nutrients

MDPI

Review

Micronutrients and Breast Cancer Progression: A Systematic Review

Olga Cuenca-Micó * and Carmen Aceves *

Instituto de Neurobiología UNAM-Juriquilla, Querétaro 76230, Mexico
* Correspondence: olgacuenca76@gmail.com (O.C.-M.); caracev@unam.mx (C.A.)

Received: 1 November 2020; Accepted: 23 November 2020; Published: 25 November 2020

Abstract: Epidemiological studies on micronutrient consumption have reported protective associations in the incidence and/or progression of various cancer types. Supplementation with some of these micronutrients has been analyzed, showing chemoprotection, low toxicity, antiproliferation, and the ability to modify epigenetic signatures in various cancer models. This review investigates the reported effects of micronutrient intake or supplementation in breast cancer progression. A PubMed search was conducted with the keywords "micronutrients breast cancer progression", and the results were analyzed. The selected micronutrients were vitamins (C, D, and E), folic acid, metals (Cu, Fe, Se, and Zn), fatty acids, polyphenols, and iodine. The majority of in vitro models showed antiproliferative, cell-cycle arrest, and antimetastatic effects for almost all the micronutrients analyzed, but these effects do not reflect animal or human studies. Only one clinical trial with vitamin D and one pilot study with molecular iodine showed favorable overall survival and disease-free interval.

Keywords: breast cancer; micronutrients; cancer

1. Introduction

Since the 1980s, there has been increasing epidemiological evidence of the relationship between inadequate intake of micronutrients and the appearance of tumor processes [1]. However, the heterogeneity of compounds, models, and types of malignancy makes it impossible to assign general effects. Breast cancer is the most common cancer in women, affecting more than two million each year. In 2018, more than 600,000 women died from breast cancer, representing approximately 15% of all cancer deaths among women worldwide [2]. There is extensive literature on nutrition and the risk of breast cancer [3–6]; however, because some nutrients and hormones play a dual role in tumor initiation and progression, these processes need to be analyzed separately [7,8]. In this review, we focus on the effects of micronutrients once the breast tumor process has been established. Given our group's interest in molecular iodine (I_2), we compared the effects and mechanisms proposed for supplementing this halogen with those of the other micronutrients. All nutrients have antitumor properties in cellular cultures; however, when scaling to in vivo models, most of the micronutrients lose these properties. Only vitamin D (Vit D) and I_2 supplements showed associations with improved overall survival (OS) and disease-free interval (DFI) in clinical trials [9,10].

Regarding the mechanisms, most of the micronutrients analyzed in this review work as antioxidants, reducing the aberrant redox environment characteristic of tumor processes. Other actions have also been described in some components. Vit D acts as a genomic regulator and folates are involved in purine/pyrimidine synthesis and methylation reactions. I_2 appears to act as a genetic modulator by joining lipids and activating nuclear receptors. Its ability to modify DNA methylation processes has also been proposed. In the progression of breast cancer, I_2 seems to be the best micronutrient for adjuvant therapy with different antitumor mechanisms, but more extensive clinical trials are needed.

2. Materials and Methods

A search of the scientific literature was carried out in PubMed on August 28, 2019, with the terms "micronutrients breast cancer progression", which yielded 425 results. All 425 papers were screened with the following inclusion criteria: original articles written in English, analyzing one or more micronutrient supplement effects in breast cancer progression. A total of 352 articles were excluded: articles published in languages other than English (15 articles), reviews (65), papers about synthetic micronutrient analogs or without micronutrients (204), articles concerning other cancers (39), articles in which there was no cancer progression (15), and methodology-aimed articles (14). Finally, 76 articles were assessed for eligibility, and 73 were included in this review. Metabolites such as carotenoids, Vit A, or coenzyme Q10 were less represented in the articles and are not analyzed.

3. Results

If we consider the percentage of papers on each nutrient, 37% were about Vit D or its natural metabolites, 27% were about metals such as copper (Cu), iron, selenium (Se), and zinc (Zn), 9% and 7% were about folates and vitamin C (Vit C), respectively, and 5% of articles analyzed in this review were on polyphenols, fatty acids, vitamin E (Vit E), and iodine. These data provide an overview of current research interest in nutrient supplementation and breast cancer progression. Next, the main results of our analysis are detailed.

3.1. Vitamin D

Vit D is characterized as a vitamin (i.e., a compound with the catalytic activity of biological processes); however, due to its metabolism and action mechanisms, it is considered as a pro-hormone. Reviews of Vit D's physiological actions suggest that its active form, calcitriol, regulates calcium and phosphate homeostasis and plays a key role in the physiology of various organs and systems. Calcitriol was mostly studied in the immune system as an immunomodulator targeting various immune cells, including monocytes, macrophages, dendritic cells, T-lymphocytes, and B-lymphocytes (B) [11,12]. Calcitriol's mechanisms of action start when it binds to the Vit D receptor (VDR). This nuclear receptor can form homodimers (VDR–VDR) or heterodimers (with the X retinoid receptor: CDR–RXR) that bind to specific genome responsive elements (VD-REs or VD/RXREs) to activate the transcription of their target genes [13]. Vit D is not the only micronutrient capable of activating these transcription factors; low-affinity nutritional ligands for VDR, such as curcumin, unsaturated fatty acids, and anthocyanins, have been described with the ability to activate this route. Others, such as resveratrol, have been described as VDR signaling enhancers [14]. The activity of VDR can be modulated epigenetically by histone acetylation. It cooperates with other nuclear receptors that are influenced by histone acetyltransferases (HATs) and several types of histone deacetylases (HDACs). HDAC inhibitors (HDACi) and demethylating drugs may contribute to Vit D metabolism [15].

Concerning cancer, studies (most of them in vitro) demonstrated antineoplastic effects of calcitriol. The molecular mechanisms include inhibition of thekinase-interacting serine/threonine-protein kinases MAPK–ERK pathway, suppression of Epidermal Growth Factor (EGFR) and Insulin-like growth factor 1 (IGF1), and inhibition of telomerase, Bcl-2, and Myc expression [16]. Specifically, in breast cancer, the maximum dose of supplementation was 100 nM, which seems sufficient to inhibit cell proliferation, increase apoptosis markers, and modify intracellular glucose metabolism parameters [17–20]. These studies showed, regardless of the cell type used, antiproliferative effects, increased redox potential, and cell-cycle arrest in G1. Most of these studies were performed on MCF-7 cells (estrogen receptor-positive: ER^+), and the supplement of this micronutrient was accompanied by significant decreases in the expression of the aromatase enzyme, estrogen receptor (ER), cyclooxygenase type 2 (Cox-2), prostaglandin E2 (PGE2), and the antiapoptotic protein Bcl-2. These prostaglandins are also associated with increases in the number of apoptotic cells [20–26]. Furthermore, studies that used breast cell lines of normal origin with the mutated Ras oncogene (MCF10A-ras) found a pro-oxidant effect

(via inhibition of the enzyme Pyr carboxylase) and a decrease in the flow of glutamine (Gln) inside the cell, generating a significant decrease in proliferation [27–29]. In general, calcitriol restores reactive oxygen species (ROS) equilibrium in tumor cells, reduces cancer proliferation, and has a relevant role in apoptosis and autophagy [30–32]. In preclinical studies, the findings are more complex and dependent on breast cancer type and doses. The differentiated cancer model (estrogen+), with a moderate concentration of Vit D supplement, did not exhibit any effects [25,28], exhibited inhibition of tumoral growth accompanied by decreases in the expression of Bcl-2, aromatase, estradiol, and Cox-2 [20], or presented an increase in apoptosis cell content with augmented p53 expression [21]. In contrast, in the triple-negative breast cancer model (immunosuppressed mice $AT1^{+}$ cells), Vit D supplementation increased the tumors' metastatic potential [33]. Finally, studies in cancer patients described that high doses (250 μg/day) did not affect tumor progression, while low supplementation (10 μg/day) reduced mortality by at least 20% [9,34]. It also has been described that Vit D deficiency or the inability to synthesize its active compound (calcitriol) accelerates tumor growth [35,36]. However, some studies showed that Vit D supplementation to restore plasma levels (time and doses) stops the tumoral growth [34], whereas, in other studies using high concentrations (1250 μg/week) sufficient to revert these deficiencies, it could not decrease cancer progression [37]. In general, calcitriol alters ROS equilibrium in cancer, reduces cancer proliferation, and has a relevant role in apoptosis and autophagy [38–40]. It appears that high serum levels are associated with better survival and DFI [41–45]. In 2010, the Institute of Medicine of the US National Academy of Sciences recommended an intake of 600 IU/day of Vit D (15 μg) to maintain adequate serum 25(OH)D for normal bone mineralization. However, the recommendation does not include the extra-skeletal effects of Vit D. On the other hand, the Endocrine Society committee suggests higher doses (1000–2000 UI equivalent to 25–50 μg) to correct deficiencies and prevent fractures and does not consider this supplementation to prevent cancer or cardiovascular diseases [46]. These descriptions agree with Goulao et al.'s recent review, which included 30 clinical studies with more than 18,000 participants, finding no evidence that Vit D supplementation alone reduces the incidence of cancer or mortality in established cancer processes [47].

3.2. Metals

3.2.1. Copper

Cu is a transition metal that the body requires as a catalytic cofactor or a structural protein component involved in redox reactions. It participates in the adequate synthesis of some metabolites, such as hemoglobin, elastin, and collagen, as well as in transporting oxygen to the mitochondrial respiratory chain. The immune system also requires Cu to perform several functions; animal models and cell cultures have been used to assess the role of Cu in the immune response. Some research showed that Cu deficiency is accompanied by a reduction in T-cell proliferation and interleukin production [48]. Lowering Cu levels in the diet increases protein oxidation and DNA methylation [49]. There are numerous Cu-dependent enzymes whose activity diminished with Cu deficiency: ceruloplasmin, superoxide dismutase (SOD), cytochrome C oxidase (COX), and ascorbic acid oxidase, among others [50]. At the molecular pathway level, Cu directly affects the phosphorylation of extracellular signal-regulated kinase (Erk) by meiotic chromosome axis-associated kinase 1 (Mek1). Mek1, a MAPK pathway kinase, has two binding sites for Cu, and its presence increases Erk phosphorylation in a dose-dependent manner [51]. For this micronutrient, the recommended daily intake is 900 μg, while the maximum tolerable level is 10 mg/day [52]. Many types of cancer have elevated intracellular Cu levels or exhibit alterations in this metal's systemic distribution [53]. In breast cancer, elevated serum Cu levels correlate with the stage and progression of the disease [54], and tumor cells have four times more Cu than healthy breast cells [55]. The addition of Cu to breast cancer cells showed opposite results depending on the cell type. In triple-negative MDA-MB-231 cells with mutated p53, the Cu supplement increased proliferation and survival and Akt phosphorylation [56].

In contrast, in MCF-7 cells positive for ER, this micronutrient increased p53 phosphorylation and the expression of p21, resulting in cell-cycle arrest in G1 and apoptosis [56]. Four articles on clinical studies exploring the relationship of Cu to breast cancer progression were analyzed for this review (see Table S4 Supplementary Materials). Serum and hair Cu levels were higher in patients than in healthy people [57,58]. Angiogenic and metastatic properties are attributed to this metal. In breast tumors, a Cu-dependent RedOx protein Memo has been reported to play an essential role in migration and metastasis (increasing intracellular ROS levels) [59]. Furthermore, a clinical study evaluating a Cu chelator effect showed a reduction in angiogenic markers [60].

3.2.2. Iron

Iron, another transition metal, acts in mammals as a cofactor of hemoproteins (hemoglobin, catalase, peroxidases, cytochromes) involved in oxygen binding, transport, and metabolism. It is also a cofactor of other proteins (without a heme group) with functions in DNA synthesis, cell proliferation and differentiation (ribonucleotide reductase), gene regulation, drug metabolism, and steroid synthesis [61]. The peptide hormone hepcidin is the primary regulator of iron metabolism in the body. This enzyme increases its expression with high hepatic iron levels, with increased levels of iron in the plasma, and during inflammation (by Interleukin 6 (IL-6) in a mechanism that involves the activation of Signal transducer and activator of transcription 3 (STAT3) [62]. In contrast, its expression is suppressed under hypoxic conditions [63]. Overall, in tumors, elevated intracellular iron levels are reported compared to their healthy cellular counterpart. Excess iron favors tumor growth [64]; thus, depleting this metal, either by reducing dietary intake or by chelating, shows inhibition of tumor growth [65]. Specifically, epidemiological studies show positive associations between dietary iron consumption and breast cancer incidence [66]. The studies analyzed in this review (Table S4, Supplementary Materials) show results consistent with those reported in the literature. Both tumor tissue and trace element quantification showed higher iron levels than healthy tissue or patients [60,67]. At the mechanistic level, in silico models suggest oncogenic Ras pathways in altered iron homeostasis in tumors [68]. Studies with cell cultures show that the most aggressive lines accumulate a more significant amount of iron [69]. The use of chelators inhibits breast carcinoma growth and causes cell-cycle arrest in the S phase accompanied by apoptosis [70].

3.2.3. Selenium

Se is a metalloid with both nutritional and toxic properties. In humans, Se's nutritional functions are carried out through 25 enzyme proteins with selenocysteine in its active center [71]. These selenoproteins have a wide range of pleiotropic effects, from antioxidant (such as glutathione peroxidases) to anti-inflammatory effects (selenoproteins) to the activate/deactivate thyroid hormones (deiodinases) [72]. The epigenetic evidence indicates that high Se exposure leads to DNA methyltransferase expression/activity [73]. The daily intake recommendation is set at 60 µg for men and 53 µg for women [74]. In cancer, Vinceti et al. [75] analyzed in a recent review 55 prospective observational studies and concluded that there is a lower incidence and mortality associated with high exposure to Se. However, in an analysis of eight clinical trials, no clear evidence was found that supplementation with Se reduced the risk of any cancer [76]. In the present review, we found five articles on Se and breast cancer (Table S4, Supplementary Materials). Three of these articles were on prospective studies [57,70,77], and the serum of Se showed lower levels in all patients than in their healthy counterparts. On the contrary, in tumors, the Se levels were higher than in the adjacent tissues. Another finding in various studies is that the decreases in circulating levels of Se correlate with the stages of disease progression [75]. The analyzed preclinical studies showed an inverse relationship between circulating levels of Se and vascular epithelial growth factor (VEGF) [78]. Se supplementation seemed to inhibit tumor progression in preclinical studies and cell cultures [79]. A decrease in Se levels appears to be widespread in cancer progression, but there is no evidence of its benefits as an adjuvant in tumor progression.

3.2.4. Zinc

Zn is an omnipresent trace element. It is found in all tissues of the body, where its most significant role is in stabilizing the structure of many proteins. This element has three main functions in the organism: catalytic (DNA synthesis, brain development, and wound healing), structural (DNA replication), and regulatory (enzymatic activity and protein stabilization). Among its many functions in the body, Zn is involved in immune response, oxidative stress, apoptosis, and aging [80]. At the regulatory level, Uciechowski and his group described epigenetic and redox-dependent mechanisms as responsible for Zn effects in the immune system [81]. Various studies established an association between Zn deficiency and cancer (in cell cultures, preclinical models, and human studies) [82,83]. In our review (Table S4, Supplementary Materials), two studies examined the amount of systemic Zn in patients with breast cancer. Measurements in serum and hair indicated a decrease in Zn compared to their healthy counterparts [57,84].

Regarding intratumor Zn levels, the results vary depending on the technique used for metal detection [85,86]. Our analysis showed that the overexpression of the Zn transporter ZIP10 in tumor cells [87] and the chelation of this metal inhibit the invasiveness of several metastatic tumor cell lines [56,87]. Like Se, systemic Zn levels decrease with the disease; however, high intratumoral concentrations occur, which is explained by the overexpression of its ZIP10 transporter. A therapeutic approach used in recent years involves Zn chelators because Zn is required for tumor cell adaptation to hypoxic conditions [88].

3.3. Folates

Folates are micronutrients of the vitamin B complex. They are acceptors/receptors of 1-carbon units and function as coenzymes involved in purine/pyrimidine synthesis and various methylation reactions [89,90]. Associations have been reported between the nutritional status of folate and chronic diseases such as cardiovascular disease, cancer, and cognitive dysfunction [91]. In cancer, depending on the time of supplementing with folate, the results could be the opposite. Thus, supplementation before the existence of preneoplastic lesions can prevent tumor development, whereas supplementation in the presence of established lesions increases tumorigenesis [92–94]. This dual role of folate in carcinogenesis has been explained as an adequate intake of folates prevents DNA damage [95], while excess folate during an established tumor process decreases the expression of tumor suppressor genes [96,97]. In this review (Table S5, Supplementary Materials), studies in preclinical models showed that high-folate diets increase tumor volume and the number of tumors, while deficiency of this nutrient significantly inhibits breast cancer [98–100]. The mechanisms via which these results have been explained are inferred from in vitro studies where folic acid supplementation increased the expression of enzymes responsible for DNA methylation and the decrease in tumor suppressor genes [Phosphatase and tensin homolog;(PTEN) and adenomatous polyposis coli (APC)] associated with increased methylation of its promoters [101]. However, studies in human patients showed conflicting results. Two studies analyzed folate consumption using a dietary questionnaire; one found an inverse association between folate consumption and mortality [102] and the other did not find any association [103]. Another study analyzing different subtypes of breast cancer found that plasma folate levels are lower in patients with human epidermal growth factor receptor 2 ($HER2^+$) and triple-negative cancer [104]; however, more in-depth studies are needed in this area.

3.4. Vitamin C

Vit C (or ascorbic acid) is an essential micronutrient present in citrus and other vegetables. Its biological functions are extensive, as they contribute to the synthesis of metabolites (carnitine, catecholamine, norepinephrine, etc.) and collaborate in the metabolism of tyrosine, tryptophan, folic acid, and cholesterol. They also participate in collagen formation and maintenance and thyroid hormone (TH) synthesis [105–108]. On the other hand, ascorbic acid supplementation strengthens the

immune system, increasing neutrophil motility, leukocyte transformation, and phagocytosis [108]. It is also a potent antioxidant [109]; this capacity makes it a supplier of reduced iron, necessary for epigenetic regulation of DNA and histone demethylation [110]. In cancer patients, Vit C deficiency is common. It has been reported that pharmacologic doses of ascorbate act as a pro-oxidant ascorbate radical, decreasing the growth and aggressiveness of ovarian, pancreatic, and glioblastoma xenografts in mice [111]. In the articles about this micronutrient in breast cancer (Table S6, Supplementary Materials), culture and preclinical models indicated that Vit C deficiency facilitates tumor growth and expansion, while supplementation reduces cell proliferation [112,113]. In studies in human patients, consumption before malignancy appeared to be associated with survival; however, once the tumor process was established, this protective effect seemed to disappear [114]. The progression of malignancy is related to decreased serum ascorbic acid, which is exacerbated if the patients have been smokers (exposed to a more significant amount of oxidants) [115,116]. A single clinical study evaluated the effect of intravenous injections of Vit C in breast cancer patients. The maximum dose they supplemented was 50 g, where plasma ascorbate concentrations averaged 18 mM. Under these conditions, they observed a reduction in serum inflammatory markers such as IL-1α, IL-2, IL-8, and tumor necrosis factor alpha (TNF-α) and a reduction in C-reactive protein levels associated with poor prognosis and worse survival rates [117]. Systemic Vit C levels are inversely related to exposure to oxidants (such as tobacco). This decrease is also observed during disease progression, which could be explained, in part, by the increase in ROS activity characteristic of tumor progression [115,116]. These effects, such as the redox pair of Vit C, depend on its concentration. An antioxidant effect is observed at a physiological range of serum Vit C between 26 and 84 μM (equivalent to an intake of 75–90 mg/day). To achieve an oxidizing effect, at least >100 μM in plasma is required, which is only achieved with intravenous injections of ascorbic acid (117). The results analyzed in this review point to a possible benefit of ascorbic acid supplementation, although clinical studies are needed to verify the effects observed in other models.

3.5. Polyphenols

Polyphenols are a group of natural compounds with phenolic structural characteristics. More than 8000 structures have been identified and are present in fruits and grains [118]. High consumption has been linked to a lower risk of cancer, cardiovascular diseases, chronic inflammation, and degenerative diseases [119,120]. The primary biological role of polyphenols is associated with their antioxidant properties; however, they have also been described as metal chelators (such as Fe^{2+}), anti-inflammatories, and promoters of probiotic actions [121–123]. In cancer, the protective effect of polyphenols is debated due to the discrepancy between study models and the use of non-physiological concentrations [124]. Although numerous possible mechanisms have been elucidated, most of the results obtained show different effects at low or high supplement concentrations [125]. These biphasic effects could be explained by their ability to modulate hormonal receptors; the chemical structure of polyphenols defines their affinity for binding to ERs. This affinity is lower than that of estradiol and allows agonist or antagonist reactions depending on the bound polyphenol (e.g., genistein is an ERα and ERβ agonist; resveratrol is an ERα antagonist and ERβ agonist) [126–128]. All the studies analyzed in this review on the effects of polyphenols on breast cancer progression (Table S7, Supplementary Materials) were conducted in cell cultures and reflect the discordant results indicated in the literature. In the MCF-7 cell model (ER^+), supplementation with small amounts of isoflavones showed increased cell proliferation [128]. At the same time, high doses inhibited growth in a dose-dependent manner and stopped the cell cycle in G1 [129]. In MDA-MB-231 cells (triple-negative model), small amounts of luteolin did not affect invasive and cell migration capabilities [130], while small quantities of naringin (0.1 μM) showed significant inhibitory competences [131]. The studies analyzed in this review do not offer a clear direction on the use of polyphenols to treat breast cancer, which is consistent with what has been published for other types of malignancies.

3.6. Fatty Acids

The fatty acids analyzed in this review are α-lipoic acid and α-linolenic acid. α-Lipoic acid is found in high concentrations in spinach, broccoli, liver, and kidney and participates in the energy metabolism of carbohydrates, proteins, and fats [132]. It is also a cofactor for mitochondrial enzymes and a potent antioxidant [133]. As a structural component of cell membranes, the location and organization of α-lipoic acid and α-linolenic acid within cellular lipids directly influence the behavior of several proteins involved in immune cell activation [134]; in fact, Jacobsen et al. associated a lower level of DNA methylation in inflammatory disease and inflammatory response with a high-fat diet [135]. The effects of dietary fatty acids have been described in numerous signaling pathways in tumorigenesis, inhibiting tumor growth and proliferation and inducing apoptosis [136]. a-Linolenic acid is present in walnuts, canola, many legumes, and green leafy vegetables [137]. It is a precursor of omega-3 fatty acids and is essential for brain development and functions, cardiovascular health, and inflammatory response [138,139]. In tumor cell cultures, antitumor properties are attributed to α-linolenic acid, due to the decrease in VEGF and metalloprotease expression and the restoration of tumor suppressor gene expression (e.g., Rb and p. 53) [140]. The same is observed with lipoic acid (Table S8, Supplementary Materials), which exhibited antitumor effects such as decreased ROS, cell-cycle arrest followed by apoptosis, and decreased proliferation [141,142]; however, when scaled in preclinical models, similar doses generated contradictory responses. In mice with HER2 overexpression, supplementation with lipoic acid increased tumor growth [143], whereas, in nude mice xenografts, the treatment significantly retarded tumor growth [144]. Very few studies were found on fatty acids in breast cancer progression and none in patients. The results of these studies show antitumor effects in cell lines; further studies in preclinical models are necessary to establish possible benefits.

3.7. Vitamin E

Vitamin E (Vit E) is a group of eight fat-soluble compounds: four tocopherols (α, β, γ, and δ) and four tocotrienols (α, β, γ, and δ). Tocopherols predominate in olive, sunflower, corn, and soybean oils, while tocotrienols are found in palm oil or rice bran [145,146]. These compounds exert antioxidant, neuroprotective, and cholesterol-lowering activities [147]. Vit E is found in higher concentrations in immune cells than in other blood cells, and it is among the best nutrients modulating the immune system [148]. This is due to its antioxidant effect in polyunsaturated fatty acids (enhanced in membranes of immune cells), subject to oxidative damage because of their high metabolic activity and defense against pathogens [149,150]. In cancer, antitumor properties have been attributed to this group of compounds, especially γ- and δ-tocotrienols, because of their effect on molecular pathways involved in inhibition, apoptosis, and autophagy [151]. In our review (Table S9, Supplementary Materials), we analyzed two studies with tocotrienols and two with tocopherols. Both tocotrienol studies showed antitumor properties due to inhibition in growth, invasiveness, and migration [115,152]. Furthermore, plasma levels of tocopherols appeared to decrease with the progression of the disease [151]. In the cell culture model, supplementation with α- and γ-tocopherol showed VEGF inhibition [152]. Vit E compounds show antitumor properties in cell cultures such as the inhibition of proliferation, migration, and invasiveness and a decrease in apoptosis markers. However, the lack of studies in preclinical and clinical models does not allow us to conclude that these compounds are effective in breast cancer progression.

3.8. Iodine

Iodine is an essential micronutrient for the development of vertebrate organisms. It is a structural constituent of THs and a regulator of thyroid gland function [153]. Thyroid hormones play an essential role in the differentiation, growth, and energy metabolism of virtually all cells in the organism [154]. Furthermore, recent studies described that iodine, in its molecular form (I_2), is a cellular modulator of organs capable of internalizing it, such as the breast, prostate, and pancreas, as well as the immune

and nervous systems [155–158]. This chemical form of iodine has antioxidant [159], antineoplastic, and apoptotic effects in several cancer cells [160,161] and exhibits modulatory properties in the immune system [10]. Fresh seaweed is an important component of the Asian diet and is the only natural I_2 source. Regular consumption of these algae is associated with a low incidence of breast diseases, such as fibrocystic disease or mastalgia and cancer, in these populations [156].

Various groups have shown the antineoplastic and immunomodulatory effects of I_2 and proposed at least two mechanisms: (1) a direct action involving its antioxidant/oxidant properties and (2) an indirect effect through iodolipid formation. In the case of direct effects, two datasets were obtained showing that (a) at low or moderate concentrations, I_2 significantly reduces lipid oxidation by competing with ROS for various cellular components or directly neutralizing HO radicals through coupling and generating iodinated species without oxidative activity i.e., hypoiodous acid (HOI) or hydrogen iodide (HI) [156,162], and (b) at high concentrations acting as a direct oxidant, I_2 dissipates the mitochondrial membrane potential, inducing mitochondria-mediated apoptosis [163]. The indirect action involves the formation of iodolipids such as 6-iodo-5-hydroxy-8,11,14-eicosatrienoic acid (also called 6-iodolactone; 6-IL) derived from arachidonic acid (AA) iodination [164]. Concerning the mammary gland, it has been described that tumors induced by methyl nitrosourea (MNU) contain AA concentrations four times higher than normal tissue and that after chronic treatment (1 week) with oral I_2 supplements, and 6-IL 15 times higher than in normal mammary tissue, suggesting that 6-IL plays a role in the antiproliferative effect of I_2 [160]. These findings have also been corroborated in the human tumor cell line MCF-7 where lipids similar to 6-IL are detected after treatment with I_2 [158] or apoptosis is triggered by I_2 or 6-IL [165,166]. In this sense, our group described that the median lethal dose (LD_{50}) of I_2 for tumor cells is four times lower than that required for cells of normal origin, which suggests that the high availability of AA in tumor cells favors their iodination, generating 6-IL and triggering apoptosis [158].

Furthermore, we showed that 6-IL is a specific ligand and a potent promoter of peroxisome proliferator-activated receptor gamma (PPARγ) expression [167]. These receptors are ligand-activated transcription factors. In addition to regulating the expression of genes involved in lipid metabolism, their activation is associated with differentiation mechanisms, generating antiproliferative and drug resistance inhibition effects in various types of cancers [168]. Only three papers were yielded from the research carried out in PubMed (Table S10, Supplementary Materials). In preclinical models (MNU-induced mammary tumors in rats, in xenografts of various cancer cells in immunosuppressed mice, or canines with spontaneous breast cancer), the continuous oral supplement of I_2 sensitized tumor cells, allowing a better antineoplastic response, decreasing tumor size, and avoiding chemoresistance [169–171]. In fact, in a murine model, the I_2 supplement allowed reducing the doses of doxorubicin (DOX) up to fourfold, maintaining the antineoplastic effect and exerting protective effects on the heart and on health in general [169]. In a canine study, I_2 supplementation, together with DOX neoadjuvant therapy, reduced the severity of side effects and improved tumor response. The tumor decline (18%) was accompanied by inhibition in the expression of resistance/invasion genes such as Survivin, drug resistance protein 1 (MDR1), and plasminogen activating urokinase (uPA). The 10-month survival analysis showed that I_2 supplementation allowed a significant increase in disease-free time (73%) and survival (90%) [171]. In clinical studies in breast cancer patients, our group showed that the coadministration of I_2 with FEC (5′-fluorouracil, epirubicin, cyclophosphamide) chemotherapy was accompanied by a greater antineoplastic response (25% decrease in tumor size) and the absence of chemoresistance processes observed in 30% of patients treated only with FEC. This effect correlated with the activation of Th1 antitumor immune signaling pathways and with overexpression of PPARγ receptors in FEC+I_2 tumor samples. We also corroborated, as in the canine protocol, that the I_2 supplement significantly attenuates intestinal, cardiac, and general health side effects [10].

In relation to the immune system's modulatory mechanisms, it has been shown that various types of immune cells can internalize I_2 and, depending on the cellular context, this element can act as an anti-inflammatory or proinflammatory agent. In vitro, I_2 has also been shown to induce the release of antitumor cytokines, such as IL-6, IL-10, and IL-8 in normal leukocytes [172,173]. Another possibility

currently explored in our laboratory is that I_2 as an oxidized agent can exert epigenetic modifications associated with the activation of essential demethylase enzymes such as DNA methyltransferase 3 (DNMT3) ([174], unpublished data).

4. Discussion

Antineoplastic properties have been described in several micronutrients for decades, but none have shown solid evidence in vivo. One of the main pitfalls for any micronutrient is its bioavailability, which is usually low when supplementation is oral. For example, the average bioavailability is 33% for Vit D, 50% for Zn, 18% for iron, 15% for α-tocopherol, and 0.006% for Vit C [175–177]. All the micronutrients analyzed in this review have antiproliferative, apoptotic, and antimetastatic properties in vitro; however, in studies in vivo, the beneficial effects diminish or disappear. This can be explained because matching the dosages from in vitro to in vivo models orally and safely is difficult and often speculative. Another problem is the effectiveness; the heterogeneity of tumors and their differential response to treatments make it necessary to evaluate each nutrient for each type of malignancy. The third stumbling block is establishing the therapeutic dose/supplementation time. Not only have contrary effects been described depending on the timing of nutrient administration (as in the case of folates and Vit C), but numerous nutrients show different results depending on the dosage.

From the various mechanisms proposed to explain the antineoplastic effects of micronutrients, the most common is related to the antioxidant capability and includes Vit C and E, metals such as Zn, iron, and Se, and I_2. In the case of Vit D, its effects are explained by the ability of its key molecule, calcitriol, to bind nuclear receptors and regulate gene expression. During tumor progression, folate treatments increase expression in DNA methylation enzymes (DNMT1), decreasing tumor suppression genes. Studies on I_2 show that, in addition to its antioxidant actions in its 6-IL form, it is a genomic modulator as an agonist of PPARγ [160]. It has also been proposed as an epigenetic modifier due to its ability to regenerate DNA demethylating enzymes, which results in increased expression of tumor suppressor genes and genes of the cytotoxic immune system [178]. In this review, we analyzed the work of the main micronutrients in breast cancer progression. Only Vit D and I_2 showed clear antitumor effects in clinical studies, and both nutrients possess the capacity for gene regulation. In their study, Madden et al. [9] administered chronically with low doses of Vit D (10 μg/day) and observed a 20% reduction in mortality (49%). The work of Moreno-Vega et al., where they showed the efficacy of I_2 supplementation (alone or combined with chemotherapy) in a 5-year pilot study, showed a 63% increase in disease-free time, a reduction in tumor size, and cytotoxic immune system activation [10]. In this direction, there are many works analyzing the combination of nutrients and chemotherapeutic therapies evidencing synergic interactions which can lead to better outcomes [179,180]. Moreover, guidelines with combinations of different nutrients for cancer patients were commissioned by ESPEN (European Society for Clinical Nutrition and Metabolism) and by the European Partnership for Action Against Cancer (EPAAC) [181]. However, for now, more clinical studies are needed to establish their antitumor properties in vivo.

5. Patents

Aceves C, Anguiano B, Delgado G, Alfaro-Hernández Y, Torres-Martel JM, Peralta G, Domínguez A, Nava-Villalba M, Sosa S, Bontempo A, Godoy-García BL. Combinación de yodo molecular y antraciclinas de uso humano para la prevención y tratamiento de canceres quimiorresistentes captadores de yodo. Register: IMPI: MX/E/2017/009914. 19/04/2017. Validity 14/11/2012–14/11/20132.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6643/12/12/3613/s1. Tables S1: Vitamin D, Cell culture, Tables S2: Vitamin D, pre-clinical studies, Table S3: Vitamin D, clinical studies, Table S4: Metals, Table S5: Folates, Table S6. Vitamin C; Table S7: Polyphenols; Table S8: Fatty Acid, Table S9: Vitamin E, Table S10: Iodine.

Author Contributions: O.C.-M., conceptualization, bibliographic search, and writing of the original draft; C.A., review and editing, and project management. All authors read and agreed to the published version of the manuscript.

Funding: This research was partially supported by grants PAPIIT-UNAM 203919 and CONACYT 583336.

Acknowledgments: The authors are grateful to Evangelina Delgado-Gonzalez and Laura Ines Garcia for technical assistance, to Francisco Javier Valles and Rafael Silva for bibliographic assistance, to Nuri Aranda and Lourdes Lara for academic support, to Alberto Lara, Omar Gonzalez, Ramon Martinez, and Maria Eugenia Rosas Alatorre for computer assistance, and to Jessica Gonzalez Norris for proofreading.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Willett, W.C. Micronutrients and cancer risk. *Am. J. Clin. Nutr.* **1994**, *59*, 1162S–1165S. [CrossRef]
2. World Health Organization. 2018. Available online: https://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en (accessed on 27 October 2019).
3. Freudenheim, J.L.; Marshall, J.R.; Vena, J.E.; Laughlin, R.; Brasure, J.R.; Swanson, M.K.; Graham, S. Premenopausal breast cancer risk and intake of vegetables, fruits, and related nutrients. *JNCI J. Natl. Cancer Inst.* **1996**, *88*, 340–348. [CrossRef] [PubMed]
4. Braga, C.; La VBecchia, C.; Negri, E.; Franceschi, S.; Parpinel, M. Intake of selected foods and nutrients and breast cancer risk: An age-and menopause-specific analysis. *Nutr. Cancer* **1997**, *28*, 258–263. [CrossRef] [PubMed]
5. Hanf, V.; Gonder, U. Nutrition and primary prevention of breast cancer: Foods, nutrients and breast cancer risk. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2005**, *123*, 139–149. [CrossRef] [PubMed]
6. Cho, E.; Holmes, M.; Hankinson, S.E.; Willett, W.C. Nutrients involved in one-carbon metabolism and risk of breast cancer among premenopausal women. *Cancer Epidemiol. Prev. Biomark.* **2007**, *16*, 2787–2790. [CrossRef] [PubMed]
7. Russo, I.H.; Russo, J. Role of hormones in mammary cancer initiation and progression. *J. Mammary Gland Biol. Neoplasia* **1998**, *3*, 49–61. [CrossRef]
8. Kim, Y.I. Role of folate in colon cancer development and progression. *J. Nutr.* **2003**, *133*, 3731S–3739S. [CrossRef]
9. Madden, J.M.; Murphy, L.; Zgaga, L.; Bennett, K. De novo vitamin D supplement use post- diagnosis is associated with breast cancer survival. *Breast Cancer Res. Treat.* **2018**, *172*, 179–190. [CrossRef]
10. Moreno-Vega, A.; Vega-Riveroll, L.; Ayala, T.; Peralta, G.; Torres-Martel, J.M.; Rojas, J.; Anguiano, B. Adjuvant Effect of Molecular Iodine in Conventional Chemotherapy for Breast Cancer. Randomized Pilot Study. *Nutrients* **2019**, *11*, 1623. [CrossRef]
11. Gil, Á.; Plaza-Diaz, J.; Mesa, M.D. Vitamin D: Classic and novel actions. *Ann. Nutr. Metab.* **2018**, *72*, 87–95. [CrossRef]
12. Baeke, F.; Takiishi, T.; Korf, H.; Gysemans, C.; Mathieu, C. Vitamin D: Modulator of the immune system. *Curr. Opin. Pharmacol.* **2010**, *10*, 482–496. [CrossRef] [PubMed]
13. Carlberg, C.; Bendik, I.; Wyss, A.; Meier, E.; Sturzenbecker, L.J.; Grippo, J.F.; Hunziker, W. Two nuclear signalling pathways for vitamin D. *Nature* **1993**, *361*, 657. [CrossRef] [PubMed]
14. Haussler, M.R.; Whitfield, G.K.; Haussler, C.A.; Sabir, M.S.; Khan, Z.; Sandoval, R.; Jurutka, P.W. 1,25-Dihydroxyvitamin D and Klotho: A tale of two renal hormones coming of age. In *Vitamins & Hormones*; Academic Press: Cambridge, MA, USA, 2016; Volume 100, pp. 165–230.
15. Karlic, H.; Varga, F. Impact of vitamin D metabolism on clinical epigenetics. *Clin. Epigenetics* **2011**, *2*, 55–61. [CrossRef]
16. Deeb, K.K.; Trump, D.L.; Johnson, C.S. Vitamin D signalling pathways in cancer: Potential for anticancer therapeutics. *Nat. Rev. Cancer* **2007**, *7*, 684. [CrossRef]
17. Krishnan, A.V.; Swami, S.; Peng, L.; Wang, J.; Moreno, J.; Feldman, D. Tissue-selective regulation of aromatase expression by calcitriol: Implications for breast cancer therapy. *Endocrinology* **2010**, *151*, 32–42. [CrossRef]
18. Shan, N.L.; Wahler, J.; Lee, H.J.; Bak, M.J.; Gupta, S.D.; Maehr, H.; Suh, N. Vitamin D compounds inhibit cancer stem-like cells and induce differentiation in triple negative breast cancer. *J. Steroid Biochem. Mol. Biol.* **2017**, *173*, 122–129. [CrossRef] [PubMed]

19. Wahler, J.; So, J.Y.; Cheng, L.C.; Maehr, H.; Uskokovic, M.; Suh, N. Vitamin D compounds reduce mammosphere formation and decrease expression of putative stem cell markers in breast cancer. *J. Steroid Biochem. Mol. Biol.* **2015**, *148*, 148–155. [CrossRef] [PubMed]
20. Yuan, L.; Jiang, R.; Yang, Y.; Ding, S.; Deng, H. 1,25-Dihydroxyvitamin D3 inhibits growth of the breast cancer cell line MCF-7 and downregulates cytochrome P4501B1 through the COX-2/PGE2 pathway. *Oncol. Rep.* **2012**, *28*, 2131–2137. [CrossRef]
21. James, S.Y.; Mackay, A.G.; Colston, K.W. Effects of 1, 25 dihydroxyvitamin D3 and its analogues on induction of apoptosis in breast cancer cells. *J. Steroid Biochem. Mol. Biol.* **1996**, *58*, 395–401. [CrossRef]
22. Koren, R.; Hadari-Naor, I.; Zuck, E.; Rotem, C.; Liberman, U.A.; Ravid, A. Vitamin D is a prooxidant in breast cancer cells. *Cancer Res.* **2001**, *61*, 1439–1444.
23. Nolan, E.; Donepudi, M.; VanWeelden, K.; Flanagan, L.; Welsh, J. Dissociation of vitamin D3 and anti-estrogen mediated growth regulation in MCF-7 breast cancer cells. *Mol. Cell. Biochem.* **1998**, *188*, 13–20. [CrossRef] [PubMed]
24. Ooi, L.L.; Zheng, Y.; Zhou, H.; Trivedi, T.; Conigrave, A.D.; Seibel, M.J.; Dunstan, C.R. Vitamin D deficiency promotes growth of MCF-7 human breast cancer in a rodent model of osteosclerotic bone metastasis. *Bone* **2010**, *47*, 795–803. [CrossRef] [PubMed]
25. Swami, S.; Krishnan, A.V.; Williams, J.; Aggarwal, A.; Albertelli, M.A.; Horst, R.L.; Feldman, B.J.; Feldman, D. Vitamin D mitigates the adverse effects of obesity on breast cancer in mice. *Endocr. Relat. Cancer* **2016**, *23*, 251–264. [CrossRef] [PubMed]
26. Paduch, R.; Kandefer-Szerszeń, M. Vitamin D, tamoxifen and β-estradiol modulate breast cancer cell growth and interleukin-6 and metalloproteinase-2 production in three-dimensional co-cultures of tumor cell spheroids with endothelium. *Cell Biol. Toxicol.* **2005**, *21*, 247–256. [CrossRef]
27. Wilmanski, T.; Zhou, X.; Zheng, W.; Shinde, A.; Donkin, S.S.; Wendt, M.; Burgess, J.R.; Teegarden, D. Inhibition of pyruvate carboxylase by 1α,25-dihydroxyvitamin D promotes oxidative stress in early breast cancer progression. *Cancer Lett.* **2017**, *411*, 171–181. [CrossRef]
28. Zhou, X.; Zheng, W.; Gowda, G.N.; Raftery, D.; Donkin, S.S.; Teegarden, D.; Teegarden, D. 1,25-Dihydroxyvitamin D inhibits glutamine metabolism in Harvey-ras transformed MCF10A human breast epithelial cell. *J. Steroid Biochem. Mol. Biol.* **2016**, *163*, 147–156. [CrossRef]
29. Zheng, W.; Tayyari, F.; Gowda, G.A.N.; Raftery, D.; McLamore, E.S.; Shi, J.; Porterfield, D.M.; Donkin, S.S.; Bequette, B.J.; Teegarden, D. 1,25-dihydroxyvitamin D regulation of glucose metabolism in Harvey-ras transformed MCF10A human breast epithelial cells. *J. Steroid Biochem. Mol. Biol.* **2013**, *138*, 81–89. [CrossRef]
30. Pluchino, L.A.; Liu, A.K.-Y.; Wang, H.-C.R. Reactive oxygen species-mediated breast cell carcinogenesis enhanced by multiple carcinogens and intervened by dietary ergosterol and mimosine. *Free Radic. Biol. Med.* **2015**, *80*, 12–26. [CrossRef]
31. García-Becerra, R.; Díaz, L.; Camacho, J.; Barrera, D.; Ordaz-Rosado, D.; Morales, A.; Ortiz, C.S.; Avila, E.; Bargalló, E.; Arrecillas, M.; et al. Calcitriol inhibits Ether-à go-go potassium channel expression and cell proliferation in human breast cancer cells. *Exp. Cell Res.* **2010**, *316*, 433–442. [CrossRef]
32. Tavera-Mendoza, L.E.; Westerling, T.; Libby, E.; Marusyk, A.; Cato, L.; Cassani, R.; Cameron, L.A.; Ficarro, S.B.; Marto, J.A.; Klawitter, J.; et al. Vitamin D receptor regulates autophagy in the normal mammary gland and in luminal breast cancer cells. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, E2186–E2194. [CrossRef]
33. Anisiewicz, A.; Pawlik, A.; Filip-Psurska, B.; Turlej, E.; Dzimira, S.; Milczarek, M.; Gdesz, K.; Papiernik, D.; Jarosz, J.; Kłopotowska, D.; et al. Unfavorable effect of calcitriol and its low-calcemic analogs on metastasis of 4T1 mouse mammary gland cancer. *Int. J. Oncol.* **2017**, *52*, 103–126. [CrossRef]
34. Amir, E.; Simmons, C.E.; Freedman, O.C.; Dranitsaris, G.; Cole, D.E.; Vieth, R.; Clemons, M. A phase 2 trial exploring the effects of high-dose (10,000 IU/day) vitamin D3 in breast cancer patients with bone metastases. *Cancer Interdiscip. Int. J. Am. Cancer Soc.* **2010**, *116*, 284–291.
35. Rossdeutscher, L.; Li, J.; Luco, A.-L.; Fadhil, I.; Ochietti, B.; Camirand, A.; Huang, D.C.; Reinhardt, T.A.; Muller, W.; Kremer, R. Chemoprevention Activity of 25-Hydroxyvitamin D in the MMTV-PyMT Mouse Model of Breast Cancer. *Cancer Prev. Res.* **2014**, *8*, 120–128. [CrossRef]
36. Williams, J.D.; Aggarwal, A.; Swami, S.; Krishnan, A.V.; Ji, L.; Albertelli, M.A.; Feldman, B.J. Tumor Autonomous Effects of Vitamin D Deficiency Promote Breast Cancer Metastasis. *Endocrinology* **2016**, *157*, 1341–1347. [CrossRef] [PubMed]

37. Peppone, L.J.; Huston, A.J.; Reid, M.E.; Rosier, R.N.; Zakharia, Y.; Trump, D.L.; Mustian, K.M.; Janelsins, M.C.; Purnell, J.Q.; Morrow, G.R. The effect of various vitamin D supplementation regimens in breast cancer patients. *Breast Cancer Res. Treat.* **2011**, *127*, 171–177. [CrossRef] [PubMed]
38. Chen, L.; Yang, R.; Qiao, W.; Yuan, X.; Wang, S.; Goltzman, D.; Miao, D. 1,25-Dihydroxy vitamin D prevents tumorigenesis by inhibiting oxidative stress and inducing tumor cellular senescence in mice. *Int. J. Cancer* **2018**, *143*, 368–382. [CrossRef] [PubMed]
39. García-Quiroz, J.; García-Becerra, R.; Santos-Martínez, N.; Barrera, D.; Ordaz-Rosado, D.; Avila, E.; Halhali, A.; Villanueva, O.; Ibarra-Sánchez, M.J.; Esparza-López, J.; et al. In vivo dual targeting of the oncogenic Ether-à-go-go-1 potassium channel by calcitriol and astemizole results in enhanced antineoplastic effects in breast tumors. *BMC Cancer* **2014**, *14*, 1–10. [CrossRef] [PubMed]
40. Li, J.; Luco, A.-L.; Ochietti, B.; Fadhil, I.; Camirand, A.; Reinhardt, T.A.; St-Arnaud, R.; Muller, W.; Kremer, R. Tumoral Vitamin D Synthesis by CYP27B1 1-α-Hydroxylase Delays Mammary Tumor Progression in the PyMT-MMTV Mouse Model and Its Action Involves NF-κB Modulation. *Endocrinology* **2016**, *157*, 2204–2216. [CrossRef] [PubMed]
41. Shin, W.-K.; Kim, Z.; Youn, H.J.; Cho, J.; Lee, J.E. Determinants of Plasma 25-Hydroxyvitamin D Concentrations among Breast Cancer Survivors in Korea. *Nutrients* **2018**, *10*, 380. [CrossRef]
42. Yao, S.; Kwan, M.L.; Ergas, I.J.; Roh, J.M.; Cheng, T.Y.D.; Hong, C.C.; Quesenberry, C.P., Jr. Higher serum levels of vitamin D at diagnosis are associated with better survival in a prospective cohort of 1,666 women with breast cancer: A case-cohort analysis in the Path-ways Study. *JAMA Oncol.* **2017**, *3*, 351. [CrossRef]
43. Thanasitthichai, S.; Chaiwerawattana, A.; Prasitthipayong, A. Association of Vitamin D Level with Clinicopathological Features in Breast Cancer. *Asian Pac. J. Cancer Prev.* **2015**, *16*, 4881–4883. [CrossRef] [PubMed]
44. Mawer, E.B.; Walls, J.; Howell, A.; Davies, M.; Ratcliffe, W.A.; Bundred, N.J. Serum 1,25-Dihydroxyvitamin D may be related inversely to disease activity in breast cancer pa-tients with bone metastases. *J. Clin. Endocrinol. Metab.* **1997**, *82*, 118–122. [PubMed]
45. Palmieri, C.; MacGregor, T.; Girgis, S.; Vigushin, D. Serum 25-hydroxyvitamin D levels in early and advanced breast cancer. *J. Clin. Pathol.* **2006**, *59*, 1334–1336. [CrossRef]
46. Feldman, D.; Krishnan, A.V.; Swami, S.; Giovannucci, E.; Feldman, B.J. The role of vitamin D in reducing cancer risk and progression. *Nat. Rev. Cancer* **2014**, *14*, 342–357. [CrossRef]
47. Goulão, B.; Stewart, F.; A Ford, J.; MacLennan, G.; Avenell, A. Cancer and vitamin D supplementation: A systematic review and meta-analysis. *Am. J. Clin. Nutr.* **2018**, *107*, 652–663. [CrossRef]
48. Percival, S.S. Copper and immunity. *Am. J. Clin. Nutr.* **1998**, *67*, 1064S–1068S. [CrossRef]
49. Ognik, K.; Cholewińska, E.; Juśkiewicz, J.; Zduńczyk, Z.; Tutaj, K.; Szlązak, R. The effect of copper nanoparticles and copper (II) salt on redox reactions and epigenetic changes in a rat model. *J. Anim. Physiol. Anim. Nutr.* **2019**, *103*, 675–686. [CrossRef]
50. Wachnik, A. The physiological role of copper and the problems of copper nutritional deficiency. *Food Nahrung* **1988**, *32*, 755–765. [CrossRef] [PubMed]
51. Turski, M.L.; Brady, D.C.; Kim, H.J.; Kim, B.-E.; Nose, Y.; Counter, C.M.; Winge, D.R.; Thiele, D.J. A Novel Role for Copper in Ras/Mitogen-Activated Protein Kinase Signaling. *Mol. Cell. Biol.* **2012**, *32*, 1284–1295. [CrossRef]
52. Trumbo, P.; Yates, A.A.; Schlicker, S.; Poos, M. Dietary reference intakes: Vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. *J. Acad. Nutr. Diet.* **2001**, *101*, 294.
53. Denoyer, D.; Masaldan, S.; La Fontaine, S.; Cater, M.A. Targeting copper in cancer therapy:'Copper That Cancer'. *Metallomics* **2015**, *7*, 1459–1476. [CrossRef]
54. Gupte, A.; Mumper, R.J. Elevated copper and oxidative stress in cancer cells as a target for cancer treatment. *Cancer Treat. Rev.* **2009**, *35*, 32–46. [CrossRef] [PubMed]
55. Kuo, H.W.; Chen, S.F.; Wu, C.C.; Chen, D.R.; Lee, J.H. Serum and Tissue Trace Elements in Patients with Breast Cancer in Taiwan. *Biol. Trace Element Res.* **2002**, *89*, 1–12. [CrossRef]
56. Ostrakhovitch, E.; Cherian, M. Differential regulation of signal transduction pathways in wild type and mutated p53 breast cancer epithelial cells by copper and zinc. *Arch. Biochem. Biophys.* **2004**, *423*, 351–361. [CrossRef] [PubMed]

57. Cihan, Y.B.; Sözen, S.; Yıldırım, S.Ö. Trace elements and heavy metals in hair of stage III breast cancer patients. *Biol. Trace Elem. Res.* **2011**, *144*, 360–379. [CrossRef] [PubMed]
58. Vaidya, S.M.; Kamalakar, P.L. Copper and ceruloplasmin levels in serum of women with breast cancer. *Indian J. Med Sci.* **1998**, *52*, 184–187.
59. Macdonald, G.; Nalvarte, I.; Smirnova, T.; Vecchi, M.; Aceto, N.; Doelemeyer, A.; Frei, A.; Lienhard, S.; Wyckoff, J.; Hess, D.; et al. Memo Is a Copper-Dependent Redox Protein with an Essential Role in Migration and Metastasis. *Sci. Signal.* **2014**, *7*, ra56. [CrossRef]
60. Chan, N.; Willis, A.; Kornhauser, N.; Ward, M.M.; Lee, S.B.; Nackos, E.; Seo, B.R.; Chuang, E.; Cigler, T.; Moore, A.; et al. Influencing the Tumor Microenvironment: A Phase II Study of Copper Depletion Using Tetrathiomolybdate in Patients with Breast Cancer at High Risk for Recurrence and in Preclinical Models of Lung Metastases. *Clin. Cancer Res.* **2017**, *23*, 666–676. [CrossRef]
61. Pantopoulos, K.; Porwal, S.K.; Tartakoff, A.; Devireddy, L. Mechanisms of mammalian iron homeostasis. *Biochemistry* **2012**, *51*, 5705–5724. [CrossRef]
62. Ganz, T. Hepcidin and iron regulation, 10 years later. *Blood J. Am. Soc. Hematol.* **2011**, *117*, 4425–4433. [CrossRef]
63. Liu, Q.; Davidoff, O.; Niss, K.; Haase, V.H. Hypoxia-inducible factor regulates hepcidin via erythropoietin-induced erythropoiesis. *J. Clin. Investig.* **2012**, *122*, 4635–4644. [CrossRef]
64. Radulescu, S.; Blanke, O.; Salgueiro, P.; Ridgway, R.A.; McGhee, E.; Anderson, K.; Ford, S.J.; Stones, D.H.; Iqbal, T.H.; Tselepis, C.; et al. Luminal Iron Levels Govern Intestinal Tumorigenesis after Apc Loss In Vivo. *Cell Rep.* **2012**, *2*, 270–282. [CrossRef]
65. Lui, G.Y.L.; Obeidy, P.; Ford, S.J.; Tselepis, C.; Sharp, D.M.; Jansson, P.J.; Kalinowski, D.S.; Kovacevic, Z.; Lovejoy, D.B.; Richardson, D.R. The Iron Chelator, Deferasirox, as a Novel Strategy for Cancer Treatment: Oral Activity against Human Lung Tumor Xenografts and Molecular Mechanism of Action. *Mol. Pharmacol.* **2012**, *83*, 179–190. [CrossRef]
66. Torti, S.V.; Manz, D.H.; Paul, B.T.; Blanchette-Farra, N.; Torti, F.M. Iron and cancer. *Annu. Rev. Rutrition* **2018**, *38*, 97–125. [CrossRef] [PubMed]
67. Chifman, J.; Arat, S.; Deng, Z.; Lemler, E.; Pino, J.C.; Harris, L.A.; Kochen, M.A.; Lopez, C.F.; Akman, S.A.; Torti, F.M.; et al. Activated Oncogenic Pathway Modifies Iron Network in Breast Epithelial Cells: A Dynamic Modeling Perspective. *PLoS Comput. Biol.* **2017**, *13*, e1005352. [CrossRef] [PubMed]
68. Coombs, M.R.P.; Grant, T.; Greenshields, A.L.; Arsenault, D.J.; Holbein, B.E.; Hoskin, D.W. Inhibitory effect of iron withdrawal by chelation on the growth of human and murine mammary carcinoma and fibrosarcoma cells. *Exp. Mol. Pathol.* **2015**, *99*, 262–270. [CrossRef] [PubMed]
69. García, F.J.A.; Fernández, D.T.; Álvarez, E.A.; González, E.B.; Montes-Bayón, M.; Medel, A.S. Iron speciation, ferritin concentrations and Fe: Ferritin ratios in different malignant breast cancer cell lines: On the search for cancer biomarkers. *Metallomics* **2016**, *8*, 1090–1096. [CrossRef] [PubMed]
70. Jablonska, E.; Socha, K.; Reszka, E.; Wieczorek, E.; Skokowski, J.; Kalinowski, L.; Wasowicz, W. Cadmium, arsenic, selenium and iron–Implications for tumor progres-sion in breast cancer. *Environ. Toxicol. Pharmacol.* **2017**, *53*, 151–157. [CrossRef] [PubMed]
71. Kryukov, G.V.; Castellano, S.; Novoselov, S.V.; Lobanov, A.V.; Zehtab, O.; Guigó, R.; Gladyshev, V.N. Characterization of Mammalian Selenoproteomes. *Science* **2003**, *300*, 1439–1443. [CrossRef] [PubMed]
72. Rayman, M. Selenium and human health. *Lancet* **2012**, *379*, 1256–1268. [CrossRef]
73. Jablonska, E.; Reszka, E. Selenium and Epigenetics in Cancer: Focus on DNA Methylation. In *Advances in Cancer Research*; Academic Press: Cambridge, MA, USA, 2017; Volume 136, pp. 193–234.
74. Rayman, M.P. The use of high-selenium yeast to raise selenium status: How does it measure up? *Br. J. Nutr.* **2004**, *92*, 557–573. [CrossRef] [PubMed]
75. Vinceti, M.; Filippini, T.; Del Giovane, C.; Dennert, G.; Zwahlen, M.; Brinkman, M.; Cres-pi, C.M. Selenium for preventing cancer. *Cochrane Database Syst. Rev.* **2018**. [CrossRef] [PubMed]
76. Gupta, S.; Narang, R.; Krishnaswami, K.; Yadav, S. Plasma selenium level in cancer patients. *Indian J. Cancer* **1994**, *31*, 192–197. [PubMed]
77. Harris, H.R.; Bergkvist, L.; Wolk, A. Selenium intake and breast cancer mortality in a cohort of Swedish women. *Breast Cancer Res. Treat.* **2012**, *134*, 1269–1277. [CrossRef]
78. Guo, C.-H.; Hsia, S.; Chen, P.-C. Distribution of Selenium and Oxidative Stress in Breast Tumor-Bearing Mice. *Nutrients* **2013**, *5*, 594–607. [CrossRef]

79. Warrington, J.M.; Kim, J.J.; Stahel, P.; Cieslar, S.R.; Moorehead, R.A.; Coomber, B.L.; Corredig, M.; Cant, J.P. Selenized milk casein in the diet of BALB/c nude mice reduces growth of intramammary MCF-7 tumors. *BMC Cancer* **2013**, *13*, 492. [CrossRef]
80. Chasapis, C.T.; Loutsidou, A.C.; Spiliopoulou, C.A.; Stefanidou, M. Zinc and human health: An update. *Arch. Toxicol.* **2012**, *86*, 521–534. [CrossRef]
81. Wessels, I.; Haase, H.; Engelhardt, G.; Rink, L.; Uciechowski, P. Zinc deficiency induces production of the proinflammatory cytokines IL-1β and TNFα in promyeloid cells via epigenetic and redox-dependent mechanisms. *J. Nutr. Biochem.* **2013**, *24*, 289–297. [CrossRef]
82. Federico, A.; Iodice, P.; Federico, P.; Del Rio, A.; Mellone, M.C.; Catalano, G. Effects of selenium and zinc supplementation on nutritional status in patients with cancer of digestive tract. *Eur. J. Clin. Nutr.* **2001**, *55*, 293. [CrossRef]
83. Prasad, A.S.; Beck, F.W.; Doerr, T.D.; Shamsa, F.H.; Penny, H.S.; Marks, S.C.; Mathog, R.H. Nutritional and zinc status of head and neck cancer patients: An interpretive review. *J. Am. Coll. Nutr.* **1998**, *17*, 409–418. [CrossRef]
84. Kopański, Z.; Piekoszewski, W.; Habiniak, J.; Wojewoda, T.; Wojewoda, A.; Schlegel-Zawadzka, M.; Sibiga, W. The clinical value of the determinations in the serum of zinc concentration in women with breast cancer. *Folia Histochem. Cytobiol.* **2001**, *39*, 84–86. [PubMed]
85. Costello, L.C.; Zou, J.; Franklin, R.B. In situ clinical evidence that zinc levels are decreased in breast invasive ductal carcinoma. *Cancer Causes Control* **2016**, *27*, 729–735. [CrossRef] [PubMed]
86. Jin, R.; Bay, B.; Tan, P.; Tan, B.K. Metallothionein expression and zinc levels in invasive ductal breast carcinoma. *Oncol. Rep.* **1999**, *6*, 871–876. [CrossRef] [PubMed]
87. Kagara, N.; Tanaka, N.; Noguchi, S.; Hirano, T. Zinc and its transporter ZIP10 are involved in invasive behavior of breast cancer cells. *Cancer Sci.* **2007**, *98*, 692–697. [CrossRef]
88. Matsui, C.; Takatani-Nakase, T.; Hatano, Y.; Kawahara, S.; Nakase, I.; Takahashi, K. Zinc and its transporter ZIP6 are key mediators of breast cancer cell survival under high glucose conditions. *FEBS Lett.* **2017**, *591*, 3348–3359. [CrossRef]
89. Nauss, K.M.; Newberne, P.M. Effects of Dietary Folate, Vitamin B12 and Methionine/Choline Deficiency on Immune Function. In *Diet and Resistance to Disease*; Springer Science and Business Media LLC: Berlin, Germany, 1981; Volume 135, pp. 63–91.
90. Bailey, L.B.; Caudill, M.A. Folate. In *Present Knowledge in Nutrition*; Elsevier: Amsterdam, The Netherlands, 2012; pp. 321–342.
91. Ebara, S. Nutritional role of folate. Congenit. *Anomalies* **2017**, *57*, 138–141. [CrossRef]
92. Kim, Y.-I. Folate: A magic bullet or a double edged sword for colorectal cancer prevention? *Gut* **2006**, *55*, 1387–1389. [CrossRef]
93. Ulrich, C.M. Folate Supplementation: Too Much of a Good Thing? *Cancer Epidemiol. Biomark. Prev.* **2006**, *15*, 189–193. [CrossRef]
94. Ulrich, C.M.; Potter, J.D. Folate and cancer—timing is everything. *Jama* **2007**, *297*, 2408–2409. [CrossRef]
95. Kim, K.-C.; Friso, S.; Choi, S.-W. DNA methylation, an epigenetic mechanism connecting folate to healthy embryonic development and aging. *J. Nutr. Biochem.* **2009**, *20*, 917–926. [CrossRef]
96. Robert, M.-F.; Morin, S.; Beaulieu, N.; Gauthier, F.; Chute, I.C.; Barsalou, A.; MacLeod, A.R. DNMT1 is required to maintain CpG methylation and aberrant gene silencing in human cancer cells. *Nat. Genet.* **2003**, *33*, 61–65. [CrossRef] [PubMed]
97. Hansen, M.F.; Jensen, S. Østrup; Füchtbauer, E.-M.; Martensen, P.M. High folic acid diet enhances tumour growth in PyMT-induced breast cancer. *Br. J. Cancer* **2017**, *116*, 752–761. [CrossRef]
98. Kotsopoulos, J.; Medline, A.; Renlund, R.; Sohn, K.-J.; Martin, R.; Hwang, S.W.; Lu, S.; Archer, M.C.; Kim, Y.-I. Effects of dietary folate on the development and progression of mammary tumors in rats. *Carcinogenesis* **2005**, *26*, 1603–1612. [CrossRef] [PubMed]
99. Lee, Y.; Lee, S.-A.; Choi, J.-Y.; Song, M.; Sung, H.; Jeon, S.; Park, S.K.; Yoo, K.Y.; Noh, D.-Y.; Lee, J.-Y.; et al. Prognosis of breast cancer is associated with one-carbon metabolism related nutrients among Korean women. *Nutr. J.* **2012**, *11*, 59. [CrossRef] [PubMed]
100. Lubecka, K.; Kaufman-Szymczyk, A.; Stefanska, B.; Fabianowska-Majewska, K. Folic acid enforces DNA methylation-mediated transcriptional silencing of PTEN, APC and RARbeta2 tumour suppressor genes in breast cancer. *Biochem. Biophys. Res. Commun.* **2013**, *430*, 623–628. [CrossRef]

101. Manshadi, S.D.; Ishiguro, L.; Sohn, K.-J.; Medline, A.; Renlund, R.; Croxford, R.; Kim, Y.-I. Folic acid supplementation promotes mammary tumor progression in a rat model. *PLoS ONE* **2014**, *9*, e84635. [CrossRef]
102. Harris, H.R.; Bergkvist, L.; Wolk, A. Folate intake and breast cancer mortality in a cohort of Swedish women. *Breast Cancer Res. Treat.* **2011**, *132*, 243–250. [CrossRef]
103. Naushad, S.M.; Pavani, A.; Rupasree, Y.; Divyya, S.; Deepti, S.; Digumarti, R.R.; Gottumukkala, S.R.; Prayaga, A.; Kutala, V.K. Association of aberrations in one-carbon metabolism with molecular phenotype and grade of breast cancer. *Mol. Carcinog.* **2011**, *51*, E32–E41. [CrossRef]
104. Rath, M. *Eradicating Heart Disease*; Health Now: New York, NY, USA, 1993.
105. Gaby, S.K.; Bendich, A.; Singh, V.S.; Machlin, L.J. *Vitamin Intake and Health: A Scientific Review*; CRC Press: New York, NY, USA, 1990.
106. Peepre, K.; Deshpandey, U.; Choudhary, P.S. Role of antioxidants on thyroid hor-mones in Wister rats. *Int. J. Sci. Res.* **2014**, *3*, 34–38.
107. Iqbal, K.; Khan, A.; Khattak, M.M.A.K. Biological Significance of Ascorbic Acid (Vitamin C) in Human Health—A Review. *Pak. J. Nutr.* **2003**, *3*, 5–13. [CrossRef]
108. Bendich, A. Antioxidant Micronutrients and Immune Responses. *Ann. N. Y. Acad. Sci.* **1990**, *587*, 168–180. [CrossRef]
109. Gillberg, L.; Ørskov, A.D.; Liu, M.; Harsløf, L.B.; Jones, P.A.; Grønbæk, K. Vitamin C–A new player in regulation of the cancer epigenome. In *Seminars in Cancer Biology*; Academic Press: Cambridge, MA, USA, 2018; Volume 51, pp. 59–67.
110. Chen, Q.; Espey, M.G.; Sun, A.Y.; Pooput, C.; Kirk, K.L.; Krishna, M.C.; Khosh, D.B.; Drisko, J.; Levine, M. Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 11105–11109. [CrossRef] [PubMed]
111. Cha, J.; Roomi, M.W.; Kalinovsky, T.; Niedzwiecki, A.; Rath, M. Lipoprotein(a) and vitamin C impair development of breast cancer tumors in Lp(a)+; Gulo-/- mice. *Int. J. Oncol.* **2016**, *49*, 895–902. [CrossRef]
112. Kim, K.-N.; Pie, J.-E.; Park, J.-H.; Park, Y.-H.; Kim, H.-W.; Kim, M.-K. Retinoic acid and ascorbic acid act synergistically in inhibiting human breast cancer cell proliferation. *J. Nutr. Biochem.* **2006**, *17*, 454–462. [CrossRef]
113. Harris, H.R.; Bergkvist, L.; Wolk, A. Vitamin C intake and breast cancer mortality in a cohort of Swedish women. *Br. J. Cancer* **2013**, *109*, 257–264. [CrossRef] [PubMed]
114. Khanzode, S.S.; Muddeshwar, M.; Khanzode, S.D.; Dakhale, G.N. Antioxidant Enzymes and Lipid Peroxidation in Different Stages of Breast Cancer. *Free Radic. Res.* **2004**, *38*, 81–85. [CrossRef] [PubMed]
115. Nagamma, T.; Baxi, J.; Singh, P. Status of Oxidative Stress and Antioxidant Levels in Smokers with Breast Cancer from Western Nepal. *Asian Pac. J. Cancer Prev.* **2014**, *15*, 9467–9470. [CrossRef] [PubMed]
116. Mikirova, N.A.; Casciari, J.; Rogers, A.; Taylor, P. Effect of high-dose intravenous vitamin C on inflammation in cancer patients. *J. Transl. Med.* **2012**, *10*, 189. [CrossRef]
117. Bravo, L. Polyphenols: Chemistry, dietary sources, metabolism, and nutritional signif-icance. *Nutr. Rev.* **1998**, *56*, 317–333. [CrossRef]
118. Milner, J.A. Reducing the Risk of Cancer. In *Functional Foods*; Springer Science and Business Media LLC: Berlin, Germany, 1994; pp. 39–70.
119. Duthie, G.G.; Brown, K.M. Reducing the Risk of Cardiovascular Disease. In *Functional Foods*; Springer Science and Business Media LLC: Berlin, Germany, 1994; pp. 19–38.
120. Andjelkovic, M.; Van Camp, J.; De Meulenaer, B.; Depaemelaere, G.; Socaciu, C.; Verloo, M.; Verhe, R. Iron-chelation properties of phenolic acids bearing catechol and galloyl groups. *Food Chem.* **2006**, *98*, 23–31. [CrossRef]
121. Miles, E.A.; Zoubouli, P.; Calder, P.C. Differential anti-inflammatory effects of phenolic compounds from extra virgin olive oil identified in human whole blood cultures. *Nutrition* **2005**, *21*, 389–394. [CrossRef] [PubMed]
122. de Souza, E.L.; De Albuquerque, T.M.R.; Dos Santos, A.S.; Massa, N.M.L.; Alves, J.L.D.B. Potential interactions among phenolic compounds and probiotics for mutual boosting of their health-promoting properties and food functionalities—A review. *Crit. Rev. Food Sci. Nutr.* **2019**, *59*, 1645–1659. [CrossRef] [PubMed]

123. Cipolletti, M.; Fernandez, V.S.; Montalesi, E.; Marino, M.; Fiocchetti, M. Beyond the Antioxidant Activity of Dietary Polyphenols in Cancer: The Modulation of Estrogen Receptors (ERs) Signaling. *Int. J. Mol. Sci.* **2018**, *19*, 2624. [CrossRef] [PubMed]
124. Sakamoto, T.; Horiguchi, H.; Oguma, E.; Kayama, F. Effects of diverse dietary phy-toestrogens on cell growth, cell cycle and apoptosis in estrogen-receptor-positive breast can-cer cells. *J. Nutr. Biochem.* **2010**, *21*, 856–864. [CrossRef] [PubMed]
125. Virgili, F.; Marino, M. Regulation of cellular signals from nutritional molecules: A specific role for phytochemicals, beyond antioxidant activity. *Free Radic. Biol. Med.* **2008**, *45*, 1205–1216. [CrossRef]
126. Liu, H.; Du, J.; Hu, C.; Qi, H.; Wang, X.; Wang, S.; Liu, Q.; Li, Z. Delayed activation of extracellular-signal-regulated kinase 1/2 is involved in genistein- and equol-induced cell proliferation and estrogen-receptor-α-mediated transcription in MCF-7 breast cancer cells. *J. Nutr. Biochem.* **2010**, *21*, 390–396. [CrossRef]
127. Murata, M.; Midorikawa, K.; Koh, M.; Umezawa, K.; Kawanishi, S. Genistein and daidzein induce cell proliferation and their metabolites cause oxidative DNA damage in relation to isoflavone-induced cancer of estrogen-sensitive organs. *Biochemistry* **2004**, *43*, 2569–2577. [CrossRef]
128. Bouallagui, Z.; Han, J.; Isoda, H.; Sayadi, S. Hydroxytyrosol rich extract from olive leaves modulates cell cycle progression in MCF-7 human breast cancer cells. *Food Chem. Toxicol.* **2011**, *49*, 179–184. [CrossRef]
129. Naso, L.G.; Badiola, I.; Clavijo, J.M.; Valcarcel, M.; Salado, C.; Ferrer, E.G.; Williams, P.A. Inhibition of the metastatic progression of breast and colorectal cancer in vitro and in vivo in murine model by the oxidovanadium(IV) complex with luteolin. *Bioorg. Med. Chem.* **2016**, *24*, 6004–6011. [CrossRef]
130. Schindler, R.; Mentlein, R. Flavonoids and Vitamin E Reduce the Release of the Angiogenic Peptide Vascular Endothelial Growth Factor from Human Tumor Cells. *J. Nutr.* **2006**, *136*, 1477–1482. [CrossRef]
131. Seifar, F.; Khalili, M.; Khaledyan, H.; Moghadam, S.A.; Izadi, A.; Azimi, A.; Shakouri, S.K. α-Lipoic acid, functional fatty acid, as a novel therapeutic alternative for central nervous system diseases: A review. *Nutr. Neurosci.* **2017**, *22*, 306–316. [CrossRef] [PubMed]
132. Koufaki, M. Therapeutic applications of lipoic acid: A patent review (2011–2014). *Expert Opin. Ther. Patents* **2014**, *24*, 993–1005. [CrossRef] [PubMed]
133. Yaqoob, P. Fatty acids as gatekeepers of immune cell regulation. *Trends Immunol.* **2003**, *24*, 639–645. [CrossRef] [PubMed]
134. Jacobsen, S.C.; Brøns, C.; Bork-Jensen, J.; Ribel-Madsen, R.; Yang, B.; Lara, E.; Hall, E.; Calvanese, V.; Nilsson, E.H.; Jørgensen, S.W.; et al. Effects of short-term high-fat overfeeding on genome-wide DNA methylation in the skeletal muscle of healthy young men. *Diabetologia* **2012**, *55*, 3341–3349. [CrossRef]
135. Farhat, D.; Lincet, H. Lipoic acid a multi-level molecular inhibitor of tumorigenesis. *Biochim. Biophys. Acta Bioenerg.* **2020**, *1873*, 188317. [CrossRef]
136. Gebauer, S.K.; Psota, T.L.; Harris, W.S.; Kris-Etherton, P.M. n−3 Fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits. *Am. J. Clin. Nutr.* **2006**, *83*, 1526S–1535S. [CrossRef]
137. Das, U.N. Essential fatty acids-a review. *Curr. Pharm. Biotechnol.* **2006**, *7*, 467–482. [CrossRef]
138. Leaf, A. Omega-3 fatty acids and prevention of arrhythmias. *Curr. Opin. Lipidol.* **2007**, *18*, 31–34. [CrossRef]
139. Deshpande, R.; Mansara, P.P.; Kaul-Ghanekar, R. Alpha-linolenic acid regulates Cox2/VEGF/MAP kinase pathway and decreases the expression of HPV oncoproteins E6/E7 through restoration of p53 and Rb expression in human cervical cancer cell lines. *Tumor Biol.* **2015**, *37*, 3295–3305. [CrossRef]
140. Dozio, E.; Ruscica, M.; Passafaro, L.; Dogliotti, G.; Steffani, L.; Pagani, A.; DeMartini, G.; Esposti, D.; Fraschini, F.; Magni, P. The natural antioxidant alpha-lipoic acid induces p27Kip1-dependent cell cycle arrest and apoptosis in MCF-7 human breast cancer cells. *Eur. J. Pharmacol.* **2010**, *641*, 29–34. [CrossRef]
141. Feuerecker, B.; Pirsig, S.; Seidl, C.; Aichler, M.; Feuchtinger, A.; Bruchelt, G.; Senekowitsch-Schmidtke, R. Lipoic acid inhibits cell proliferation of tumor cells in vitro and in vivo. *Cancer Biol. Ther.* **2012**, *13*, 1425–1435. [CrossRef] [PubMed]
142. Menéndez, J.A.; Vazquez-Martin, A.; Ropero, S.; Colomer, R.; Lupu, R. HER2 (erbB-2)-targeted effects of the omega-3 polyunsaturated fatty acid, alpha-linolenic acid (ALA; 18:3n-3), in breast cancer cells: The "fat features" of the "Mediterranean diet" as an "anti-HER2 cocktail". *Clin. Transl. Oncol.* **2006**, *8*, 812–820. [CrossRef] [PubMed]

143. Rossi, C.; Di Lena, A.; La Sorda, R.; Lattanzio, R.; Antolini, L.; Patassini, C.; Piantelli, M.; Alberti, S. Intestinal tumour chemoprevention with the antioxidant lipoic acid stimulates the growth of breast cancer. *Eur. J. Cancer* **2008**, *44*, 2696–2704. [CrossRef] [PubMed]
144. Wang, L.; Newman, R.K.; Newman, C.W.; Jackson, L.L.; Hofer, P.J. Tocotrienol and fatty acid composition of barley oil and their effects on lipid metabolism. *Plant Foods Hum. Nutr.* **1993**, *43*, 9–17. [CrossRef] [PubMed]
145. Sookwong, P.; Nakagawa, K.; Murata, K.; Kojima, Y.; Miyazawa, T. Quantitation of Tocotrienol and Tocopherol in Various Rice Brans. *J. Agric. Food Chem.* **2007**, *55*, 461–466. [CrossRef] [PubMed]
146. Colombo, M.L. An Update on Vitamin E, Tocopherol and Tocotrienol—Perspectives. *Molecules* **2010**, *15*, 2103–2113. [CrossRef]
147. Lewis, E.D.; Meydani, S.N.; Wu, D. Regulatory role of vitamin E in the immune system and inflammation. *IUBMB Life* **2019**, *71*, 487–494. [CrossRef] [PubMed]
148. Coquette, A.; Vray, B.; Vanderpas, J. Role of vitamin E in the protection of the resident macrophage membrane against oxidative damage. *Arch. Int. Physiol. Biochim.* **1986**, *94*, 29–34.
149. Hatam, L.J.; Kayden, H.J. A high-performance liquid chromatographic method for the determination of tocopherol in plasma and cellular elements of the blood. *J. Lipid Res.* **1979**, *20*, 639–645. [PubMed]
150. Constantinou, C.; Charalambous, C.; Kanakis, D. Vitamin E and cancer: An update on the emerging role of γ and δ tocotrienols. *Eur. J. Nutr.* **2020**, *59*, 1–13. [CrossRef]
151. Algayadh, I.G.; Dronamraju, V.; Sylvester, P.W. Role of Rac1/WAVE2 Signaling in Mediating the Inhibitory Effects of γ-Tocotrienol on Mammary Cancer Cell Migration and Invasion. *Biol. Pharm. Bull.* **2016**, *39*, 1974–1982. [CrossRef] [PubMed]
152. Elangovan, S.; Hsieh, T.-C.; Wu, J.M. Growth inhibition of human MDA-mB-231 breast cancer cells by delta-tocotrienol is associated with loss of cyclin D1/CDK4 expression and accompanying changes in the state of phosphorylation of the retinoblastoma tumor suppressor gene product. *Anticancer Res.* **2008**, *28*, 2641–2647. [PubMed]
153. Cavalieri, R.R. Iodine Metabolism and Thyroid Physiology: Current Concepts. *Thyroid* **1997**, *7*, 177–181. [CrossRef] [PubMed]
154. Yen, P.M. Physiological and Molecular Basis of Thyroid Hormone Action. *Physiol. Rev.* **2001**, *81*, 1097–1142. [CrossRef]
155. Aceves, C.; Anguiano, B. Is Iodine an Antioxidant and Antiproliferative Agent for the Mammary and Prostate Glands? In *Comprehensive Handbook of Iodine*; Elsevier BV: Amsterdam, The Netherlands, 2009; pp. 249–257.
156. Aceves, C.; Anguiano, B.; Delgado, G. The extrathyronine actions of iodine as antioxidant, apoptotic, and differentiation factor in various tissues. *Thyroid* **2013**, *23*, 938–946. [CrossRef]
157. Elio Torremante, P.; Rosner, H. Antiproliferative effects of molecular iodine in cancers. *Curr. Chem. Biol.* **2011**, *5*, 168–176.
158. Arroyo-Helguera, O.; Anguiano, B.; Delgado, G.; Aceves, C. Uptake and antiproliferative effect of molecular iodine in the MCF-7 breast cancer cell line. *Endocr. Relat. Cancer* **2006**, *13*, 1147–1158. [CrossRef]
159. Smyth, P.P. Role of iodine in antioxidant defence in thyroid and breast disease. *BioFactors* **2003**, *19*, 121–130. [CrossRef]
160. Aceves, C.; García-Solís, P.; Omar, A.-H.; Vega-Riveroll, L.; Delgado, G.; Anguiano, B. Antineoplastic effect of iodine in mammary cancer: Participation of 6-iodolactone (6-IL) and peroxisome proliferator-activated receptors (PPAR). *Mol. Cancer* **2009**, *8*, 33. [CrossRef]
161. Aceves, C.; Anguiano, B.; Delgado, G. Is Iodine A Gatekeeper of the Integrity of the Mammary Gland? *J. Mammary Gland. Biol. Neoplasia* **2005**, *10*, 189–196. [CrossRef]
162. Venturi, S. Evolutionary significance of iodine. *Curr. Chem. Biol.* **2011**, *5*, 155–162.
163. Shrivastava, A.; Tiwari, M.; Sinha, R.A.; Kumar, A.; Balapure, A.K.; Bajpai, V.K.; Sharma, R.; Mitra, K.; Tandon, A.; Godbole, M.M. Molecular Iodine Induces Caspase-independent Apoptosis in Human Breast Carcinoma Cells Involving the Mitochondria-mediated Pathway. *J. Biol. Chem.* **2006**, *281*, 19762–19771. [CrossRef] [PubMed]
164. Dugrillon, A.; Uedelhoven, W.; Pisarev, M.; Bechtner, G. Gartner R: Identification of delta-iodolactone in iodide treated human goiter and its inhibitory effect on proliferation of human thyroid follicles. *Horm. Metab. Res.* **1994**, *26*, 465–469. [CrossRef] [PubMed]

165. Nava-Villalba, M.; Nuñez-Anita, R.E.; Bontempo, A.; Aceves, C. Activation of peroxisome proliferator-activated receptor gamma is crucial for antitumoral effects of 6-iodolactone. *Mol. Cancer* **2015**, *14*, 1–11. [CrossRef]
166. Rösner, H.; Torremante, P.; Möller, W.; Gärtner, R. Antiproliferative/cytotoxic ac-tivity of molecular iodine and iodolactones in various human carcinoma cell lines. No inter-fering with EGF-signaling, but evidence for apoptosis. *Exp. Clin. Endocrinol. Diabetes* **2010**, *118*, 410. [CrossRef]
167. Nuñez-Anita, R.; Arroyo-Helguera, O.; Cajero-Juárez, M.; López-Bojorquez, L.; Aceves, C. A complex between 6-iodolactone and the peroxisome proliferator-activated receptor type gamma may mediate the antineoplasic effect of iodine in mammary cancer. *Prostaglandins Other Lipid Mediat.* **2009**, *89*, 34–42. [CrossRef]
168. Aiello, A.; Pandini, G.; Frasca, F.; Conte, E.; Murabito, A.; Sacco, A.; Genua, M.; Vigneri, R.; Belfiore, A. Peroxisomal Proliferator-Activated Receptor-γ Agonists Induce Partial Reversion of Epithelial-Mesenchymal Transition in Anaplastic Thyroid Cancer Cells. *Endocrinology* **2006**, *147*, 4463–4475. [CrossRef]
169. Alfaro, Y.; Delgado, G.; Cárabez-Trejo, A.; Anguiano, B.; Aceves, C. Iodine and doxorubicin, a good combination for mammary cancer treatment: Antineoplastic adjuvancy, chemoresistance inhibition, and cardioprotection. *Mol. Cancer* **2013**, *12*, 1–45. [CrossRef]
170. Mendieta, I.; Nuñez-Anita, R.E.; Nava-Villalba, M.; Zambrano-Estrada, X.; Delgado-González, E.; Anguiano, B.; Aceves, C. Molecular iodine exerts antineoplastic effects by diminishing proliferation and invasive potential and activating the immune response in mammary cancer xenografts. *BMC Cancer* **2019**, *19*, 261. [CrossRef]
171. Zambrano-Estrada, X.; Landaverde-Quiroz, B.; Dueñas-Bocanegra, A.A.; De Paz-Campos, M.A.; Hernández-Alberto, G.; Solorio-Perusquia, B.; Trejo-Mandujano, M.; Pérez-Guerrero, L.; Delgado-González, E.; Anguiano, B.; et al. Molecular iodine/doxorubicin neoadjuvant treatment impair invasive capacity and attenuate side effect in canine mammary cancer. *BMC Veter. Res.* **2018**, *14*, 87. [CrossRef]
172. Ii, F.R.S.; Brooks, A.D.; Eskin, B.A.; Johannes, G.J. Iodine Alters Gene Expression in the MCF7 Breast Cancer Cell Line: Evidence for an Anti-Estrogen Effect of Iodine. *Int. J. Med Sci.* **2008**, *5*, 189–196. [CrossRef]
173. Bilal, M.Y.; Dambaeva, S.; Kwak-Kim, J.; Gilman-Sachs, A.; Beaman, K.D. A Role for Iodide and Thyroglobulin in Modulating the Function of Human Immune Cells. *Front. Immunol.* **2017**, *8*, 1573. [CrossRef] [PubMed]
174. Cuenca-Micó, O. Efectos del Yodo Molecular/Quimioterapia en los Patrones de Metilación de Células Inmunes Asociadas a Tumores de Cáncer Mamario. Ph.D. Thesis, INB, UNAM, Juriquilla, Mexico, 2021. in progress.
175. Hunt, J.R. Bioavailability of iron, zinc, and other trace minerals from vegetarian diets. *Am. J. Clin. Nutr.* **2003**, *78*, 633S–639S. [CrossRef] [PubMed]
176. Burton, G.W.; Traber, M.G. Vitamin E: Antioxidant activity, biokinetics, and bioa-vailability. *Annu. Rev. Nutr.* **1990**, *10*, 357–382. [CrossRef] [PubMed]
177. Vinson, J.; Al Kharrat, H.; Andreoli, L. Effect of Aloe vera preparations on the human bioavailability of vitamins C and E. *Phytomedicine* **2005**, *12*, 760–765. [CrossRef] [PubMed]
178. Cuenca-Micó, O.; González-Delgado, E.; Aceves, C. Molecular Iodine Activates cytotoxic immune response in breast cancer tumor microenviroment. *Am. Assoc. Immnol.* **2020**, *204* (Suppl. 1), 241.8.
179. Alayev, A.; Berger, S.M.; Kramer, M.Y.; Schwartz, N.S.; Holz, M.K. The combination of rapamycin and resveratrol blocks autophagy and induces apoptosis in breast cancer cells. *J. Cell. Biochem.* **2015**, *116*, 450–457. [CrossRef]
180. Guo, C.-H.; Hsia, S.; Chung, C.-H.; Lin, Y.-C.; Shih, M.-Y.; Chen, P.-C.; Peng, C.-L.; Henning, S.M.; Hsu, G.-S.W.; Li, Z. Nutritional Supplements in Combination with Chemotherapy or Targeted Therapy Reduces Tumor Progression in Mice bearing Triple-negative Breast Cancer. *J. Nutr. Biochem.* **2020**, *87*, 108504. [CrossRef]
181. Arends, J.J.; Bachmann, P.P.; Baracos, V.V.; Barthelemy, N.N.; Bertz, H.H.; Bozzetti, F.; Fearon, K.C.; Hütterer, E.E.; Isenring, E.E.; Kaasa, S.; et al. ESPEN guidelines on nutrition in cancer patients. *Clin. Nutr.* **2017**, *36*, 11–48. [CrossRef]