Taiwanese women,” Journal of Clinical Nutrition, vol. 98, no. 2, pp. 434–443, 2007.
[211] M. Lajous, I. Romieu, S. Sabia, M.-C. Boutron-Ruault, and F. Clavel-Chapelon, “Dietary intake of folate, vitamin B12 and postmenopausal breast cancer in a prospective study of French women,”*Cancer Causes and Control*, vol. 17, no. 9, pp. 1209–1213, 2006.

[212] M. J. Shrubsbole, F. Jin, Q. Dai et al., “Dietary folate intake and breast cancer risk: results from the shanghai breast cancer study,”*Cancer Research*, vol. 61, no. 19, pp. 7136–7141, 2001.

[213] D. Yang, R. N. Baumgartner, M. L. Slattery et al., “Dietary Intake of Folate, B-Vitamins and Methionine and Breast Cancer Risk among Hispanic and Non-Hispanic White Women,”*PLoS ONE*, vol. 8, no. 2, Article ID e54495, 2013.

[214] M. J. Shrubsbole, X. O. Shu, H.-L. Li et al., “Dietary B vitamin and methionine intakes and breast cancer risk among Chinese women,”*American Journal of Epidemiology*, vol. 173, no. 10, pp. 1171–1182, 2011.

[215] S. C. Larsson, E. Giovannucci, and A. Wolk, “Folate and risk of breast cancer: A meta-analysis,”*Journal of the National Cancer Institute*, vol. 99, no. 1, pp. 64–76, 2007.

[216] S. M. Zhang, W. C. Willett, J. Selhub et al., “Plasma folate, vitamin B6, vitamin B12, homocysteine and risk of breast cancer,”*Journal of the National Cancer Institute*, vol. 95, pp. 373–380, 2003.

[217] W. Wu, S. Kang, and D. Zhang, “Association of vitamin B 6, vitamin B12 and methionine with risk of breast cancer: A dose-response meta-analysis,”*British Journal of Cancer*, vol. 109, no. 7, pp. 1926–1944, 2013.

[218] C. Agnoli, S. Grioni, V. Krogh et al., “Plasma riboflavin and vitamin B-6, but not homocysteine, folate, or vitamin B-12, are inversely associated with breast cancer risk in the european prospective investigation into cancer and nutrition-varcese cohort,”*Journal of Nutrition*, vol. 146, no. 6, pp. 1227–1234, 2016.

[219] J. M. He, C. Leping, and L. Dequan, “Association between dietary intake of folate, Vitamin B-6, B-12 & MTHFR, MTR Genotype and breast cancer risk,”*Genetics and Molecular Research*, vol. 13, no. 84, pp. 8925–8931, 2014.

[220] E. Ma, M. Iwasaki, M. Kobayashi et al., “Dietary intake of folate, vitamin B2, vitamin B6, vitamin B12, genetic polymorphism of related enzymes, and risk of breast cancer: A case-control study in Japan,”*Nutrition and Cancer*, vol. 61, no. 4, pp. 447–456, 2009.

[221] Q. Jiang-hua, J. De-chuang, L. Zhen-duo, C. Shu-de, and L. Zhen, “Association of methylenetetrahydrofolate reductase and methionine synthase polymorphisms with breast cancer risk and interaction with folate, vitamin B6, and vitamin B12 intakes,”*Tumor Biology*, vol. 35, no. 12, pp. 11895–11901, 2014.

[222] Z. Weiwei, C. Leping, and L. Dequan, “Association between dietary intake of folate, vitamin B6, B12 & MTHFR, MTR Genotype and breast cancer risk,”*Pakistan Journal of Medical Sciences*, vol. 30, no. 1, pp. 106–110, 2014.

[223] Y. Liu, L.-S. Zhou, X.-M. Xu, L.-Q. Deng, and Q.-K. Xiao, “Association of dietary intake of folate, vitamin B6 and B12 and MTHFR genotype with breast cancer risk,”*Asian Pacific Journal of Cancer Prevention*, vol. 14, no. 9, pp. 5189–5192, 2013.

[224] E. Ma, M. Iwasaki, I. Junko et al., “Dietary intake of folate, vitamin B6, and vitamin B12, genetic polymorphism of related enzymes, and risk of breast cancer: A case-control study in Brazilian women,”*BMCMedicine*, vol. 9, article no. 122, 2009.

[225] S. Pirouzpanah, F.-A. Taleban, P. Mehdipour, and M. Atri, “Association of folate and other one-carbon related nutrients with hypermethylation status and expression of RARB, BRCA1, and RASSFIA genes in breast cancer patients,”*Journal of Molecular Medicine*, vol. 93, no. 8, pp. 917–934, 2015.

[226] X. Xu, M. D. Gammon, J. G. Wemut et al., “B-vitamin intake, one-carbon metabolism, and survival in a population-based study of women with breast cancer,”*Cancer Epidemiology Biomarkers and Prevention*, vol. 17, no. 8, pp. 2109–2116, 2008.

[227] J. Wohlrab, N. Bangemann, A. Kleine-Tebbe et al., “Barrier protective use of skin care to prevent chemotherapy-induced cutaneous symptoms and to maintain quality of life in patients with breast cancer,”*Breast Cancer: Targets and Therapy*, vol. 6, pp. 115–122, 2014.

[228] S. Straka, J. L. Lester, R. M. Cole et al., “Incorporation of eicosapentaenoic and docosahexaenoic acids into breast adipose tissue of women at high risk of breast cancer: A randomized clinical trial of dietary fish and n-3 fatty acid capsules,”*Molecular Nutrition and Food Research*, vol. 59, no. 9, pp. 1780–1790, 2015.

[229] C. Pouchieu, V. Chajès, F. Laporte et al., “Prospective associations between plasma saturated, monounsaturated and polyunsaturated fatty acids and overall and breast cancer risk - modulation by antioxidants: A nested case-control study,”*PLoS ONE*, vol. 9, no. 2, 2014.

[230] R. E. Patterson, S. W. Flatt, V. A. Newman et al., “Marine fatty acid intake is associated with breast cancer prognosis,”*Journal of Nutrition*, vol. 141, no. 2, pp. 201–206, 2011.

[231] Y. Cao, L. Hou, and W. Wang, “Dietary total fat and fatty acids intake, serum fatty acids and risk of breast cancer: A meta-analysis of prospective cohort studies,”*International Journal of Cancer*, vol. 138, no. 8, pp. 1894–1904, 2016.

[232] P. M. Witt, J. H. Christensen, E. B. Schmidt et al., “Marine n-3 polyunsaturated fatty acids in adipose tissue and breast cancer risk: A case-cohort study from Denmark,”*Cancer Causes and Control*, vol. 20, no. 9, pp. 1715–1721, 2009.

[233] W. Zhihui, Y. Weihua, W. Zupei, and H. Jinlin, “Fish consumption and risk of breast cancer: meta-analysis of 27 observational studies,”*Nutrition Hospitallaria*, vol. 33, no. 3, p. 282, 2016.

[234] D. Engeset, E. Alsaker, E. Lund et al., “Fish consumption and breast cancer risk. The European Prospective Investigation into Cancer and Nutrition (EPIC),”*International Journal of Cancer*, vol. 119, no. 1, pp. 175–182, 2006.

[235] T. M. Brasky, J. W. Lampe, J. D. Potter, R. E. Patterson, and E. White, “Specialty supplements and breast cancer risk in the Vitamins and Lifestyle (VITAL) cohort,”*Cancer Epidemiology Biomarkers and Prevention*, vol. 19, no. 7, pp. 1696–1708, 2010.

[236] J. Kim, S.-Y. Lim, A. Shin et al., “Fatty fish and fish omega-3 fatty acid intakes decrease the breast cancer risk: A case-control study,”*BMC Cancer*, vol. 9, article no. 216, 2009.

[237] L. R. Orr, J. Bruce Redmon, M. S. Kurzer, and S. K. Raatz, “Effect of high omega-3 fatty acid diet on markers of breast cancer risk in postmenopausal women,”*The FASEB Journal*, vol. 23, supplement 558.2, no. 1, 2009.

[238] J. S. Zheng, X. J. Hu, Y. M. Zhao, J. Yang, and D. Li, “Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies,”*British Medical Journal*, vol. 346, Article ID e3706, 2013.

[239] B. Yang, X.-L. Ren, Y.-Q. Fu, J.-L. Gao, and D. Li, “Ratio of n-3/n-6 PUFAs and risk of breast cancer: A meta-analysis of 274135 adult females from 11 independent prospective studies,”*BMC Cancer*, vol. 14, no. 1, article no. 105, 2014.

[240] H. J. Murff, X. Shu, H. Li et al., “Dietary polyunsaturated fatty acids and breast cancer risk in Chinese women: a prospective cohort study of omega-3,”*International Journal of Cancer*, vol. 128, no. 6, pp. 1434–1441, 2011.
N. K. Khankari, P. T. Bradshaw, S. E. Steck et al., “Polyunsaturated fatty acid interactions and breast cancer incidence: A population-based case-control study on Long Island, New York,” Annals of Epidemiology, vol. 25, no. 12, pp. 929–935, 2015.

L. D. Yee, J. L. Lester, R. M. Cole et al., “ω-3 fatty acid supplements in women at high risk of breast cancer have dose-dependent effects on breast adipose tissue fatty acid composition,” The American Journal of Clinical Nutrition, vol. 91, no. 5, pp. 1185–1194, 2010.

C. J. Fabian, B. F. Kimler, T. A. Phillips et al., “Modulation of breast cancer risk biomarkers by high-dose omega-3 fatty acids: Phase II pilot study in postmenopausal women,” Cancer Prevention Research, vol. 8, no. 10, pp. 922–931, 2015.

S. Alam, D. Katiyar, R. Goel, A. Vats, and A. Mittal, “Role of herbal in cancer management,” The Journal of Phytopharmalogy, vol. 2, pp. 46–51, 2013.

S. Eberlin, L. M. B. dos Santos, and M. L. S. Queiroz, “Uncaria tomentosa extract increases the number of myeloid progenitor cells,” Phytomedicine, vol. 8, no. 4, pp. 275–282, 2016.

C. Signori, C. Dubrock, J. P. Richie et al., “Administration of omega-3 fatty acids and Raloxifene to women at high risk of breast cancer: Interim feasibility and biomarkers analysis from a clinical trial,” European Journal of Clinical Nutrition, vol. 66, no. 8, pp. 878–884, 2012.

C. Signori, J. P. Richie, B. Prokopczyk et al., “Effect of omega-3 fatty acids alone and in combination with raloxifene on biomarkers of breast cancer risk in postmenopausal healthy women at high risk,” Journal of Clinical Oncology, vol. 29, e1036, no. 15, 2011.

P. Bougnoux, N. Hajjaji, M. N. Ferrasson, B. Giraudouc, C. Couet, and O. Floch, “Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid: a phase II trial,” British Journal of Cancer, vol. 101, no. 12, pp. 1978–1985, 2009.

H. L. Hutchins-Wiese, K. Picho, B. A. Watkins et al., “High-Dose eicosapentaenoic acid and docosahexaenoic acid supplementation reduces bone resorption in postmenopausal breast cancer survivors on aromatase inhibitors: A pilot study,” Nutrition and Cancer, vol. 66, no. 1, pp. 68–76, 2014.

D. García Giménez, E. García Prado, T. Sáenz Rodríguez, A. Fernández Arche, and R. De La Puerta, “Cytotoxic effect of the pentacyclic oxindole alkaloid mitraphylline isolated from uncaria tomentosa bark on human ewing’s sarcoma and breast cancer cell lines,” Planta Medica, vol. 76, no. 2, pp. 133–136, 2010.

Y. Sheng, L. Li, K. Holmgren, and R. W. Pero, “DNA repair enhancement of aqueous extracts of Uncaria tomentosa in a human volunteer study,” Phytomedicine, vol. 8, no. 4, pp. 275–282, 2001.

Y. Sheng, R. W. Pero, and H. Wagner, “Treatment of chemotherapy-induced leukopenia in a rat model with aqueous extract from Uncaria tomentosa,” Phytomedicine, vol. 7, no. 2, pp. 137–143, 2000.

S. Eberlin, L. M. B. dos Santos, and M. L. S. Queiroz, “Uncaria tomentosa extract increases the number of myeloid progenitor cells in the bone marrow of mice infected with Listeria monocytogenes,” International Immunopharmacology, vol. 5, no. 7–8, pp. 1235–1246, 2005.

I. Farias, M. do Carmo Araújo, and E. S. Zimmermann, “Uncaria tomentosa stimulates the proliferation of myeloid progenitor cells,” Journal of Ethnopharmacology, vol. 137, no. 1, pp. 856–863, 2011.
migration and invasion of MDA-MB-231 breast cancer cells in vitro,” Oncology Reports, vol. 37, no. 4, pp. 2016–2024, 2017.

[300] L. C. Ferreira, A. S. Arbab, B. V. Jardim-Perassi et al., “Effect of curcumin on pro-angiogenic factors in the xenograft model of breast cancer,” Anti-Cancer Agents in Medicinal Chemistry, vol. 15, no. 10, pp. 1285–1296, 2015.

[301] T.-L. Chiu and C.-C. Su, “Curcumin inhibits proliferation and migration by increasing the Bax to Bcl-2 ratio and decreasing NF-kappaB expression in breast cancer MDA-MB-231 cells,” International Journal of Molecular Medicine, vol. 23, no. 4, pp. 469–475, 2009.

[302] H. Zong, F. Wang, Q.-X. Fan, and L.-X. Wang, “Curcumin inhibits metastatic progression of breast cancer cell through suppression of urokinase-type plasminogen activator by NF-kappaB signaling pathways,” Molecular Biology Reports, vol. 39, no. 4, pp. 4803–4808, 2012.

[303] S. Bimonte, A. Barbieri, G. Palma et al., “Dissecting the role of curcumin in tumour growth and angiogenesis in mouse model of human breast cancer,” BioMed Research International, vol. 2015, Article ID 878134, 2015.

[304] H.-W. Lai, S.-Y. Chien, S.-J. Kuo et al., “The potential utility of curcumin in the treatment of HER-2-overexpressed breast cancer: an in vitro and in vivo comparison study with herceptin,” Evidence-Based Complementary and Alternative Medicine, vol. 2012, Article ID 486568, 12 pages, 2012.

[305] H. Fan, Y. Liang, B. Jiang et al., “Curcumin inhibits intracellular fatty acid synthase and induces apoptosis in human breast cancer MDA-MB-231 cells,” Oncology Reports, vol. 35, no. 5, pp. 2631–2656, 2016.

[306] C. E. Carroll, M. R. Ellersieck, and S. M. Hyder, “Curcumin inhibits MPA-induced secretion of VEGF from T47-D human breast cancer cells,” Menopause, vol. 15, no. 3, pp. 570–574, 2008.

[307] G. Chakraborty, S. Jain, S. Kale et al., “Curcumin suppresses breast tumour angiogenesis by abrogating osteopontin-induced VEGF expression,” Molecular Medicine Reports, vol. 1, no. 5, pp. 641–646, 2008.

[308] Y. H. Soung and J. Chung, “Curcumin inhibition of the functional interaction between integrin alpha6beta4 and the epidermal growth factor receptor,” Molecular Cancer Therapeutics, vol. 10, no. 5, pp. 883–891, 2011.

[309] M. M. Yallapu, M. Jaggi, and S. C. Chauhan, “Curcumin nanoformulations: a future nanomedicine for cancer,” Drug Discovery Today, vol. 17, no. 1-2, pp. 71–80, 2012.

[310] M. Z. Ahmad, S. A. Alkahtani, S. Akhter et al., “Progress in nanotechnology-based drug carrier in designing of curcumin nanomedicines for cancer therapy: Current state-of-the-art,” Journal of Drug Targeting, vol. 24, no. 4, pp. 273–293, 2016.

[311] M. M. Yallapu, S. F. Othman, E. T. Curtis et al., “Curcumin-loaded magnetic nanoparticles for breast cancer therapeutics and imaging applications,” International Journal of Nanomedicine, vol. 7, pp. 1761–1779, 2012.

[312] P. Verderio, P. Bonetti, M. Colombo, L. Pandolfi, and D. Prosperi, “Intracellular drug release from curcumin-loaded PLGA nanoparticles induces G2/M block in breast cancer cells,” Biomacromolecules, vol. 14, no. 3, pp. 672–682, 2013.

[313] Y. Cai, Z. Sun, X. Fang et al., “Synthesis, characterization and anti-cancer activity of Pluronic F68–curcumin conjugate micelles,” Drug Delivery, vol. 23, no. 7, pp. 2587–2595, 2016.

[314] S. Somasundaram, Edmund N. A., Moore D. T., Small G. W., Shi Y. Y., and Orlowski R. Z., “Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer,” Cancer Research, vol. 62, no. 13, pp. 3868–3875, 2002.

[315] N. T. Zaveri, “Green tea and its polyphenolic catechins: medicinal uses in cancer and noncancer applications,” Life Sciences, vol. 78, no. 18, pp. 2073–2080, 2006.

[316] R. L. Thangapazham, N. Passi, and R. K. Maheshwari, “Green tea polyphenol and epigallocatechin gallate induce apoptosis and inhibit invasion in human breast cancer cells,” Cancer Biology and Therapy, vol. 6, no. 12, pp. 1938–1943, 2007.

[317] R. L. Thangapazham, A. K. Singh, A. Sharma, J. Warren, J. P. Gaddipati, and R. K. Maheshwari, “Green tea polyphenols and its constituent epigallocatechin gallate inhibits proliferation of human breast cancer cells in vitro and in vivo,” Cancer Letters, vol. 245, no. 1-2, pp. 232–241, 2007.

[318] Z. Wang, N. Wang, S. Han et al., “Dietary Compound Isolevitinigen Inhibits Breast Cancer Neoangiogenesis via VEGF/VEGFR-2 Signaling Pathway,” PLoS ONE, vol. 8, no. 7, Article ID e68566, 2013.

[319] A. H. Wu and L. M. Butler, “Green tea and breast cancer,” Molecular Nutrition and Food Research, vol. 55, no. 6, pp. 921–930, 2011.

[320] E. Lecumberri, Y. M. Dupertuis, R. Milrabell, and C. Pichard, “Green tea polyphenol epigallocatechin-3-gallate (EGCG) as adjuvant in cancer therapy,” Clinical Nutrition, vol. 32, no. 6, pp. 894–903, 2013.

[321] F. Farabegoli, A. Papi, G. Bartolini, R. Ostman, and M. Orlandi, “(-)-epigallocatechin-3-gallate downregulates Pg-P and BCRP in a tamoxifen resistant MCF-7 cell line,” Phytomedicine, vol. 17, no. 5, pp. 356–362, 2010.

[322] T. Luo, J. Wang, Y. Yin et al., “(-)-Epigallocatechin gallate sensitizes breast cancer cells to paclitaxel in a murine model of breast carcinoma,” Breast Cancer Research, vol. 12, no. 1, article R8, 2010.

[323] Y. Zhou, J. Tang, Y. Du, J. Ding, and J.-Y. Liu, “The green tea polyphenol EGCG potentiates the antiproliferative activity of sunitinib in human cancer cells,” Tumor Biology, vol. 37, no. 7, pp. 8555–8566, 2016.

[324] S.-H. Tu, C.-Y. Ku, C.-T. Ho et al., “Tea polyphenol (-)-epigallocatechin-3-gallate inhibits nicotine- and estrogen-induced α9-nicotinic acetylcholine receptor upregulation in human breast cancer cells,” Molecular Nutrition & Food Research, vol. 55, no. 3, pp. 455–466, 2011.

[325] Y. Li, Y.-Y. Yuan, S. M. Meenan, and T. O. Tollefsbol, “Synergistic epigenic reactivation of estrogen receptor-α (ERα) by combined green tea polyphenol and histone deacetylase inhibitor in ERα-negative breast cancer cells,” Molecular Cancer, vol. 9, article no. 274, 2010.

[326] C. I. Coleman, J. H. Hebert, and P. Reddy, “The effects of Panax ginseng on quality of life,” Journal of Clinical Pharmacy and Therapeutics, vol. 28, no. 1, pp. 5–15, 2003.

[327] E. Ernst, “Prescribing herbal medications appropriately,” The Journal of Family Practice, vol. 53, no. 12, pp. 985–988, 2004.

[328] J.-M. Lü, Q. Yao, and C. Chen, “Ginseng compounds: an update on their molecular mechanisms and medical applications,” Current Vascular Pharmacology, vol. 7, no. 3, pp. 293–302, 2009.

[329] M. Blumenthal, “Herb sales down 15 percent in mainstream market,” HerbalGram, vol. 31, p. 69, 2001.

[330] D. L. Barton, H. Liu, S. R. Dakhil et al., “Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2,” Journal of the National Cancer Institute, vol. 105, no. 16, pp. 1230–1238, 2013.

[331] J.-N. Lai, C.-T. Wu, and J.-D. Wang, “Prescription pattern of Chinese herbal products for breast cancer in Taiwan: a
population-based study,” Evidence-Based Complementary and Alternative Medicine, vol. 2012, Article ID 891893, 7 pages, 2012.

[332] J.-H. Kang, K.-H. Song, J.-K. Woo et al., “Ginsenoside Rpi from Panax ginseng exhibits anti-cancer activity by down-regulation of the IGF-IR/Akt pathway in breast cancer cells,” Plant Foods for Human Nutrition, vol. 66, no. 3, pp. 298–305, 2011.

[333] J. H. Kwak, J. Y. Park, D. Lee et al., “Inhibitory effects of ginseng sapogenins on the proliferation of triple negative breast cancer MDA-MB-231 cells,” Bioorganic and Medicinal Chemistry Letters, vol. 24, no. 23, pp. 5409–5412, 2014.

[334] A. S. Wong, C. M. Che, and K. W. Leung, “Recent advances in ginseng as cancer therapeutics: a functional and mechanistic overview,” Natural Product Reports, vol. 32, no. 2, pp. 256–272, 2015.

[335] B. Kim, D. Kim, J. Park, Y. Surh, and H. Na, “Ginsenoside Rg3 inhibits constitutive activation of NF-kappaB signaling in human breast cancer (MDA-MB-231) cells: ERK and Akt as potential upstream targets,” Journal of Cancer Prevention, vol. 19, no. 1, pp. 23–30, 2014.

[336] B. M. Kim, D. Kim, J. Park, H. Na, and Y. Surh, “Ginsenoside Rg3 induces apoptosis of human breast cancer (MDA-MB-231) cells,” Journal of Cancer Prevention, vol. 18, no. 2, pp. 177–185, 2013.

[337] M. Miao, Q. Liu, and Y. R. Liu, “Chemo-sensitivity enhancing effects of Shenqi injection on various chemotherapeutic drugs,” Chinese Traditional and Herbal Drugs, vol. 44, pp. 875-876, 2013.

[338] N.-H. Lee and C.-G. Son, “Systematic Review of Randomized Controlled Trials Evaluating the Efficacy and Safety of Ginseng,” JAMS Journal of Acupuncture and Meridian Studies, vol. 4, no. 2, pp. 85–97, 2011.

[339] J. T. Coon and E. Ernst, “Panax ginseng: a systematic review of adverse effects and drug interactions,” Drug Safety, vol. 25, no. 5, pp. 323–344, 2002.

[340] R. Baber, M. Hickey, and M. Kwik, “Therapy for menopausal symptoms during and after treatment for breast cancer: Safety considerations,” Drug Safety, vol. 28, no. 12, pp. 1085–1100, 2005.

[341] H. H. Henneicke-von Zepelin, “60 years of Cimicifuga racemosa medicinal products: Clinical research milestones, current study findings and current development,” Wiener Medizinische Wochenschrift, vol. 167, no. 7-8, pp. 147–159, 2017.

[342] S. Rockwell, Y. Liu, and S. A. Higgins, “Alteration of the effects of cancer therapy agents on breast cancer cells by the herbal medicine black cohosh,” Breast Cancer Research and Treatment, vol. 90, no. 3, pp. 233–239, 2005.

[343] H.-Y. Sun, B.-B. Liu, J.-Y. Hu et al., “Novel cycloartane triterpenoid from Cimicifuga foetida (Sheng ma) induces mitochondrial apoptosis via inhibiting Raf/MEK/ERK pathway and Akt phosphorylation in human breast carcinoma MCF-7 cells,” Chinese Medicine (United Kingdom), vol. 11, no. 1, article no. 1, 2016.

[344] Y. Kong, F. Li, Y. Nian et al., “KHF16 is a leading structure from Cimicifuga foetida that suppresses breast cancer partially by inhibiting the NF-κB signaling pathway,” Theranostics, vol. 6, no. 6, pp. 875–886, 2016.

[345] G. G.-L. Yue, S. Xie, J. K.-M. Lee et al., “New potential beneficial effects of actein, a triterpene glycoside isolated from Cimicifuga species, in breast cancer treatment,” Scientific Reports, vol. 6, Article ID 35263, 2016.

[346] L. S. Einbond, J. Mighty, S. Redenti, and H.-A. Wu, “Actein induces calcium release in human breast cancer cells,” Fitoterapia, vol. 91, pp. 28–38, 2013.

[347] U. Weissenstein, M. Kunz, K. Urech, U. Regueiro, and S. Baumgartner, “Interaction of a standardized mistletoe (Vismum album) preparation with antitumor effects of Trastuzumab in vitro,” BMC Complementary and Alternative Medicine, vol. 16, no. 1, article no. 271, 2016.

[348] V. L. Davis, M. J. Jayo, A. Ho et al., “Black cohosh increases metastatic mammary cancer in transgenic mice expressing c-erbB2,” Cancer Research, vol. 68, no. 20, pp. 8377–8383, 2008.

[349] H. Maroof, Z. M. Hassan, A. M. Mobarez, and M. A. Mohamad-Abadi, “Lactobacillus acidophilus could modulate the immune response against breast cancer in murine model,” Journal of Clinical Immunology, vol. 32, no. 6, pp. 1353–1359, 2012.

[350] D. Seidlova-Wuttke, O. Hesse, H. Jarry et al., “Evidence for selective estrogen receptor modulator activity in a black cohosh (Cimicifuga racemosa) extract: Comparison with estradiol-17B,” European Journal of Endocrinology, vol. 149, no. 4, pp. 351–362, 2003.

[351] W. Wuttke, C. Gorkow, and D. Seidlova-Wuttke, “Effects of black cohosh (Cimicifuga racemosa) on bone turnover, vaginal mucosa, and various blood parameters in postmenopausal women: a double-blind, placebo-controlled, and conjugated estrogens-controlled study,” Menopause, vol. 13, no. 2, pp. 185–196, 2006.

[352] W. Wuttke, D. Seidlova-Wuttke, and C. Gorkow, “The Cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: Effects on menopause symptoms and bone markers,” Maturitas, vol. 44, pp. S67–S77, 2003.

[353] R. D. Koos, “Minireview: putting physiology back into estrogens’ mechanism of action,” Endocrinology, vol. 152, no. 12, pp. 4481–4488, 2011.

[354] B. A. Pockaj, J. G. Gallagher, C. L. Loprinzi et al., “Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG trial N01CC,” Journal of Clinical Oncology, vol. 24, no. 18, pp. 2836–2841, 2006.

[355] B. A. Pockaj, C. L. Loprinzi, J. A. Sloan et al., “Pilot evaluation of black cohosh for the treatment of hot flashes in women,” Cancer Investigation, vol. 22, no. 4, pp. 515–521, 2004.

[356] T. Niffler and J. Freudenstein, “Coadministration of the aromatase inhibitor fermonest and an isopropanolic extract of black cohosh in a rat model of chemically induced mammary carcinoma,” Planta Medica, vol. 73, no. 4, pp. 318–322, 2007.

[357] B. J. Gurley, S. F. Gardner, M. A. Hubbard et al., “In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes,” Clinical Pharmacology and Therapeutics, vol. 77, no. 5, pp. 415–426, 2005.

[358] B. J. Gurley, A. Swain, M. A. Hubbard et al., “Clinical assessment of CYP2D6-mediated herb-drug interactions in humans: Effects of milk thistle, black cohosh, goldenseal, kava kava, and St. John’s wort, and Echinacea,” Molecular Nutrition and Food Research, vol. 52, no. 7, pp. 755–763, 2008.

[359] S. Belisle, J. Blake, R. Basson et al., “Canadian Consensus Conference on menopause, 2006 update,” Journal of Obstetrics and Gynaecology Canada, vol. 28, 1, no. 2, pp. 57–594, 2006.

[360] R. Walji, H. Boon, E. Guns, D. Oneschuk, and J. Younus, “Black cohosh (Cimicifuga racemosa) [L. Nutt.] Safety and efficacy for cancer patients,” Supportive Care in Cancer, vol. 15, no. 8, pp. 913–921, 2007.

[361] J. Freudenstein, C. Dasenbrook, and T. Nisslein, “Lack of promotion of estrogen-dependent mammary gland tumours in...
vivo by an isopropanolic Cimicifuga racemosa extract,” *Cancer Research*, vol. 62, no. 12, pp. 3448–3452, 2002.

[362] R. Teschke, “Black cohosh and suspected hepatotoxicity: inconsistencies, confounding variables, and prospective use of a diagnostic causality algorithm. A critical review,” *Menopause*, vol. 17, no. 2, pp. 426–440, 2010.

[363] A. Büssing, “Biological and pharmacological properties of *Viscum album* L.,” in *Mistletoe. The Genus Viscum*, Harwood Academic Publishers, Amsterdam, The Netherlands, 2000.

[364] T. Hajto, K. Hostanska, J. Fischer, and R. Saller, “Immunomodulatory effects of Viscum album agglutinin-I on natural immunity,” *Anti-Cancer Drugs*, vol. 8, no. 1, pp. S43–S46, 1997.

[365] I. F. Pryme, S. Bardocz, A. Pusztai, and S. W. B. Ewen, “Suppression of growth of tumour cell lines in vitro and tumours in vivo by mistletoe lectins,” *Histology and Histopathology*, vol. 21, no. 3, pp. 283–299, 2006.

[366] M. Harmsma, M. Ummelen, W. Dignef, K. J. Tusenius, and N. E. Gardin, “Immunological response to mistletoe (*Viscum album* L.) in cancer patients: a four-case series,” *Phytotherapy Research*, vol. 23, no. 3, pp. 407–411, 2009.

[367] G. S. Son, W. S. Ryu, H. Y. Kim, S. U. Woo, K. H. Park, and J. W. Bae, “Immunologic response to mistletoe extract (*Viscum album* L.) after conventional treatment in patients with operable breast cancer,” *Journal of Breast Cancer*, vol. 13, no. 1, pp. 14–18, 2010.

[368] G. Kelter, J. M. Schierholz, I. U. Fischer, and H. H. Fiebig, “Cytotoxic activity and absence of tumour growth stimulation of standardized mistletoe extracts in human tumour models in vitro,” *Anticancer Research*, vol. 1A, pp. 223–233, 2007.

[369] U. Weissenstein, M. Kunz, K. Ureich, and S. Baumgartner, “Interaction of standardized mistletoe (*Viscum album*) extracts with chemotherapeutic drugs regarding cytostatic and cytotoxic effects in vitro,” *BMC Complementary and Alternative Medicine*, vol. 14, article no. 6, 2014.

[370] C.-E. Hong, A.-K. Park, and S.-Y. Lyu, “Synergistic anticancer effects of lectin and doxorubicin in breast cancer cells,” *Molecular and Cellular Biochemistry*, vol. 394, no. 1-2, pp. 225–235, 2014.

[371] J. Beuth, H. L. Ko, H. Schneider et al., “Intratumoural application of standardized mistletoe extracts down regulates tumour weight via decreased cell proliferation, increased apoptosis and necrosis in a murine model,” *Anticancer Research*, vol. 26, no. 6B, pp. 4451–4456, 2006.

[372] L. S. Guo, H. X. Li, C. Y. Li et al., “Synergistic antitumour activity of vitamin D3 combined with metformin in human breast carcinoma MDA-MB-231 cells involves m-TOR related signaling pathways,” *Pharmazie*, vol. 70, no. 2, pp. 117–122, 2015.

[373] M. Thill, K. Reichert, A. Woeste et al., “Combined treatment of breast cancer cell lines with vitamin D and COX-2 inhibitors,” *Anticancer Research*, vol. 35, no. 2, pp. 1189–1195, 2015.

[374] M. C. Kahya, M. Naziroğlu, and B. Çiğ, “Selenium reduces mobile phone (900 MHz)-induced oxidative stress, mitochondrial function, and apoptosis in breast cancer cells,” *Biological Trace Element Research*, vol. 160, no. 2, pp. 285–293, 2014.

[375] C. L. Rock, C. Doyle, W. Demark-Wahnefried et al., “Nutrition and physical activity guidelines for cancer survivors,” *CA: A Cancer Journal for Clinicians*, vol. 62, no. 4, pp. 243–274, 2012.

[376] W. C. R. F. a. I. F. C. R. WCRF, *Cancer Survivors*, 2015, http://www.dietandcancerreport.org/cancer_prevention_recommendations/recommendation_cancer_survivors.php.

[377] H. Greenlee, M. L. Kwan, I. J. Ergas et al., “Changes in vitamin and mineral supplement use after breast cancer diagnosis in the Pathways Study: A prospective cohort study,” *BMC Cancer*, vol. 14, no. 1, article no. 382, 2014.

[378] J. Saquib, B. A. Parker, L. Natarajan et al., “Prognosis following the use of complementary and alternative medicine in women diagnosed with breast cancer,” *Complementary Therapies in Medicine*, vol. 20, no. 5, pp. 283–290, 2012.

[379] S. Nechuta, W. Lu, Z. Chen et al., “Vitamin supplement use during breast cancer treatment and survival: a prospective cohort study,” *Cancer Epidemiology Biomarkers & Prevention*, vol. 20, no. 2, pp. 262–271, 2011.

[380] G. R. Zirpoli, P. M. Brennan, C.-C. Hong et al., “Supplement use during an intergroup clinical trial for breast cancer (SO221),” *Breast Cancer Research and Treatment*, vol. 137, no. 3, pp. 903–913, 2013.

[381] M. Harvie, “Nutritional supplements and cancer: potential benefits and proven harms,” *American Society of Clinical Oncology educational book/*ASCO. *American Society of Clinical Oncology. Meeting*, pp. e478–e486, 2014.

[382] L. H. Kushi, C. Doyle, M. McCullough et al., “American Cancer Society guidelines on nutrition and physical activity for cancer prevention: reducing the Risk of Cancer with Healthy Food Choices and Physical Activity,” *CA Cancer Journal for Clinicians*, vol. 62, no. 1, pp. 30–67, 2012.

[383] Cancer Research UK, *The Safety of Vitamins and Dietary Supplements*, 2015, http://www.cancerresearchuk.org/about-cancer/cancers-in-general/treatment/complementary-alternative/about/harm/the-safety-of-vitamins-and-diet-supplements.

[384] B. D. Lawenda and J. B. Blumberg, “Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy?” *Journal of the National Cancer Institute*, vol. 100, no. 11, pp. 773–783, 2008.

[385] G. M. D’Andrea, “Use of antioxidants during chemotherapy and radiotherapy should be avoided,” *A Cancer Journal for Clinicians*, vol. 55, no. 5, pp. 319–321, 2005.

[386] C. Walker, “Antioxidant supplements do not improve mortality and may cause harm,” *American Family Physician*, vol. 78, no. 9, pp. 1079–1080, 2008.

[387] G. Bjelakovic, D. Nikolova, L. L. Gluud, R. G. Simonetti, and G. M. D’Andrea, “Use of antioxidants during chemotherapy and radiotherapy should be avoided,” *A Cancer Journal for Clinicians*, vol. 55, no. 5, pp. 319–321, 2005.

[388] C. Walker, “Antioxidant supplements do not improve mortality and may cause harm,” *American Family Physician*, vol. 78, no. 9, pp. 1079–1080, 2008.

[389] G. Bjelakovic, D. Nikolova, L. L. Gluud, R. G. Simonetti, and G. M. D’Andrea, “Use of antioxidants during chemotherapy and radiotherapy should be avoided,” *A Cancer Journal for Clinicians*, vol. 55, no. 5, pp. 319–321, 2005.
[426] Z. Hong, C. Tian, and X. Zhang, “Dietary calcium intake, vitamin D levels, and breast cancer risk: A dose-response analysis of observational studies,” *Breast Cancer Research and Treatment*, vol. 136, no. 1, pp. 309–312, 2012.

[427] A. Hjartåker, M. Thoresen, D. Engeset, and E. Lund, “Dairy consumption and calcium intake and risk of breast cancer in a prospective cohort: The Norwegian Women and Cancer study,” *Cancer Causes and Control*, vol. 21, no. 11, pp. 1875–1885, 2010.

[428] L. N. Anderson, “Vitamin D-related genetic variants, interactions with vitamin D exposure, and breast cancer risk among caucasian women in Ontario,” *Cancer Epidemiology, Biomarkers & Prevention*, vol. 20, no. 8, pp. 1708–1717, 2011.

[429] M. L. McCullough, R. M. Bostick, and T. L. Mayo, “Vitamin D gene pathway polymorphisms and risk of colorectal, breast, and prostate cancer,” *Annual Review of Nutrition*, vol. 29, pp. 111–132, 2009.

[430] Y. N. Uchida, E. C. D. Lyra, M. L. H. Katayama et al., “Calcitriol supplementation effects on Ki67 expression and transcriptional profile of breast cancer specimens from post-menopausal patients,” *Clinical Nutrition*, vol. 33, no. 1, pp. 136–142, 2014.

[431] S. Singh, J. Cuzick, D. Mesher, B. Richmond, and A. Howell, “Effect of baseline serum vitamin D levels on aromatase inhibitors induced musculoskeletal symptoms: Results from the IBIS-II, chemoprevention study using anastrozole,” *Breast Cancer Research and Treatment*, vol. 132, no. 2, pp. 625–629, 2012.

[432] A. C. Shapiro, S. A. Adlis, K. Robien et al., “Erratum: Randomized, blinded trial of vitamin D3 for treating aromatase inhibitor-associated musculoskeletal symptoms (AIMSS),” *Breast Cancer Research and Treatment*, vol. 157, no. 2, p. 403, 2016.

[433] M. Chung, J. Lee, T. Terasawa, J. Lau, and T. A. Trikalinos, “Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force,” *Annals of Internal Medicine*, vol. 155, no. 12, pp. 827–838, 2011.

[434] S. Bourke, M. J. Bolland, A. Grey et al., “The impact of dietary calcium intake and vitamin D status on the effects of zoledronate,” *Osteoporosis International*, vol. 24, no. 1, pp. 349–354, 2013.

[435] Y. Rhee, K. Song, S. Park, H. S. Park, S.-K. Lim, and B. W. Park, “Efficacy of a combined alendronate and calcitriol agent (Maxmarvil®) in Korean postmenopausal women with early breast cancer receiving aromatase inhibitor: A double-blind, randomized, placebo-controlled study,” *Endocrine Journal*, vol. 60, no. 2, pp. 167–172, 2013.

[436] S. D. Manshadi, L. Ishiguro, K.-J. Sohn et al., “Folic acid supplementation promotes mammary tumor progression in a rat model,” *PLoS ONE*, vol. 9, no. 1. Article ID e84635, 2014.

[437] M. Lajous, J. de Batlle, C. Ricci et al., “Biomarkers of folate and vitamin B12 and breast cancer risk: report from the EPIC cohort,” *International Journal of Cancer*, vol. 140, no. 6, pp. 1246–1259, 2017.

[438] C. M. Ulrich, “Folate and cancer prevention: a closer look at a complex picture,” *The American Journal of Clinical Nutrition*, vol. 86, pp. 271–273, 2007.

[439] P. Bougnoux, N. Hajjaji, K. Maheno, C. Couet, and S. Chevalier, “Fatty acids and breast cancer: sensitization to treatments and prevention of metastatic re-growth,” *Progress in Lipid Research*, vol. 49, no. 1, pp. 76–86, 2010.