



## RESEARCH ARTICLE

## Vitamins and Provitamins Intake as New Insights to Prevent and/or to Treat breast Cancer: A Systemic Review

Laya A<sup>1,2\*</sup>, Koubala BB<sup>2,3</sup>, Pathak KP<sup>4</sup> and Bueno V<sup>5</sup>

<sup>1</sup>Department of Biological Sciences, Faculty of Science, University of Maroua, Cameroon

<sup>2</sup>Department of Life and Earth Sciences, Higher Teacher's Training College of Maroua, University of Maroua, Cameroon

<sup>3</sup>Department of Chemistry, Faculty of Science, University of Maroua, Cameroon

<sup>4</sup>Faculty of Social Science, Nepal Open University, Nepal

<sup>5</sup>Center for the Study of Aging, Escola Paulista de Medicina, Universidade Federal de São Paulo, Brazil

\*Corresponding author: Laya A, Department of Biological Sciences, Faculty of Science, University of Maroua, P.O. Box 46 Maroua, Cameroon, Tel: (+237)-653759511



### Abstract

Female Breast Cancer (BC) is the most diagnosed cancer across the world. The present systematic review aimed to update the new insights of vitamins and provitamins to prevent and/or to treat BC. Vitamins and provitamins are natural products that have been implicated to prevent and to treat BC. However, it is still scarce and non-consensual as reported in the literature. A systematic literature review was conducted to identify studies through PubMed, Medline, and AMBASE up to June 27, 2021 solely on the association between vitamins (or provitamins) and BC prevention or treatment. The related grey literature also was used. The results of 127 relevant publications after exclusion of 7715 papers revealed that natural vitamins and provitamins were used to prevent or to treat BC. It has been clear evidence that vitamins and provitamins reduce the risk of BC, which acting by various mechanisms with significant inverse effect and effective use in the treatment of BC. There is no indication for publication bias found, however there was high heterogeneity among studies. Despite its limitations, our systematic review provide the most comprehensive studies updated summary evidence to date on the association between vitamins, provitamins and BC prevention, treatment or therapeutic issues. The natural dietary of these nutrients may be encouraged among population in order to reduce the risk of BC. Thus, we hope that our publication will help for further investigation such as a large clinical trials to confirm the findings of the present study.

### Keywords

Breast cancer, Vitamins, Provitamins, Mechanism, Prevention

### Introduction

In the last decades, the World Health Organization states that cancer is the second leading cause of death worldwide among noncommunicable diseases. Worldwide, an estimated number of 19.3 million new cancer cases (18.1 million without skin cancer) occurred in 2020 [1]. The global cancer burden is expected to be around 28.4 million cases in 2040, hence as a 47% rise from 2020. Female Breast Cancer (BC) is the most common diagnosed cancer and surpassed lung cancer, with an estimated over 2.3 million new cases (11.7%) and with 6.9% deaths [1]. To date, almost more than two of every five people can be develop cancer in their lifetime. The consumption of dietary modifications are one of the most promising lifestyle changes that can adjust the risk of developing cancer from human by nearly 40% [2] and for this reason the diet-cancer linkages was studied over the past decades [3]. These studies have been showed high link with nutrients quality ingested by human. Thus, numerous studies have identified some bioactive nutrients to prevent or to reduce risk of certain types of cancers during the life [4-8]. This suggest that a good diet, rich in fruits and vegetables which contain bioactive nutrients, is significant in the prevention of cancer development, which is in agreement with a large number of scientific papers identifying a range of bioactive compounds

to prevent cancer. Certain nutrients such as vitamins, minerals, peptides, fatty acids, phenolics, and fibres may affect DNA repair, inflammation and hormones and growth factors via regulation of gene expression as well as the association to the antioxidant properties and improvement of the immune response. Particularly, epidemiological studies have correlated diet with cancer incidence and aggressiveness in many centuries [8,9]. Among these studies, vitamins and provitamins have been associated with a protective effect on cancer incidence in relation with lifestyle [10-14]. Fact, vitamins are organic compounds derived from plants and animals as well, however, provitamin A for example, are only synthesized in plants suggest that they need to obtain carotenoid from their diets. Vitamins and provitamins have been implicated to prevent and to treat cancer by the mechanisms of pathways involving cell growth, death and antioxidant properties as well [15-17]. However, the efficiency of effect of vitamins or provitamins may differ accordingly the stage and type of cancer as well as mechanism involving in respect with age, race and other factors as well. Therefore, individual or synergism effect of the bioactive nutrients also may be potentially important in cancer-related prevention and treatment. While, many of studies showed some conflicting and/or inconclusive findings [18-21], which may be link to the methods or vitamins sources used in the study as well as race, age, menopausal status (pre-menopause and post-menopause) and the number of patients considered in different studies.

In this systematic review, we aimed to summarize the most up-to-date the relevant papers on multiple role of different vitamins and provitamins to prevent and to treat BC incidence and progression, with special attention to natural vitamins/provitamins. Hence, we would highlight the associations between vitamins/provitamins intake and breast cancer prevention and treatment, which shows insight into the comprehensive understanding of food quality intake as well as association with BC. This study also provides the comprehensive perspective for innovation and mechanism of dietary therapy and prevention of BC patients.

## Materials and Methods

A literature research was conducted by utilising Google Scholar, PubMed, Medline, Scopus databases and library sources by selecting the terminologies "Breast cancer, prevention and treatment of Breast cancer", "Breast cancer and vitamins/provitamins", "tumor", "mammary glands", "angiogenesis", "Breast cancer control" etc. We searched for meta-analysis, pooled analyses, epidemiological studies, systematic reviews, prospective cohort studies, qualitative reviews and clinical studies evaluating the association between bioactive nutrients (vitamins and provitamins) and BC up until June 27, 2021. The search was not restricted by study design, and both peer-reviewed and grey

literature were included. We searched some related grey literature from American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and American Urological Association (AUA). When a large cohort study conducted after a meta-analysis was found, it was also used. Parameters used were only vitamins or provitamins (A and D) for prevention or treatment of BC.

We excluded studies that were not written on the BC and prevention or treatment and synthetic vitamins as well. Only the papers need to do focus on the association between vitamins/provitamins and breast cancer. Duplicate publications were deleted and title and abstract were checked for relevance. We found more than Seven thousand eighty hundred and fifty-two (7852) papers and after removal of those (7715) not meet our criteria after abstract and full text review, only one hundred and twenty seven (127) relevant publications among them as a selective compilation of approaches and methodologies for our study.

## Dietary Source of Vitamins and Provitamins

### Dietary source of vitamins

This part was include in the present systematic review in order to know different sources of all vitamins or provitamins used by human in their diet. Vitamins are known as an essential compounds for the normal functioning and development of the human body. These substances are classified in two classes, fat-soluble and water-soluble and act as important antioxidant compounds. Vitamin A is a fat-soluble found naturally in animal and their products [22]. It is all-trans retinol, which is an isoprenoid side chain found in animal tissue [23]. Vitamin D (active form: 1,25-dihydroxyvitamin D) was synthesized in the skin from a cholesterol like precursor (7-dehydrocholesterol) by exposure to sunlight or can be provided from animal products [24-26]. There are 7 different types of vitamin D, however, only two major forms, D2 and D3 which are showed important role in human body [26,27].

Vitamin E is a fat-soluble found in a wide variety of plants such as vegetables and fruits, animal or their products, however, the main source is the plant oil [27,28]. Tocopherols and tocotrienols are the two part of vitamin E compounds which differ in their saturation state of isoprenoid side chain [28,29] which confer high antioxidant activity. However, their concentrations vary within the variety and plant species. The vitamin C is a water-soluble nutrients found mainly in fruits, vegetables and in small quantity in animal products [30]. Vitamin C is another important antioxidant used in human diet. Vitamins B are common micronutrients found in vegetables, fruits or in algae and edible mushrooms [31,32]. These vitamins are also found in animal products and some of them in yeasts as well. Vitamin K is also a fat-soluble nutrient, found in plant

vegetables, plant oil and in small amount in animal products [33,34].

### Dietary Source of provitamin A and D

Provitamin A and D are all fat-soluble nutrients found both plants and animals or their products acting as important natural antioxidants. Provitamin A provided from carotenoids which are pigments universally synthesized by all terrestrial and aquatic photoautotrophs, including plants, algae, some non-photosynthetic bacteria, some insects, and some fungi [35]. The structure of carotenoids is based on a C40 isoprenoid backbone that may be acyclic or modified to have one or both ends modified into rings with diverse structural modifications [3]. Lycopene,  $\beta$ -carotene,  $\alpha$ -carotene, lutein, zeaxanthin, and  $\beta$ -cryptoxanthin are the most common carotenoids in human serum, however, only  $\beta$ -carotene,  $\alpha$ -carotene and  $\beta$ -cryptoxanthin are the sources of provitamin A, therefore the most common precursors of vitamin A. Provitamin A refers to those carotenoid precursors that are biologically active as retinol.

Provitamin D are resulting of the synthesized of vitamin D by microalgae and wild mushrooms. These forms are ergosterol (vitamin D<sub>2</sub>) which can be found in wild mushrooms, and ultraviolet-B (UVB) exposed fungi and yeast [36], 7-dehydrocholesterol in order to synthesize vitamin D<sub>3</sub> by UVB exposure [37]. Provitamin D<sub>3</sub> was synthesized only in microalgae [36].

### Prevention and treatment of breast cancer

**Vitamin A:** BC remains the most common tumor found in women and one of the three most common cancers worldwide in the last years [38,39]. Natural vitamin A, or an All-Trans Retenoic Acids (ATRA), the active metabolite of vitamin A are used to prevent and to treat BC acting by many molecular mechanisms as described in different studies. Vitamin A acts by promoting the apoptosis and inhibiting angiogenesis of human BC cells or impact as antioxidant by scavenging free radicals. In line of prevention, Kim, et al. [40] found in their study, serum vitamin A levels and their relationships with other biomarkers in Korean BC patients that the serum concentration of vitamin A was associated with a seven-fold decrease in risk of benign breast disease and a six-fold decrease in risk of BC. Their results were consistent with some researchers who reported also a high reduced risk association of BC with vitamin A or provitamin A [41,40]. While, the molecular mechanism of vitamin A against breast cancer is variable and some were described by many researchers such as Mangiarotti, et al. [42] and Wu, et al. [43], who reported that ATRA induces re-differentiation of transformed cells during the early stages of the neoplastic process and promotes the apoptosis of human BC cells by regulating the Tet Methylcytosine Dioxygenase 2-Protein Kinase C zeta (TET2-PKC) pathway. Fact, the

apoptose was the one mechanism known to be induced as reported by Bernardo, et al. [44] who observed that the pro-apoptotic signaling induced by retinoic acid and dsRNA was under the control of interferon regulatory factor-3 in BC cells which may lead to the death of tumor. For instance, in retinoid-sensitive cell-lines and tumors, ATRA stimulated a viral-mimicry response involving the activation of the interferon (IFN) and antigen-presentation pathways as well as other biological processes controlling the sensitivity of tumors to immune checkpoint inhibitors [45]. Further, retinoic acid may inhibit telomerase activation through inducing histone deacetylation in estrogen receptor-negative BC cells for deaths [46]. Furthermore, retinoic acid can impair estrogen signaling in BC cells by interfering with the activation of LSD1 via protein kinase A and may inhibit aromatase activation and expression, which indicates that the estrogen supply inside BC cells is insufficient to maintain cancer cell growth [47,48]. Hence, the vitamin A suggesting as important to be used for reducing risk of BC as well as to treat BC, however further molecular investigation will be done to confirm the findings for the effective therapy.

**Provitamin A:** The provitamin A are mainly provided from  $\beta$ -carotene,  $\alpha$ -carotene and  $\beta$ -cryptoxanthin, however, some carotenoids such as lutein, for example, selectively induced apoptosis in MCF-7 BC cells but not in normal human mammary cells [49]. It was reported that  $\beta$ -carotene (provitamin A), at the physiologically concentration of just 1  $\mu$ M, can decrease the expression of Bcl-2 and PARP, and NF- $\kappa$ B in human BC MCF-7 cells [50] by inhibiting the genes regulation of hormone involved in proliferation of cells. Fact,  $\beta$ -carotene treatments can also inhibit the activation of Akt and Erk1/2, subsequently decreasing phosphorylation of Bad and downregulate superoxide dismutase-2 (Sod-2, an antioxidant enzyme), its transactivation factor Nrf-2, and Endoplasmic Reticulum (ER) stress marker X-box Binding Protein 1 (XBP-1) levels [51]. Several lines of evidence suggest that carotenoids such as lycopene,  $\beta$ -carotene, lutein, and astaxanthin have the ability to modulate the NF- $\kappa$ B pathway, in some cases by inhibiting cancer cell growth via NF- $\kappa$ B pathway [52-54].

Some studies carried out such as in a pooled analysis of eight cohort studies comprising 3055 cases of BC and 3956 control subjects, showed a statistically significant inverse association which was observed between BC and levels of plasma/serum provitamin A ( $\alpha$ -carotene,  $\beta$ -carotene) and lutein + zeaxanthin, lycopene, and total carotenoids [51,55]. This inverse association was strong for some receptors such as estrogen receptor-negative (ER-) compared to ER+ tumors [56]. Another systematic review and meta-analysis of eight cohorts, one clinical trial, and one pooled study, comprising 19,450 BC case, dietary intake of  $\beta$ -carotene was significantly associated with improved BC survival (RR of 0.70) [57]. The provitamin A can act also as antioxidant because

having the ability to scavenge ROS molecules which can induce the lysis of BC line [58,59], thus reduce DNA damage in cancerous tissues in human patients. For instance, a study has shown that addition of lutein and  $\beta$ -carotene to ROS-inducing doxorubicin at a low dose of 0.2-3.2  $\mu$ M is effective against BC cell lines MCF-7 and MDA-MB-231 without influencing the redox status (lipid peroxides (LPx), so the ROS, and lactate dehydrogenase levels) in normal breast epithelial MCF 10A cells [60]. Bohlke, et al. [61] reported also in a case-control study in Greece, included eight hundred and twenty women with histologically confirmed BC were compared with 1548 control women, among premenopausal women, provitamin A ( $\beta$ -carotene) was inversely associated with BC risk. Fulan, et al. [62] indicated that both the total intake of vitamin A and retinol could reduce BC risk. In addition, Bakker, et al. [63] found in a nested case-control study within the European prospective that high concentration of plasma provitamin A ( $\beta$ -carotene and  $\alpha$ -carotene) are associated with low BC risk of ER-tumors. During their study, an investigation into Cancer and Nutrition cohort, 1502 female incident BC case was included, with an over sampling of premenopausal ( $n = 582$ ) and estrogen receptor-negative (ER-) cases ( $n = 462$ ). Provitamin A is one the best antioxidant compounds that had different mechanisms to inhibit proliferation of cell tumor or to induce apoptosis of BC.

**Vitamin K:** The different forms of Vitamin K has been proved to have a negative effect on BC in many studies, which was shown by both *in vitro* and *in vivo* studies [35,36]. Vitamin K can act in different pathways mechanism signals which consists of the production of ROS, via the 1-electron cycling of the quinone as well as by the oxidative capacity of the cell is exceeded by the increased redox-cycling of menadione and the production of ROS, resulting in its death [64,65]. Secondly, the mechanism is linked on cell cycle arrest and apoptosis induced by modulation of transcription factors, and finally the deaths of cell lines [66]. Noto, et al. [67] found in their study that vitamin K3 (13.8  $\mu$ g/mL) produced a 50% inhibition of BC cell lines and, when combined with vitamin C (99.01  $\mu$ g/mL), K3 (1.38  $\mu$ g/mL) increased inhibition by 74% suggesting their synergism to inhibit. It was demonstrated also that, when both vitamin C and K3 concentrations were increased (104  $\mu$ mol/L and 105 nmol/L, respectively), a high effect was observed with a 93% inhibition [67]. Also, Miyazawa, et al. [68] found that vitamin K2 induced non-apoptotic cell death along with autophagy, in triple negative BC cell lines. However, cell death phenotype induced by vitamin K2 appears to differ among the type of cancers suggesting the possibility of using vitamin K2 for the BC therapy and prevention without side effects as reported for conventional drug.

**Vitamin C:** Consumption of vitamin C is very important for our body and lower consumption of vitamin C might increase BC risk. Fact, vitamin C acts as antioxidants

and by many pathways molecular mechanisms to be effective as anticancer. For example, Zasowska-Nowak, et al. [17] observed an effect of high-dose vitamin C in advanced-stage cancer patients and found that vitamin C is effective against BC in all stages, however this can be varied with age or race. Vitamin C can generate the cell cycle arrest, caspase-independent autophagy mediated by beclin-1 and LC3 II, apoptosis via induction of apoptosis-inducing factor, induction of oxidative DNA damage, apoptosis mediated by Bax protein signalling, release of cytochrome C from mitochondria, activation of caspase 9 and caspase 3, and cleavage of poly [ADP-ribose] polymerase in a ROS-dependent manner. Gan, et al. [69] reported that the vitamin C inhibits TNBC (Triple Negative Breast Cancer) metastasis by acting the expression of SYNPO2 and YAP1 and therefore vitamin C may thus have a potential role in the prevention and treatment of TNBC metastasis. Vollbracht, et al. [70] found that the administration of vitamin C with standard anti-cancer therapy in the first postoperative year of women with BC resulted in significantly enhanced performance status and reduction of complaints induced by the disease and chemo-radiotherapy. Similarly, the positive impact of high-dose vitamin C on patients' performance status was also reported by the same author in the epidemiological retrospective study with 125 women with primary non-metastasized BC, receiving a basic anti-tumor therapy with vitamin C at a dose of 7.5 g once a week for at least 4 weeks. Women who received vitamin C had a significantly better performance status during adjuvant therapy and the aftercare follow-up than those who did not receive vitamin C. Carr, et al. [71] reported two case studies demonstrating improvement in a control of pain after administration of vitamin C therapy for four weeks in women with BC. In the same way, Zeng, et al. [72] found that high-dose vitamin C inhibits cell migration and invasion of BC cell lines through suppressing epithelial-mesenchymal transition. Harris, et al. [73] found in their meta-analysis that post-diagnosis vitamin C supplement use was associated with a reduced risk of mortality as well as dietary vitamin C intake was significantly associated with a reduced risk of total mortality and BC specific mortality. Furthermore, Bohlke, et al. [61] reported in a case-control study in Greece, included eight hundred and twenty women with histologically confirmed BC were compared with 1548 control women, among premenopausal women, vitamin C was inversely associated with BC risk. Recently, Zhang, et al. [74] found that high vitamin C intake is significantly associated with reduced BC incidence and mortality. Thus, it may be considered as an anticancer nutrient for BC patients.

**Vitamin E:** The experimental model studies *in vitro* and *in vivo* conducted by Afam, et al. [75] had shown such as antioxidative, pro-antioxidative, anti-inflammatory, modulation of cell signaling, antiproliferation,

antiangiogenesis, and apoptosis induction effects of vitamin E as well. Vitamin E had first acted as a non-antioxidant,  $\alpha$ -tocopherol had inhibited muscle proliferation activity and protein kinase C activity [4]. Jiang [76] reported that Vitamin E ( $\alpha$ -tocopherol) was used to inhibit cancer promoting pathways, including cyclooxygenase and 6-lipoxygenase eicosanoids, NF $\kappa$ B and signal transducer and activator of transcription factor. The reduced activity of protein kinase B and of NF- $\kappa$ B was shown to mediate tocotrienol reduced mammalian cancer cell proliferation [77]. Ripon, et al. [4] found an inverse association between vitamin E and BC which was exhibited to be a major difference in serum vitamin E levels and the consumption of vitamin E in cases or controls. Fact, vitamin E supplementation inhibited mammal's tumor cell proliferation and induced cell death in a dose responsive manner [78-80]. Kline, et al. [81] reported that vitamin E forms can induce BC cells to undergo apoptosis. Malafa and Neitzel [82] found also that the vitamin E inhibits the growth of BC cells *in vitro* and *in vivo*. In addition, serum concentrations of vitamins E was significantly lower in Korean BC patients and in benign breast disease patients than in healthy controls [42]. Vitamin E is potentially used for the treatment of BC in women as a chemotherapeutic agent [78-80,83,84]. Moreover, Abraham, et al. [85] stated that vitamin E is linked with an inverse effect on BC suggesting vitamin E can delays BC risks or use for its treatment. Also, Lajous, et al. [86] reported that high folate intake was associated with decreased BC risk which was in agreement with Hu, et al. [87] who found that severe  $\alpha$ -tocopherol deficiency could increase BC risk.

Torun, et al. [88] found a decreased serum levels of vitamin E in BC patients compared to controls suggesting the important role vitamin E for prevention from BC. Hence, Ben-Chioma and Elekima [89] proposed that the BC patients had reduced level of vitamin E suggests the possible risk of BC. Turley, et al. [90] stated that vitamin E may be of clinical use in the treatment of aggressive human BC, particularly those that are refractory to antiestrogen therapy. Other studies give evidence of a general inhibition of cell proliferation by dl- $\alpha$ -tocopherol, with breast [91]. Bohlke, et al. [61] reported in a case-control study in Greece, included eight hundred and twenty women with histologically confirmed BC were compared with 1548 control women, among premenopausal women, vitamin E was inversely associated with BC risk. Recent study of Godazandeh, et al. [92] demonstrated that for the treatment, vitamin E could be effective in breast pain-relieving and decreasing nodularity with minimal side effects in comparison with drugs. Vitamin E may inhibit the cancer formation by acting as antioxidant (quenching of free radicals) or by direct influences on tumor cells by reducing the tumor growth by induction of differentiation as well as cell cycle inhibition of

apoptosis and elimination of tumor cells especially when the reinforcement of the immune system is induced. Thus, an advantage for using vitamin E in human cancer therapy is high that lead to conclude that can be used to prevent BC and to treat as well by acting via apoptotic activity as reported by Theriault, et al. [93]. Kilne, et al. [81].

**Vitamin D:** The vitamin D affects the cell cycle, apoptosis, hormone receptors, angiogenesis, and hypoxia, all of which are related to the BC growth, progression and metastasis [94]. Kim, et al. [42] found that severe vitamin D deficiency was found more prevalent in BC patients of Korean women than in healthy controls. Similarly, vitamin D level was significantly lower in BC patients with estrogen receptor-negative or triple-negative subtypes than in those with other subtypes [42]. National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, 1971-1975 to 1992 found that vitamin D reduce the risk of BC [95]. A trend toward cases of BC in woman with intakes of vitamin D above 400 IU (10  $\mu$ g)/day was found associated with an 8% reduction in the risk of BC [65]. Shin, et al. [59] found also that vitamin D intake of 500 IU or more per day was associated with a significant 28% lower risk of BC in premenopausal women. Similarly, Yin, et al. [4] found in their meta-analysis, serum vitamin D and BC risk, that in case-control studies with measurement of 25 (OH) D after diagnosis showed an inverse association which was consistent with the results of Garland, et al. [96] who found a 50% lower risk of BC associated with a serum 25 (OH) D level P52 ng/mL, compared to 613 ng/mL in their study by searching the Medline database for 1966-2006. Chen, et al. [97] found in their meta-analysis that there was a significant inverse relationship between vitamin D intake and BC risk, with an overall Relative Risk (RR) of high versus low vitamin D intake for BC of 0.91 and the highest quintile of circulating 25 (OH) D was found to be associated with a 45% decrease in BC when compared with the lowest quintile. Similar inverse association was obtained by Mohr, et al. [98] in their pooled analysis of 11 case-control studies that individuals in the highest quintile versus the lowest quintile of 25 (OH) D concentrations had a reduction in BC risk, in which serum 25 (OH) D level of 47 ng/mL was associated with a 50% lower risk of BC. Also, an inverse association was found by Stoll, et al. [99] in their systematic review of 37 studies, by Shekarriz-Foumani, et al. [100] in their systematic review who reviewed (14) studies and found that serum 25 (OH) D deficiency had been very prevalent among BC neoplasms. For BC-controlled studies, case-control studies consistently find an inverse correlation between 25 (OH) D and BC risk [101,102]. These studies suggest that elevated serum 25 (OH) D through the sun exposure and dietary intake more than 400 IU per day vitamin D supplementation decreased BC risk and recurrence. Al-Azhri, et al. [103] concluded in their study that vitamin D3 treatment

can be effective against aggressive BC. Many other researchers reported significant reduction risks as well as effective therapy of BC using vitamin D [9,94,104-109]. Furthermore, meta-analyses of population studies demonstrate an inverse relationship between vitamin D status and BC risk [110] which is consistent with the results of Tavera-Mendoza, et al. [111] who reported a number of epidemiological studies had shown that sufficient vitamin D serum levels might be protective against BC. Moreover, severe 25 (OH) D deficiency was associated with aggressive behavior of BC [112] suggesting that low circulatory 25 (OH) D could be associated with increased risk of BC. Fact, high blood 25 (OH) D levels were significantly associated with lower BC mortality (pooled RR¼ 0.58, 95% CI: 0.40-0.85) [109], and also high vitamin D levels have been shown to be associated with increased survival in patients with BC [113], however the mechanisms for vitamin D-mediated suppression of BC-relevant gene expression appear as being complex [114].

Vitamin D may exert antiproliferative, prodifferentiating, antiangiogenic and antimetastatic effects in BC cells, thus retards the development and growth of tumours as reported by Deeb, et al. [115] and Kulling, et al. [116]. Song, et al. [117] found in their study, vitamin D intake, blood vitamin D levels, and the risk of BC: A dose-response meta-analysis of observational studies that BC risk was inversely related to blood vitamin D levels. For Story [14], vitamin D in combination with Zinc and fatty acid ( $\omega$ -3 PUFAs) would be ideal for treating BC. Mohr, et al. [98] reported that high serum 25 (OH) D was associated with lower mortality from BC suggest that the serum 25 (OH) D in all patients with BC could be restored to the normal range (30-80 ng/ml). Janowsky, et al. [118] found a consistent data with a protective effect of 1,25-D for BC in white women suggesting in this a clinic-based case control study that race and age can affect significantly the results of study. Hossain, et al. [119] reported that 25 (OH) D deficiency was directly related to BC and total vitamin D and supplemental vitamin D intakes had an inverse relationship with this outcome. Shirazi, et al. [120] in their study found that women with low levels of 25OHD3, as compare to women in the middle tertile, had a high risk of breast tumours with an unfavourable prognosis. The circulating form of vitamin D may induce normal cellular proliferation by regulating genes that control the mechanism and induce differentiation, apoptosis and inhibiting angiogenesis of cell cancer [121,122].

**Vitamin B:** Vitamins B (B6, B9 and B12) play important roles in nucleotide biosynthesis and biological methylation reactions, aberrancies of which have all been implicated in carcinogenesis [123] and vitamins B1 and B2 can inhibit inflammation as well. Fact, one-carbon metabolism, related B vitamins (folate, thiamine, riboflavin, niacin, pantothenic acid,

pyridoxine, cobalamin), comprises a complex network of biochemical pathways that donate methyl groups for many important biological processes [124]. Thus, many studies investigated the associations between B vitamins and BC risk, however, mainly focused only on folate (vitamin B9), vitamin B6 and B12 [125]. For example, in China, Shrubsole, et al. [126] found in their study evidence of a decreased risk of BC associated with high consumption of folate among women who do not regularly consume alcohol suggesting alcohol may increase the risk of BC. Similar observation was done by Xu, et al. [127], who found that higher dietary intake of vitamin B1 and B3 was associated with improved survival during the followup period. The meta-analysis of observational studies indicates also that vitamin B2 intake could decrease BC risk [128], however may vary with age. Razeghian, et al. [129] compared the levels of folic acid, B6, and B12 in the plasma of 85 people with BC were measured and compared with healthy people and found a significant inverse trend observed between folate intake and vitamin B6 intake and BC risk. Zeng, et al. [72] reported also that the folate intake decreases the risk of oestrogen receptor (ER) negative (-) and ER-/progesterone receptor (PR)- BC, with pooled risk ratios of 0.88 [95% confidence interval (CI): 0.78-1.00] and 0.82 (95% CI: 0.68-0.97), respectively and an increment of folate intake of 100 µg per day was associated with a decreased risk of ER and ER-/PR-BC.

Similar case was reported by Ren, et al. [130] who found in their meta-analysis titled association of folate intake and plasma folate level with the risk of BC: A dose-response meta-analysis of observational studies a high folate intake correlated with a low BC risk in premenopausal women. Recently, Egnell, et al. [131] found in their study that the dietary pyridoxine intakes were inversely associated with BC risk. In this way, total thiamin intake was borderline inversely associated with BC risk, so they concluded that their prospective cohort study suggesting pyridoxine and thiamin were inversely associated with BC risk. It was also reported that high plasma vitamin B6 and riboflavin lower BC risk, especially in premenopausal women [132]. In addition, Lurie, et al. [133] found that high circulating levels of vitamin B6 are associated with a reduced risk of invasive postmenopausal BC. Zhang, et al. [134] found also that folate and vitamin B6 have the potential to be chemopreventive against BC and that ensuring adequate circulating levels of folate and vitamin B6 by consuming foods that are rich in these nutrients. Shrubsole, et al. [135] reported that high intake of folate by Chinese women was associated with decreased BC risk. Furthermore, a randomized trial of combined folic acid, vitamin B6, and vitamin B12 revealed significantly reduced BC risk among women in the treatment arm of older (> 65-years-old) [136]. Lin, et al. [137] found an evidence that high circulating concentrations of folate, vitamin B6, and vitamin B12 are associated with overall

risk reduction of BC suggesting one-carbon metabolism may be an important pathway that could be targeted to improve BC survival. Another experimental study suggested that vitamin B6 exerts other anticarcinogenic effects by reducing cell proliferation, nitric oxide production and angiogenesis [138], and clinical studies provide evidence that vitamin B6 play a role in protection of BC [139]. Further large sample study are greatly needed to confirm their association [140]. Our study indicated that vitamins B have an important role in preventing or treating of BC when taking by BC patient.

### Limitations

There are many limitations of this study. The different analyses of the data provided by the individual studies were limited and heterogenous. The results reported were differed from one to another with an estimation of risk may be less accurate than if individual data had been available. Authors used also different methods to evaluate inverse association between vitamins and breast cancer or to treat, which can affect the comparability of different studies linked with heterogeneity among studies and publications bias is impossible to be excluded when the number studies is low. In addition, missing relevant publications is possible, even if we searched via Medline, EMBASE, PubMed, etc.

### Conclusion

The current review summarizes the available literature on the role of natural products, vitamins and provitamins to prevent and to treat BC. Data literature on BC associated with different were limited however, the findings of the present study indicated that natural vitamins and provitamins were inversely associated with risk of BC and used for an effective therapy. The menopausal status, race, and age as well had effectiveness to prevent or to treat BC. These findings support some recommendations for increasing the intake of vitamins and provitamins in order to prevent BC. Some studies such as clinical trials in the future will be very important in order to confirm the findings.

### Future Study

Despite the extensive effort to understand the inverse relationship between vitamins or provitamins in breast cancer development, prevention and treatment, many issues remain unclear hence clinical trials will be needed.

### Funding Source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Competing Interest Statement

There are no conflict of interest for this paper.

### References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, et al. (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 71: 209-249.
- Anand P, Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST, et al. (2008) Cancer is a preventable disease that requires major lifestyle changes, *Pharm Res* 25: 2097-2116.
- Rowles III, John W (2020) Carotenoids and their role in cancer prevention. *BBA- Mol Cell Biol Lipids* 1865: 158613.
- Yin L, Grandi N, Raum E, Haug U, Arndt V, et al. (2010) Meta-analysis: Serum vitamin D and breast cancer risk. *Eur J Cancer* 46: 2196-2205.
- Cui J, Gong M, He Y, Li Q, He T, et al. (2016) All-trans retinoic acid inhibits proliferation, migration, invasion and induces differentiation of hepa1-6 cells through reversing EMT in vitro. *Int J Oncol* 48: 349-357.
- Li Y, Zhang Y, Liu X, Wang M, Wang P, et al. (2018) Lutein inhibits proliferation, invasion and migration of hypoxic breast cancer cells via downregulation of HES1. *Int J Oncol* 52: 2119-2129.
- Ripon MDSH, Habib MAH, Hossain M, Ahmed N, Kibria T, et al. (2020) Role of Vitamin E in Prevention of Breast Cancer: An Epidemiological Review. *Asian J Adv Res Reports* 11: 37-47. Article no.AJARR.58489.
- Suwannasom N, Kao I, Pruß A, Georgieva R, Bäumler H, et al. (2020) Riboflavin: The Health Benefits of a Forgotten Natural Vitamin. *Int J Mol Sci* 21: 950.
- Kotepui M (2016) Diet and risk of breast cancer. *Contemp Oncol (Pozn)* 20: 13-19.
- Freudenheim JL, Marshall JR, Vena JE, Laughlin R, Brasure JR, et al. (1996) Premenopausal breast cancer risk and intake of vegetables, fruits, and related nutrients. *J Natl Cancer Inst* 88: 340-348.
- Dorgan JF, Sowell A, Swanson CA, Potischman N, Miller R, et al. (1998) Relationships of serum carotenoids, retinol, a-tocopherol, and selenium with breast cancer risk: Results from a prospective study in Columbia, Missouri (United States). *Cancer Causes Control* 9: 89-97.
- Kiely M, Hodgins S J, Merrigan BA, Tormey S, Kiely PA, et al. (2015) Real-time cell analysis of the inhibitory effect of vitamin K2 on adhesion and proliferation of breast cancer cells. *Nutr Res* 35: 736-743.
- Koklesova L, Alena Liskova A, Samec M, Zhai K, Abotaleb M, et al. (2020) Carotenoids in Cancer Metastasis-Status Quo and Outlook. *Biomolecules* 10: 1653.
- Story MJ (2021) Essential sufficiency of zinc, u-3 polyunsaturated fatty acids, vitamin D and magnesium for prevention and treatment of COVID-19, diabetes, cardiovascular diseases, lung diseases and cancer. *Biochimie* 187: 94-109.
- Niranjana R, Gayathri SN, Mol T, et al. (2015) Carotenoids modulate the hallmarks of cancer cells. *J Funct Foods* 18: 968-985.
- Carazo A, Macáková K, Matoušová K, Krčmová LK, Protti M, et al. (2021) Vitamin A Update: Forms, Sources, Kinetics, Detection, Function, Deficiency, Therapeutic Use and Toxicity. *Nutrients* 13: 1703.
- Zasowska-Nowak A, Nowak PJ, Ciałkowska-Rysz A (2020) High-Dose Vitamin C in Advanced-Stage Cancer Patients. *Nutrients* 13: 735.

18. Robien K, Cutler GJ, Lazovich D (2007) Vitamin D intake and breast cancer risk in postmenopausal women: the Iowa women's health study. *Cancer Causes Control* 18: 775-782.
19. Kawase T, Matsuo K, Suzuki T, Hirose K, Hosono S, et al. (2010) Association between vitamin D and calcium intake and breast cancer risk according to menopausal status and receptor status in Japan. *Cancer Sci* 101: 1234-1240.
20. den Hollander P, Savage MI, Brown PH (2013) Targeted therapy for breast cancer prevention. *Front Oncol* 3: 250.
21. Fernandez-Lazaro CI, Romanos-Nanclares AR, Sanchez-Bayona R, Gea A, Sayon-Orea C, et al. (2021) Dietary calcium, vitamin D, and breast cancer risk in women: findings from the SUN cohort. *Eur J Nutr* 60: 3783-3797.
22. Rodriguez-Amaya DB (1997) Carotenoids and food preparation: the retention of provitamin A carotenoids in prepared, processed, and stored foods. Arlington, John Snow and Opportunities for Micronutrient Interventions Project.
23. Olson JA, Vitamin A, In: Brown ML, et al. (1990) Present knowledge in nutrition. (6<sup>th</sup> edn), Washington, DC: International Life Sciences Institute-Nutrition Foundation 96-107.
24. Feldman D, Glorieux FH, Pike JW, et al. (1997) Vitamin D. Academic, New York.
25. Nair R, Maseeh A (2012) Vitamin D: The "sunshine" vitamin. *J Pharmacol Pharmacother* 3: 118-126.
26. Ljubic A, Jacobsen C, Holdt SL, Jacobsen J (2020) Microalgae *Nannochloropsis oceanica* as a future new natural source of vitamin D3. *Food Chem* 320: 126627.
27. Ravisankar P, Reddy A A, Nagalakshmi B, Koushik OS, Kumar BV, et al. (2015) The Comprehensive Review on Fat Soluble Vitamins. *IOSR J Pharma* 5: 12-28.
28. Laya A, Koubala BB (2020) Changes in Vitamin E and  $\beta$ -Carotene Contents in Various Edible Cassava Leaves (*Manihot esculenta* Crantz) of Different Ages across Multiple Seasons. *Inter J Agro* 8.
29. Gheorghie G, Stoian AP, Gaman MA, et al. (2019) The benefits and risks of antioxidant treatment in liver diseases. *Rev Chim* 70: 651-655.
30. Ferraro PM, Curhan GC, Gambaro G, Taylor EN (2016) Total, Dietary, and Supplemental Vitamin C Intake and Risk of Incident Kidney Stones. *Am J Kidney Dis* 67: 400-407.
31. Nakos M, Pepelanova I, Beutel S, Krings U, Berger RG, et al. (2017) Isolation and analysis of vitamin B-12 from plant samples. *Food Chem* 216: 301-308.
32. Zhao L, Zhao X, Xu Y, Liu X, Zhang J, et al. (2020) Simultaneous determination of 49 amino acids, B vitamins, flavonoids, and phenolic acids in commonly consumed vegetables by ultra-performance liquid chromatography-tandem mass spectrometry. *Food Chem* 344: 128712.
33. Kaneki M, Hosoi T, Ouchi Y, Orimo H (2006) Pleiotropic actions of vitamin K: Protector of bone health and beyond? *Nutrition* 22: 845-852.
34. Elder SJ, Haytowitz DB, Howe J, Peterson JW, Booth SL (2006) Vitamin K contents of meat, dairy, and fast food in the U.S. diet. *J. Agric Food Chem* 54: 463-467.
35. Saini RK, Nile SH, Park SW (2015) Carotenoids from fruits and vegetables: Chemistry, analysis, occurrence, bioavailability and biological activities. *Food Res Int* 76: 735-824.
36. Jäpelt RB, Jakobsen J (2013) Vitamin D in plants: a review of occurrence, analysis, and biosynthesis. *Front Plant Sci* 4: 136.
37. Pilz S, März W, Cashman KD, Kiely ME, Whiting SJ, et al. (2018) Rationale and plan for Vitamin D Food Fortification: A Review and Guidance Paper. *Front Endocrinol* 9: 373.
38. Blasiak J, Pawlowska E, Chojnacki J, Szczepanska J, Fila M, et al. (2020) Vitamin D in Triple-Negative and BRCA1-Deficient Breast Cancer-implications for pathogenesis and therapy. *Int J Mol Sci* 21: 3670.
39. Costantini L, Magno S, Albanese D, et al. (2018) Characterization of human breast tissue microbiota from core needle biopsies through the analysis of multi-hypervariable 16S-rRNA gene regions. *Sci Rep* 8: 16893.
40. Kim MK, Ahn SH, Son BH, Sung MK (2010) Plasma antioxidant concentration, not superoxide dismutase polymorphism, is associated with breast cancer risk in Korean women. *Nutr Res* 30: 705-713.
41. Kim JA, Choi R, Won H, Kim S, Choi HJ, et al. (2020) Serum Vitamin Levels and Their Relationships with Other Biomarkers in Korean Breast Cancer Patients. *Nutrients* 12: 2831.
42. Mangiarotti R, Danova M, Alberici R, Pellicciari C (1998) All-trans retinoic acid (atra)-induced apoptosis is preceded by g1 arrest in human mcf-7 breast cancer cells. *Br J Cancer* 77: 186-191.
43. Wu MJ, Kim MR, Chen YS, Yang JY, Chang CJ (2017) Retinoic acid directs breast cancer cell state changes through regulation of tet2-pkczeta pathway. *Oncogene* 36: 3193-3206.
44. Bernardo AR, Cosgaya JM, Aranda A, Jimenez Lara AM (2017) Pro-apoptotic signaling induced by Retinoic acid and dsRNAs under the control of Interferon Regulatory Factor-3 in breast cancer cells. *Apoptosis* 22: 920-932.
45. Bolis M, Paroni G, Fratelli M, Vallerga A, Guarrera L, et al. (2020) All-Trans Retinoic Acid Stimulates Viral Mimicry, Interferon Responses and Antigen Presentation in Breast-Cancer Cells. *Cancers* 12: 1169.
46. Phipps SM, Love WK, White T, Andrews LG, Tollefsbol TO, et al (2009) Retinoid-induced histone deacetylation inhibits telomerase activity in estrogen receptor-negative breast cancer cells. *Anticancer Res* 29: 4959-4964.
47. Ciolino HP, Dai Z, Nair V (2011) Retinol inhibits aromatase activity and expression in vitro. *J Nutr Biochem* 22: 522-526.
48. Chen Q, Ross AC (2012) All-trans-retinoic acid and the glycolipid alphasgalactosylceramide combined reduce breast tumor growth and lung metastasis in a 4T1 murine breast tumor model. *Nutr Cancer* 64: 1219-1227.
49. Sumantran VN, Zhang R, David S, Lee S, Wicha MS (2000) Differential Regulation of Apoptosis in Normal versus Transformed Mammary Epithelium by Lutein and Retinoic Acid. *Cancer Epidemiol Biomarkers Prev* 9: 257-263.
50. Shree GS, Prasad KY, Arpitha HS, Deepika UR, Kumar KN, et al. (2017)  $\beta$ -carotene at physiologically attainable concentration induces apoptosis and down-regulates cell survival and antioxidant markers in human breast cancer (MCF-7) cells. *Mol Cell Biochem* 436: 1-12.
51. Saini RK, Keum Y-S, Daglia M, et al. (2020) Dietary carotenoids in cancer chemoprevention and chemotherapy: A review of emerging evidence. *Pharmacol Res* 157: 104830.

52. Cho SO, Kim MH, Kim H (2018)  $\beta$ -Carotene inhibits activation of NF- $\kappa$ B, activator protein-1, and STAT3 and regulates abnormal expression of some adipokines in 3T3-L1 adipocytes. *J Cancer Prev* 23: 37-43.
53. Gong X, Marisiddaiah R, Zaripheh S, Wiener D, Rubin LP, et al. (2016) Mitochondrial  $\beta$ -carotene 9',10'-oxygenase modulates prostate cancer growth via NF- $\kappa$ B inhibition: alycopene-independent function. *Mol Cancer Res* 14: 966-975.
54. Kim J, Park MK, Li WQ, Qureshi AA, Cho E, et al. (2019) Association of vitamin A intake with cutaneous squamous cell carcinoma risk in the United States. *JAMA Dermatol* 155: 1260-1268.
55. Kaegi E (1998) Unconventional therapies for cancer: 5. Vitamins A, C and E. on behalf of the Task Force on Alternative Therapies of the Canadian Breast Cancer Research Initiative. *CMAJ* 158: 1157-1159.
56. Eliassen AH, Hendrickson SJ, Brinton LA, Buring JE, Campos H, et al. (2012) Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies. *J Natl Cancer Inst* 104: 1905-1916.
57. He J, Gu Y, Zhang S (2018) Vitamin A and Breast Cancer Survival: A Systematic Review and Meta-analysis. *Clin Breast Cancer* 18: 1389-1400.
58. Fiedor J, Burda K (2014) Potential role of carotenoids as antioxidants in human health and disease. *Nutrients* 6: 466-488.
59. Shin MH, Holmes MD, Hankinson SE, Wu K, Colditz GA, et al. (2002) Intake of dairy products, calcium, and vitamin D and risk of breast cancer. *J Natl Cancer Inst* 94: 1301-1311.
60. Vijay K, Sowmya PR-R, Arathi BP, Shilpa S, Shwetha HJ, et al. (2018) Low-dose doxorubicin with carotenoids selectively alters redox status and upregulates oxidative stress-mediated apoptosis in breast cancer cells. *Food Chem Toxicol* 118: 675-690.
61. Bohlke K, Spiegelman D, Trichopoulou A, Katsouyanni K, Trichopoulos D (1999) Vitamins A, C and E and the risk of breast cancer: results from a case-control study in Greece. *Br J Cancer* 79: 23-29.
62. Fulan H, Changxing J, Baina WY, Wencui Z, Chungqing L, et al. (2011) Retinol, vitamins A, C, and E and breast cancer risk: a meta-analysis and meta-regression. *Cancer Causes Control* 22: 1383-1396.
63. Bakker MF, Peeters PHM, Klaassen VM, Bueno-de-Mesquita HB, Jansen EH, et al. (2016) Plasma carotenoids, vitamin C, tocopherols, and retinol and the risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition cohort. *Am J Clin Nutr* 103: 454-464.
64. Sun L, Yoshii Y, Miyagi K, Ishida A (1999) Proliferation inhibition of glioma cells by vitamin K2. *No Shinkei Geka* 27: 119-125.
65. Mamede AC, Tavares SD, Abrantes AM, Trindade J, Maia JM, et al. (2011) The Role of Vitamins in Cancer: A Review. *Nutr Cancer* 63: 479-494.
66. Lamson DW, Plaza SM (2003) The anticancer effects of vitamin K. *Altern Med Rev* 8: 303-318.
67. Noto V, Taper HS, Jiang YH, Janssens J, Bonte J, et al. (1989) Effects of sodium ascorbate (vitamin C) and 2-methyl-1,4-naphthoquinone (vitamin K3) treatment on human tumor cell growth in vitro. I. Synergism of combined vitamin C and K3 action. *Cancer* 63: 901-906.
68. Miyazawa K, Moriya S, Kokuba H, Hino H, Takano N, et al. (2020) Vitamin K2 induces non-apoptotic cell death along with autophagosome formation in breast cancer cell lines. *Breast Cancer* 27: 225-235.
69. Gan L, Camarena V, Mustafi S, Wang G (2019) Vitamin C Inhibits Triple-Negative Breast Cancer Metastasis by Affecting the Expression of YAP1 and Synaptopodin 2. *Nutrients* 11: 2997.
70. Vollbracht C, Schneider B, Leendert V, Weiss G, Auerbach L, et al. (2018) Intravenous vitamin C administration improves quality of life in breast cancer patients during chemo-/radiotherapy and aftercare: Results of a retrospective, multicentre, epidemiological cohort study in Germany. *In Vivo* 25: 983-990.
71. Carr AC, Vissers MCM, Cook J (2014) Relief from cancer chemotherapy side effects with pharmacologic vitamin C. *N. Z. Med J* 127: 66-70.
72. Zeng J, Wang K, Ye F, Lei L, Zhou Y, et al. (2019) Folate intake and the risk of breast cancer: an up-to-date meta-analysis of prospective studies. *Eur J Clin Nutri* 73: 1657-1660.
73. Harris HR, Orsini N, Wolk A (2014) Vitamin C and survival among women with breast cancer: A Meta-analysis. *Eur J Cancer* 50: 1223-1231.
74. Zeng LH, Wang QM, Feng LY, Ke YD, Xu QZ, et al. (2019) High-dose vitamin C suppresses the invasion and metastasis of breast cancer cells via inhibiting epithelial mesenchymal transition. *Onco Targets Ther* 12: 7405-7413.
75. Afam IOJ, Silungwe H, Takalani T, Omolola AO, Udeh HO, et al. (2021) Antioxidant-rich natural fruit and vegetable products and human health. *Inter J Food Propert* 24: 41-67.
76. Jiang Q (2017) Natural forms of vitamin E as effective agents for cancer prevention and therapy. *Adv Nutr* 15: 850-867.
77. Shah SJ, Sylvester PW (2005) Tocotrienol-induced cytotoxicity is unrelated to mitochondrial stress apoptotic signaling in neoplastic mammary epithelial cells. *Biochem Cell Biol* 83: 86-95.
78. Nesaretnam K, Stephen R, Dils R, Darbre P (1998) Tocotrienols inhibit the growth of human breast cancer cells irrespective of estrogen receptor status. *Lipids* 33: 461-469.
79. Yu W, Simmons-Menchaca M, Gapor A, Sanders BG, Kline K (1999) Induction of apoptosis in human breast cancer cells by tocopherols and tocotrienols. *Nutr Cancer* 33: 26-32.
80. McIntyre BS, Briski KP, Gapor A, Sylvester PW (2000) Antiproliferative and apoptotic effects of tocopherols and tocotrienols on preneoplastic and neoplastic mouse mammary epithelial cells (44544). *Proc Soc Exp Biol Med* 224: 292-301.
81. Kline K, Yu W, Sanders BG (2004) Vitamin E and Breast Cancer. *J Nutr* 134: 3458S-3462S.
82. Malafa MP, Neitzel LT (2000) Vitamin E Succinate Promotes Breast Cancer Tumor Dormancy. *J Surg Res* 93: 163-170.
83. Yu W, Sanders BG, Kline K (2003) RRR- $\alpha$ -tocopheryl succinate-induced apoptosis of human breast cancer cells involves Bax translocation to mitochondria. *Cancer Res* 63: 2483-2491.
84. Sylvester P, McIntyre B, Gapor A, Briski KP (2001) Vitamin E inhibition of normal mammary epithelial cell growth is associated with a reduction in protein kinase C $\alpha$  activation. *Cell Prolif* 34: 347-357.

85. Abraham A, Kattoor AJ, Saldeen T, Mehta JL (2019) Vitamin E and its anticancer effects. *Crit Rev Food Sci Nutr* 59: 2831-2838.
86. Lajous M, Romieu I, Sabia S, Boutron-Ruault MC, Clavel-Chapelon F (2006) Folate, vitamin B12 and postmenopausal breast cancer in a prospective study of French women. *Cancer Causes Control* 17: 1209-1213.
87. Hu F, Wu Z, Li G, Teng C, Liu Y, et al. (2015) The plasma level of retinol, vitamins A, C and  $\alpha$ -tocopherol could reduce breast cancer risk? A meta-analysis and meta-regression. *J Cancer Res Clin Oncol* 141: 601-614.
88. Torun M, Akgul S, Sargin H (1995) Serum vitamin E level in patients with breast cancer. *J Clin Pharm Ther* 20: 173-178.
89. Ben-Chioma AE, Elekima I (2018) Evaluation of Vitamin E and Selenium Levels in Breast Cancer Patients in Port Harcourt Metropolis, Nigeria. *J Advan Medici Medic Res* 28: 1-7.
90. Turley JM, Tao Fu, Ruscetti FW, Mikovits JA, Bertolette DC, et al. (1997) Vitamin E Succinate Induces Fas-mediated Apoptosis in Estrogen Receptor Negative Human Breast Cancer Cells. *Cancer Res* 57: 881-890.
91. Sigounas G, Anagnostou A, Steiner M (1997) DL- $\alpha$ -Tocopherol induces apoptosis in erythroleukemia, prostate, and breast cancer cells. *Nutr Cancer* 28: 30-35.
92. Godazandeh G, Shahram AI, Motlaq TM, Sahebnaasagh A, Bazi A (2021) The comparison of the effect of flaxseed oil and vitamin E on mastalgia and nodularity of breast fibrocystic: a randomized double blind clinical trial. *J Pharm Health Care Sci* 7: 4.
93. Theriault A, Chao JT, Wang Q, Gapor A, Adeli K (1999) Tocotrienol: a review of its therapeutic potential. *Clin Biochem* 32: 309-319.
94. Aung TT, Chandana SR, D'Silva KJ, et al. (2009) The role of vitamin D in breast cancer. *Oncol Rev* 3: 19-25.
95. John EM, Schwartz GG, Dreon DM, Koo J (1999) Vitamin D and Breast Cancer Risk: The NHANES I Epidemiologic Follow-up Study, 1971-1975 to 1992. National Health and Nutrition Examination Survey. *Cancer Epidemiol Biomarkers Prev* 8: 399-406.
96. Garland CF, Gorham ED, Mohr SB, Grant WB, Giovannucci EL, et al. (2007) Vitamin D and prevention of breast cancer: pooled analysis. *J Steroid Biochem Mol Biol* 103: 708-711.
97. Chen P, Hu P, Xie D, Qin Y, Wang F, et al. (2010) Meta-analysis of vitamin D, calcium and the prevention of breast cancer. *Breast Cancer Res Treat* 121: 469-477.
98. Mohr SB, Gorham ED, Kim J, Hofflich H, Garland CF, et al. (2014) Meta-Analysis of Vitamin D Sufficiency for Improving Survival Of Patients With Breast Cancer. *Anticancer Res* 34: 1163-1166.
99. Stoll F, Akladios CY, Mathelin C, et al. (2013) Vitamin D and breast cancer: Is there a link? *Gynecol Obstet Fertil* 41: 242-250.
100. Shekarriz-Foumani R, Khodaie F (2016) The correlation of plasma 25-hydroxyvitamin D deficiency with risk of breast neoplasms: A systematic review. *Iran J Cancer Prev* 9: e4469.
101. Bilinski K, Boyages J (2013) Association between 25-hydroxyvitamin D concentration and breast cancer risk in an Australian population: an observational case-control study. *Breast Cancer Res Treat* 137: 599-607.
102. Park S, Lee DH, Jeon JY, Ryu J, Kim S, et al. (2015) Serum 25-hydroxyvitamin D deficiency and increased risk of breast cancer among Korean women: a case-control study. *Breast Cancer Res Treat* 152: 147-154.
103. Al-Azhri J, Zhang Y, Bshara W, Zirpoli G, McCann SE, et al. (2016) Tumor Expression of Vitamin D Receptor and Breast Cancer Histopathological Characteristics and Prognosis. *Clin Cancer Res* 23: 97-103.
104. Welsh J, Wietzke JA, Zinser GM, Byrne B, Smith K, et al. (2003) Vitamin D-3 Receptor as a Target for Breast Cancer Prevention. *J Nutr* 133: 2425S-2433S.
105. Welsh J (2004) Vitamin D and breast cancer: Insights from animal models. *Am J Clin Nutr* 80: 1721S-1724S.
106. Cui Y, Rohan TE (2006) Vitamin D, Calcium, and Breast Cancer Risk: A Review. *Cancer Epidemiol Biomarkers Prev* 15: 1427-1437.
107. Garland CF, Garland FC, Gorham ED, Lipkin M, Newmark H, et al. (2006) The Role of Vitamin D in Cancer Prevention. *Am J Public Health* 96: 252-261.
108. Krishnan AV, Feldman D (2011) Mechanisms of the Anti-Cancer and Anti-Inflammatory Actions of Vitamin D. *Annu Rev Pharmacol Toxicol* 51: 311-336.
109. Kim Y, Je Y (2014) Vitamin D intake, blood 25(OH) D levels, and breast cancer risk or mortality: A meta-analysis. *Br J Cancer* 110: 2772-2784.
110. Narvaez CJ, Matthews D, LaPorta E, Simmons KM, Beaudin S, et al. (2014) The impact of vitamin D in breast cancer: genomics, pathways, metabolism. *Front Physiol* 5: 213.
111. Tavera-Mendoza LE, Westerling T, Libby E, Marusky A, Cato L, et al. (2017) Vitamin D receptor regulates autophagy in the normal mammary gland and in luminal breast cancer cells. *Proc Natl Acad Sci* 114: E2186-E2194.
112. Patel PS, Franky D, Shaha FD, Patel KR, Gokani RA, et al. (2020) Clinical significance of serum 25 hydroxyvitamin D in breast cancer: An Indian scenario. *J Steroid Biochem Mol Biol* 202: 105726.
113. Autier P, Boniol M, Pizot C, Mullie P (2014) Vitamin D status and ill health: A systematic review. *Lancet Diabetes Endocrinol* 2: 76-89.
114. Zhang X, Harbeck N, Jeschke U, Doisneau-Sixou S (2017) Influence of vitamin D signaling on hormone receptor status and HER2 expression in breast cancer. *J Cancer Res Clin Oncol* 143: 1107-1122.
115. Deeb KK, Trump DL, Johnson CS (2007) Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. *Nat Rev Cancer* 7: 684-700.
116. Kulling PM, Olson KC, Olson TL, Feith DJ, Loughran TP (2017) Vitamin D in hematological disorders and malignancies. *Eur J Haematol* 98: 187-197.
117. Song D, Deng Y, Liu K, Zhou L, Li N, et al. (2019) Vitamin D intake, blood vitamin D levels, and the risk of breast cancer: a dose-response meta-analysis of observational studies. *AGING* 11: 12708-12732.
118. Janowsky EC, Lester GE, Weinberg CR, Millikan RC, Schildkraut JM, et al. (1999) Association between low levels of 1,25-dihydroxyvitamin D and breast cancer risk. *Public Health Nutri* 2: 283-291.
119. Hossain S, Beydoun MA, Beydoun HA, Chen X, Zonderman AB, et al. (2019) Vitamin D and breast cancer: A systematic review and meta-analysis of observational studies. *Clin Nutr ESPEN* 30: 170-184.

120. Shirazi L, Almquist M, Borgquist S, Malm J, Manjer J (2016) Serum vitamin D (25OHD3) levels and the risk of different subtypes of breast cancer: A nested case-control study. *The Breast* 28: 184-190.
121. Bertone-Johnson ER, Chen WY, Holick MF, Hollis BW, Colditz GA, et al. (2005) Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 14: 1991-1997.
122. Garland CF, Gorham ED, Mohr SB, Garland FC (2009) Vitamin D for cancer prevention: global perspective. *Ann Epidemiol* 19: 468-483.
123. Kim SJ, Zuchniak A, Sohn KJ, Lubinski J, Demsky R, et al. (2016) Plasma folate, vitamin B-6, and vitamin B-12 and breast cancer risk in BRCA1- and BRCA2-mutation carriers: a prospective study. *Am J Clin Nutr* 104: 671-677.
124. Stevens VL, McCullough ML, Pavluck AL, Talbot JT, Feigelson HS, et al. (2007) Association of polymorphisms in one-carbon metabolism genes and postmenopausal breast cancer incidence. *Cancer Epidemiol Biomarkers Prev* 16: 1140-1147.
125. Bassett JK, Baglietto L, Hodge AM, Severi G, Hopper JL, et al. (2013) Dietary intake of B vitamins and methionine and breast cancer risk. *Cancer Causes Control* 24: 1555-1563.
126. Shrubsole MJ, Jin F, Dai Q, Shu X-O, Potter JD, et al. (2001) Dietary Folate Intake and Breast Cancer Risk: Results from the Shanghai Breast Cancer Study. *Cancer Res* 61: 7136-7141.
127. Xu X, Gammon MD, Wetmur JG, Bradshaw PT, Teitelbaum SL, et al. (2008) B-Vitamin Intake, One-Carbon Metabolism, and Survival in a Population-Based Study of Women with Breast Cancer. *Cancer Epidemiol Biomarkers Prev* 17: 2109-2116.
128. Yu L, Tan Y, Zhu L (2017) Dietary vitamin B2 intake and breast cancer risk: a systematic review and meta-analysis. *Arch Gynecol Obstet* 295: 721-729.
129. Razeghian E, Mohammed B, Nemati AH, et al. (2020) Folic acid, vitamin B6, B12, and breast cancer incidence. *Spring* 5: 4-6.
130. Ren X, Xu P, Zhang D, Liu K, Song D, et al. (2020) Association of folate intake and plasma folate level with the risk of breast cancer: A dose-response meta-analysis of observational studies. *AGING* 12: 21355-21375.
131. Egnell M, Fassier P, Lécuyer L, Zelek L, Vasson MP, et al. (2017) B-Vitamin Intake from Diet and Supplements and Breast Cancer Risk in Middle-Aged Women: Results from the Prospective Nutri Net-Santé Cohort. *Nutrients* 9: 488.
132. Agnoli C, Grioni S, Krogh V, et al. (2016) 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-Varese Cohort 1-3. *The J Nutri Nutrition Epidemiol* 1-8.
133. Lurie G, Wilkens LR, Shvetsov YB, Ollberding NJ, Franke AA, et al. (2012) Prediagnostic Plasma Pyridoxal 50-Phosphate (Vitamin B6) Levels and Invasive Breast Carcinoma Risk: Multiethnic Cohort 9.
134. Zhang SM, Willett WC, Selhub J, Hunter DJ, Giovannucci EL, et al. (2003) Plasma folate, vitamin B6, vitamin B12, homocysteine, and risk of breast cancer. *J Natl Cancer Inst* 95: 373-380.
135. Zhang SM, Cook NR, Albert CM, Gaziano JM, Buring JE, et al. (2008) Effect of Combined Folic Acid, Vitamin B6, and Vitamin B12 on Cancer Risk: Results from a Randomized Trial. *JAMA* 300: 2012-2021.
136. Shrubsole MJ, Shu XO, Li HL, Cai H, Yang G, et al. (2011) Dietary B Vitamin and Methionine Intakes and Breast Cancer Risk Among Chinese Women. *Am J Epidemiol* 173: 1171-1182.
137. Lin J, Lee IM, Cook NR, Selhub J, Manson JE, et al. (2008) Plasma folate, vitamin B-6, vitamin B-12, and risk of breast cancer in women. *Am J Clin Nutr* 87: 734-743.
138. Matsubara K, Komatsu S, Oka T, Kato N (2003) Vitamin B6-mediated suppression of colon tumorigenesis, cell proliferation, and angiogenesis. *J Nutr Biochem* 14: 246-250.
139. Yang D, Baumgartner RN, Slattery ML, Wang C, Giuliano AR, et al. (2013) Dietary intake of folate, B-vitamins and methionine and breast cancer risk among Hispanic and non-Hispanic white women. *PLoS One* 8: 54495.
140. Liu Y, Zhou L-S, Xu X-M, Deng L-Q, Xiao Q-K (2013) Association of Dietary Intake of Folate, Vitamin B6 and B12 and MTHFR Genotype with Breast Cancer Risk. *Asian Pac J Cancer Prev* 14: 5189-5191.