*Send Orders for Reprints to reprints@benthamscience.net*

*Endocrine, Metabolic & Immune Disorders-Drug Targets,* **XXXX,** ***XX*****, 1-11**


**REVIEW ARTICLE**

# Nutraceuticals and Oral Supplements in Cancer Prevention: A Narrative Review

Giovanni De Pergola[1,2,#,*], Simonetta Marucci[3,#], Filomena Corbo[4,#], Guido Almerighi[5, #], Nadia Cerutti[6,#], Vincenzo Triggiani[7], Danila De Vito[8], Fabio Castellana[9], and Roberta Zupo[9,*]

*[1]Unit of Geriatrics and Internal Medicine, National Institute of Gastroenterology "Saverio de Bellis," Research Hospital, Castellana Grotte, 70013 Bari, Italy; [2]Clinical Nutrition Unit, Medical Oncology, Department of Biomedical Science and Human Oncology, University of Bari, School of Medicine, 70124 Bari, Italy; [3]Biomedical Campus University. Dept. "Sciences and Technologies for Man and the Environment". Via Alvaro del Portillo 21, Rome. Italy, [4]Department of Pharmacy-Drug Sciences, University of Bari "Aldo Moro", 70125 Bari, Italy; [5]Center for Dysmetabolic Diseases and Atherosclerosis, Azienda Ospedaliera G. Brotzu, Cagliari, Italy; [6]Diabetology, Civil Hospital of Vigevano, Pavia, Italy; [7]Interdisciplinary Department of Medicine-Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases. University of Bari "Aldo Moro", School of Medicine, Policlinico, Piazza Giulio Cesare 11, 70124 Bari, Italy; [8]Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari "Aldo Moro", Bari, Italy; [9]Unit of Data Sciences and Technology Innovation for Population Health, National Institute of Gastroenterology "Saverio de Bellis," Research Hospital, Castellana Grotte, Bari, Italy*

**ARTICLE HISTORY**

Received: February 28, 2022
Revised: March 18, 2022
Accepted: April 12, 2022

*DOI:*
*10.2174/1871530322666220527152414*

**Abstract:** ***Background*****:** Epidemiological studies have shown that food is a compelling means of maintaining a state of well-being and preventing diseases. Many malignant diseases are related to nutrition, and the nutrient-organism interaction could define the balance between health and disease. Nutrients and dietary components influence epigenetic phenomena and modify drug response so that food-organism interactions may influence individual predisposition to disease and its potential therapeutic response.

***Aims*****:** In this review, we highlighted emerging opinions and data on a large cluster of nutraceuticals, as well as functional foods and specific dietary patterns, with respect to cancer, including breast, pancreas, prostate, and colorectal. Only those nutraceuticals and nutritional supplements yielding sufficient and convincing data have been reported in this review; molecules with inconclusive clinical evidence will not be discussed.

***Conclusion*****:** Growing and accumulating evidence is validating the use of nutraceuticals in cancer settings. However, a knowledge gap remains in terms of causal evidence for several compounds where a window for further clinical studies is left.

**Keywords:** Cancer, nutraceuticals, diet, supplementation, functional foods, dietary patterns.

## 1. INTRODUCTION

A substantial body of evidence surrounds the link between diet and the development or progression of several malignancies such as colon, breast, and prostate cancer, thus defining these malignancies as diet-related. Nutraceuticals are diet components able to provide both nutritional benefits and pharmaceutical effects, and their potential therapeutic activity may be antioxidant as well as anti-inflammatory and, consequently, anti-cancer. From a bromatological standpoint, nutraceuticals are dietary constituents, extracts, or food derivatives such as vitamins, amino acids, and minerals that may have potential health benefits beyond their nutritional value; nutritionally speaking, they are a source of both nutrients (carbohydrates, proteins, fats) and non-nutrient (*e.g.*, prebiotics, probiotics, phytochemicals, enzyme regulators), and such nutraceutical properties lead to label the food as functional. Nowadays, there is an abundance of terminology in this context, and multiple definitions and designations of nutraceuticals in the literature can often lead to confusion. To be considered functional, a food must simultaneously meet three conditions, such as, be part of a regular daily diet and be a natural ingredient (*i.e.*, not found in pills, capsules, or any other medical or pharmacological form). Its consumption

[*]Address correspondence to this author at Unit of Geriatrics and Internal Medicine, National Institute of Gastroenterology "Saverio de Bellis," Research Hospital, Castellana Grotte, 70013 Bari, Italy;
E-mail: giovanni.depergola@irccsdebellis.it
[#]On behalf of the (AME/Associazione Medici Endocrinology), Nutration and Nutraceuticals Commission.

 

must improve/regulate a specific metabolic process/ mechanism, thereby preventing or controlling some health diseases. More recently, the use of nutraceuticals is emerging as a promising tool in cancer prevention because of their relative abundance, bioavailability, safety, low-cost efficacy, and host immunocompatibility. Moreover, the primary advantage of using plant-derived nutraceuticals over the most popular cytostatic drugs is minimal side effects and reduced toxicity.

This narrative review article describes the benefits of nutraceuticals, functional supplements, and dietary patterns in cancer prevention settings. To this end, a separate search was performed in the US National Library of Medicine (PubMed, Bethesda, MD 20894, USA), Medical Literature Analysis and Retrieval System Online (MEDLINE), EMBASE, Scopus, Ovid, and Google Scholar to find original articles, meta-analyses, technical reports, letters to the editor, and systematic and narrative review articles that were useful for our purpose. The last search was done on July 31st, 2021, and the bottom timeline was set at the beginning of 2017 (Table **1**). The knowledge of biological pathways involving major nutraceuticals with advantages over cancer will be more closely discussed. Fig. **1** shows a graphical representation of this overview. Supplementary Table **1** provides an overview of cancer sites that may benefit from the consumption of particular chemicals and functional foods.

**Table 1. Search strategy used in the US National Library of Medicine (PubMed) and Medical Literature Analysis and Retrieval System Online (MEDLINE) and adapted to the other sources, according to selected descriptors.**

| Strategy | Descriptors Used |
|---|---|
| # 1 | (Healthy Dietary Pattern*) OR (Healthy Diet*) OR (Healthy Eating) OR (Plant Based Diet*) OR (Mediterranean Diet*) OR (Nutraceutic*) OR (Phytochemic*) OR (Functional Food*) OR (Functional Diet*) OR (Supplement*) OR (Food*) |
| # 2 | (Cancer*) OR (Neoplasm*) |
| # 3 | #1 AND #2 |
| Filters: Time frame: 2017-2021. Number of papers: 28,801. Last update: 31st July 2021 | |

## 2. VITAMIN D AND CALCIUM

Vitamin D is the name given to a group of fat-soluble pro-hormones (substances that usually have little hormonal activity on their own but that the body can turn into hormones). Vitamin D helps the body use calcium and phosphorus to make strong bones and teeth. Skin exposed to the sun can make vitamin D, and vitamin D can also be obtained from some foods. Fish (not just fatty fish), egg yolk, and offal such as liver are all good sources of vitamin D(3). Sometimes, it is added to some fortified foods, such as milk. A number of epidemiologic studies have investigated whether people with higher vitamin D intake or higher blood levels of vitamin D have lower risks of specific cancers. Some specific mechanisms are discussed as follows. The binding of vitamin D to specific receptors leads to transcriptional activation or repression of target genes, resulting in apoptotic [1], antiproliferative [2], and immunomodulatory effects, thus resulting in the antineoplastic activity of vitamin D and lower risk of metastatic disease [1]. Such evidence is strengthened by clinical data, as the prevalence of vitamin D deficiency is high in cancer patients [3,4], with one study reporting vitamin D deficiency in 72% of cancer patients [5,6]. In a recent multicenter randomized, double-blind, placebo-controlled clinical trial involving a sample who did not have cancer, supplementation with vitamin D3 (cholecalciferol, 2000 IU/d) for a median intervention period of 5.3 years was shown to reduce the incidence of advanced (metastatic or fatal) cancer, with the most substantial risk reduction observed in normal-weight individuals [7]. A meta-analysis of prospective cohort studies showed that higher 25-idrossivitaminD (25(OH)D) concentration was associated with a 19% lower risk of cancer mortality, and the risk of cancer mortality was 2% lower for each 20 nmol/L increase in 25(OH)D concentration [8]. Together, these results suggest that vitamin D supplementation may operate through a general rather than site-specific mechanism to reduce the risk of advanced cancer. However, it should be noted that randomized controlled trials have shown that vitamin D supplementation does not result in a low incidence of invasive cancer [9]. As for calcium, a study of 200 participants with an 8-year follow-up showed that calcium alone (1200 mg/d of calcium carbonate) or in combination with vitamin D (1000 IU/d of vitamin D3) could reduce the risk of invasive cutaneous squamous cell carcinoma (SCC), but not basal cell carcinoma (BCC) [10].

**Fig. (1).** Biological pathways involving major nutraceuticals with advantages over cancer. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

## 3. VITAMIN C

Water-soluble vitamin found in many foods, particularly fruits and vegetables. This vitamin is an antioxidant that can scavenge reactive oxygen species preventing DNA damage and other critical effects in cancer transformation [11]. Specifically, an oxidized form of vitamin C, dehydro-

ascorbate, is transported through glucose transporters, and cancer cells switch from oxidative phosphorylation to glycolysis in energy production. Therefore, excess vitamin C may limit glucose transport and ATP production resulting in a lack of energy and cell death. Vitamin C can change cancer cells' metabolomic and epigenetic profiles, and activation of ten-eleven translocation proteins and downregulation of pluripotency factors by the vitamin can eradicate cancer stem cells. Metastasis, the primary reason for cancer-related deaths, requires the breakdown of collagen-containing anatomical barriers, the synthesis of which is promoted by vitamin C. Vitamin C induces the degradation of hypoxia-inducible factor-1 (HIF-1), essential for cancer cell survival under hypoxic conditions and can stimulate the immune system through activation of natural killer (NK) and T cells and monocytes. Pharmacological doses of vitamin C can inhibit cancer transformation in several pathways and induce pro-oxidant effects, which are detrimental to cancer cells.

## 4. VITAMIN E

Vitamin E is a fat-soluble plant antioxidant found in a variety of nuts, seeds, vegetables and oils, making it easy to add to your diet. As the primary form of vitamin E, α-Tocopherol (α-T) has the most significant activity in performing the essential antioxidant functions of this vitamin [12]. Due to the involvement of oxidative stress in carcinogenesis, the cancer-preventive activity of α-T has been extensively studied, and lower vitamin E intake or nutritional status are associated with increased cancer risk, as well as α-T supplementation to vitamin E-deficient populations has shown beneficial effects in lowering cancer risk in some intervention studies. However, several extensive intervention studies with α-T conducted in North America have not demonstrated a cancer-preventing effect [12]. More recent studies have focused on the γ- and δ- forms of tocopherols and tocotrienols (T3), and compared with α-T, these forms have much lower systemic bioavailability. Still, they have shown more robust antitumor activities in many studies in animal models and cell lines [12].

## 5. CURCUMIN

Curcumin is a natural polyphenol derived from turmeric and is well known to inhibit many types of cancer growth. In particular, this substance diffuses through cell membranes into the endoplasmic reticulum, mitochondria, and nucleus, where it exerts actions with antioxidant properties. Therefore, its use has been advocated for chemopreventive, antimetastatic, and anti-angiogenic purposes. Unfortunately, the hydrophobic nature of the curcumin molecule often limits its bioavailability, which is why many studies focus on the chemical modification of this compound. Current research aims to modify structures that improve the pharmacokinetic parameters of curcumin, such as the formation of nanoparticles, complexes with metals, or the synthesis of curcumin derivatives with functional substituents that enable tumor targeting. A recent study suggests that curcumin selectively inhibits prostate CAFs (cancer-associated fibroblasts) by inducing apoptosis and G2-M phase cell cycle arrest, indicating a novel application of curcumin in cancer therapy [13].

## 6. RESVERATROL

Resveratrol is a member of the stilbenes group of chemicals, which are phenolic compounds found in a variety of edible plants, including vines, berries and peanuts, and are a key component of the Mediterranean diet. Several research have been conducted on their bioactivity and potential health advantages. Most records, in particular, indicated a path of beneficial biological effects, such as antioxidant, anti-inflammatory, and antiproliferative actions [14]. Resveratrol has been investigated more than any other of the recognized stilbenes. Many research have focused on different elements of resveratrol's anti-cancer capabilities, demonstrating its high efficacy in addressing multiple cancer characteristics. Targeting the components of the tumor microenvironment is a viable technique in cancer therapy since the tumor microenvironment plays such an important role in the formation and spread of cancer, and cancer cells collaborate with a cast of normal cells to aid cancer's malignant behavior. In this regard, resveratrol can target the tumor microenvironment by changing the activity of various components around cancer cells, thanks to some biological activities [14].

## 7. INOSITOL

Inositol is a sugar that affects the body's natural insulin response and a number of hormones linked to mood and cognition. Although it is commonly referred to as vitamin B8, it is not a vitamin in the literal sense. Cantaloupe, citrus fruits, and a variety of fiber-rich meals all contain inositol naturally (such as beans, brown rice, corn, sesame seeds, and wheat bran). It's also available as a supplement, and it's used to treat a variety of medical ailments, including metabolic and mood disorders.

Inositol and its phosphates are naturally occurring dietary components that are beneficial to human health and may have a role in cancer prevention. In order to produce diets with high myo-inositol content that might be used to monitor therapeutic and/or preventative efficacy in illnesses such as cancer, researchers will need to monitor inositol and its concentration in the blood. Strong observational evidence relating inositol and phosphates to preventing and curing colitis-induced carcinogenesis has been noted in a recent study [15]. IBD-induced free radicals, IP3-mediated AKT signaling, the phospholipase A2/inositol-arachidonic acid metabolic pathway, and active eicosanoids are all thought to be important physiologic processes in DNA damage/genetic instability, cell proliferation, and angiogenesis, according to experts. As a result, these events lead to IBD-induced carcinogenesis, while inositol blocks these events, preventing IBD-induced cancer formation. Exogenous inositol will be part of an intracellular inositol pool that will (a) impede IP3/AKT signaling and (b) inhibit PGE2 and LTB4 formation by inhibiting phospholipase A2/inositol-arachidonic acid release and COX2, as well as prevent inflammation-induced nitro oxidative stress.

## 8. LYCOPENE

Lycopene is a member of the carotenoid family and is commonly found in tomatoes. Common foods high in

lycopene include guavas, cooked tomatoes, watermelon, grapefruit, papaya, sweet red peppers, persimmons, asparagus, red cabbage and mango. In terms of its anticancer effects, lycopene is often associated with a reduced risk of prostate cancer, and its use as a dietary supplement in terms of preventatives is widespread [16]. Lycopene's anticancer efficacy is based on its capacity to decrease oncogene expression and stimulate pro-apoptotic pathways, according to previous scientific findings. The notion that lycopene reduces cancer through resolving inflammation is being investigated in recent studies. Lycopene's anti-cancer system also includes the immune system, as it regulates immune cells to prevent tumor growth and progression. Finally, lycopene has been discovered to perform a unique role in lung cancer prevention [16].

## 9. POLYUNSATURATED FATTY ACIDS (PUFAS)

PUFAs are biologically active dietary components found in a wide range of plant and animal sources, including salmon, vegetable oils, and various nuts and seeds. Individual PUFAs produce prostaglandins and leukotrienes, which have different biological activities and induce pro- and anti-inflammatory responses *via* many signaling pathways that control cell proliferation, death, and angiogenesis. Polyunsaturated fatty acids (PUFAs) appear to play a role in cancer risk and progression, according to mounting data. Alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) belong to the n-3 family of PUFAs, whereas linolenic acid (LA) and arachidonic acid belong to the n-6 family (AA). EPA and DHA are anti-inflammatory lipid mediator precursors, whereas AA is a pro-inflammatory lipid mediator precursor. Collectively, PUFAs play crucial roles in maintaining cellular homeostasis, and perturbations in dietary intake or metabolism of PUFAs could result in cellular dysfunction and contribute to cancer risk and progression. Regarding n-6 PUFAs, evidence from prospective studies indicated that high blood levels of n-6 PUFAs were associated with an 8% lower risk of all cancers than low blood levels of n-6 PUFAs. In contrast, intake of n-6 PUFAs was not significantly associated with cancer risk [17]. Many studies have suggested that a larger consumption of n-3 polyunsaturated fatty acids may have some cancer-preventive properties; however, the true relationship between cancer risk and n-3 polyunsaturated fatty acids is still debated. The data regarding the link between omega-3 fatty acid intake and cancer outcomes was summarized and evaluated in a recent meta-analysis study [18]. Despite a large number of meta-analyses on the subject, only minor relationships have been found in several malignancies, with significant caveats. However, physicians and researchers should interpret observed links between -3 fatty acid consumption and cancer risks with caution due to the lack of evidence.

## 10. PROBIOTICS, PREBIOTICS, POSTBIOTICS, ANTIBIOTICS, AND FECAL MICROBIOTA TRANS-PLANTATION

Several research have looked into the role of probiotics in cancer prevention and treatment. The human gut microbiota is closely linked to the development of cancers. Tumors can result from the colonization of specific intestinal bacteria in specific sites, alteration of the gut microbiota, and intestinal immunological disorders. Meanwhile, the gut microbiota can help with tumor therapy by affecting the efficacy of anti-tumor medications, targeted therapy with tailored probiotics, and fecal microbiota transplantation, as well as participating in immune modulation and influencing the efficacy of anti-tumor drugs. In this setting, probiotic bacteria can reduce the incidence of hepatocellular carcinoma (HCC) by regulating the host gut microbiota to promote beneficial microbe development and inhibit HCC-associated dysbiosis, hence decreasing pathogen-associated molecular patterns-mediated hepatic inflammation. Probiotics have antiviral activities against hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, ameliorate obesity, and risk of Nonalcoholic Fatty Liver Disease (NAFLD)/Nonalcoholic steatohepatitis (NASH). Also, their antioxidant, anti-proliferative, anti-angiogenic, and anti-metastatic properties can also help to inhibit HCC progression. Probiotics also increase the expression of tumor suppressor genes while decreasing the expression of oncogenes. Furthermore, metabolites produced by probiotics through the breakdown of dietary phytochemicals may help to reduce the risk of HCC. The potential of probiotics as an adjuvant therapy for HCC risk reduction and management is demonstrated by these various anticancer pathways [19]. To reverse established microbial dysbiosis, gut microbiota modulation is also a novel strategy for preventing and treating colorectal cancer (CRC) [20]. Probiotics' potential mechanisms of action are modifying intestinal microbiota, improving colonic physicochemical conditions, producing anticancerogenic and antioxidant metabolites against carcinogenesis, decreasing intestinal inflammation, and producing harmful enzymes. Colorectal cancer prevention is linked to changes in the gut microbiota's quantitative and qualitative composition, as well as changes in metabolic activity and physicochemical circumstances. It is also worth noting that the effect varies depending on the bacterial strain and the dose given. The findings revealed that probiotics and synbiotics can help prevent colorectal cancer [21]. Changes in the composition and metabolic activity of the intestinal microbiota, reduced inflammation, induction of apoptosis and inhibition of tumor growth, modulation of immune responses and cell proliferation; improved function of the intestinal barrier; production of anticarcinogenic compounds, and modulation of oxidative stress were the main mechanisms identified [21]. Different strategies have been employed, including probiotics, prebiotics, antibiotics, and fecal microbiota transplantation [22]. However, although these strategies show promising results by correcting microbiota composition, modulating the innate immune system, enhancing gut barrier function, preventing pathogen colonization, and exerting selective cytotoxicity against tumor cells, they are accompanied by risks and controversies that potentially introduce clinical complications [22]. Given the customized host response to gut microbiome modification, tailored microbiome therapy could be the key to successful therapeutic treatment [22]. Live or dead probiotics are used as cancer biotherapeutic medicines, as well as their metabolites, such as short-chain fatty acids, inhibitory protein compounds, polysaccharides, nucleic acids, and ferrichrome. The effectiveness of these biotherapeutics in preventing and treating various types of cancer is linked to probiotic bacterial or fungal strains, probiotic dose, and exposure time. Probiotics

can be employed as a supplementary agent to enhance or modulate existing treatment techniques, in addition to their direct anti-tumor effects. Chemotherapy and radiation frequently cause unpleasant treatment-related side effects that have a direct influence on these patients' quality of life, and probiotics are being used to address these difficulties. Probiotics reduce the incidence of treatment-related side effects in oncology patients by altering gut microbiota composition, according to a recent systematic review of randomized controlled trials. Probiotic strains may play an important role in preventing or mitigating treatment-related side effects in oncology patients [23].

## 11. BERBERINE

Berberine, a natural isoquinoline alkaloid, has attracted attention for its potent chemosensitizing and chemoprotective properties [24]. Also known as berberine hydrochloride, it is a compound found in several plants, including goldenseal, barberry, Oregon grape, and turmeric. Berberine as a nutraceutical can affect various processes involved in tumor development, including proliferation, invasion, angiogenesis, and metastasis. In addition, berberine has shown anti-inflammatory properties that make it an ideal option for preventing inflammation-associated cancers. Berberine effectively sensitizes tumors refractory to chemotherapy and radiation therapy, facilitating the various events underlying resistance to treatment [24]. It also shields the heart, liver, lungs, and kidneys from the harmful effects of these treatments [24].

## 12. LIGNANS

Lignans are a class of phytoestrogens that contain enterolactone and enterodiol. Whole grains (barley, rye, and wheat), seeds, nuts, legumes, vegetables, and fiber-rich foods (cereals, vegetables, and fruits) all contain enterolactone and enterodiol. Flaxseed and sesame seeds are the most abundant sources of enterolactone precursors.

Enterolactone (EL) is a bioactive phenolic metabolite known as mammalian lignan derived from dietary lignans. The anticancer properties of EL have been reported at both preclinical and clinical levels [25]. EL has been shown to have effective anticancer and/or preventive activities against a variety of cancers *in vivo* and *in vitro*, including breast, prostate, colorectal, lung, ovarian, endometrial, cervical, and hepatocellular carcinoma. Reported laboratory studies indicate a clear role of EL in preventing cancer progression at various stages, including cancer cell proliferation, survival, angiogenesis, inflammation, and metastasis. EL has been reported to reduce risk, decrease mortality rates, and improve overall survival in the clinical setting, particularly in breast, prostate, colon, gastric, and lung cancer. In addition, human *in vitro* cell culture studies has provided strong evidence for the anticancer and antimetastatic mechanisms of EL in several cancer types. On this basis, EL may be a promising candidate for dietary supplements and nutraceuticals.

## 13. LACTOFERRIN

Lactoferrin (LF) is an iron-binding glycoprotein produced primarily in human and bovine milk, and it is also widely distributed in mammals. A recent review has outlined its anticancer properties [26]. It has a high bioavailability, selectivity for tumor cells, and a wide variety of molecular targets that affect tumor proliferation, survival, migration, invasion, and metastasis after oral treatment. Furthermore, depending on whether it works on normal or malignant cells, it can stimulate or hinder cell proliferation and migration. Importantly, administration of LF is highly tolerated and has no significant adverse effects. Moreover, it can prevent the development or inhibit cancer growth by stimulating the adaptive immune response. Finally, LF has recently been found to be an ideal carrier for chemotherapeutics, including for the treatment of brain tumors, because of its ability to cross the blood-brain barrier, so overall, it appears to be a promising tool for cancer prevention and treatment, especially in combination therapies.

## 14. THEAFLAVINES

Theaflavin is a chemical composed of antioxidant polyphenols. This plant-based molecule, which is often present in black tea, has been clinically demonstrated to reduce the development of free radicals in the body. Theaflavins have been shown to inhibit the proliferation, survival, and migration of many cancer cells and promote apoptosis [27]. Treatment with theaflavins has been associated with increased levels of cleaved polymerase (ADP-ribose) (PARP) and cleaved caspases-3, -7, -8, and -9, all markers of apoptosis, and increased expression of the proapoptotic marker Bcl-2-associated protein X (Bax) and a concomitant reduction in the antiapoptotic marker B-cell lymphoma 2 (Bcl-2) [27]. In addition, theaflavin treatment reduced phosphorylated levels of Akt, the phosphorylated mechanical target of rapamycin (mTOR), phosphate-idylinositol 3-kinase (PI3K), and c-Myc with increased expression of the tumor suppressor p53 [27].

## 15. KAEMPFEROL

Kaempferol is a flavonol, a flavonoid-type polyphenol. Brussels sprouts, tea, grapefruit, broccoli, apples, onions, red wine, and various berries are among the foods that contain it. This substance has been discovered to have a health-protective impact on humans. It has been shown in studies to protect against heart disease and cancer. Kaempferol, a naturally occurring flavonoid found in several plants, has a wide range of therapeutic properties such as antioxidant and anti-inflammatory and plays a significant role in reducing cancer [28]. Kaempferol acts through several mechanisms: It induces apoptosis, decreases cell viability, downregulates phosphoinositide 3-kinase (PI3K)/AKT (protein kinase B) and human leukemia virus/lymphoma T-I cell signaling pathways, suppresses protein expression of markers related to epithelial-mesenchymal transition, including N-cadherin, E-cadherin, Slug, and Snail, and metastasis-related markers such as metallopeptidase 2 [28].

## 16. SPECIFIC CANCER SITES

### 16.1. Breast Cancer

Breast cancer is the most common malignancy and the leading cause of cancer death in adult women worldwide.

More than 85% of breast cancer cases are not hereditary, caused by extrinsic modifiable lifestyle factors, including dietary habits, which are crucial in cancer prevention. Several epidemiological studies have suggested the inverse correlation between vegetable and fruit intake and breast cancer incidence in general terms. Many natural products in the diet, such as soy, pomegranate, mangosteen, citrus, apple, grape, mango, cruciferous vegetables, ginger, garlic, black cumin, macro edible mushrooms, and cereals, have been shown in extensive experimental studies to influence the development and progression of breast cancer [29]. Their anti-breast cancer effects involve various mechanisms of action, such as reduction of estrogen receptor alpha (ER-α) expression and activity, inhibition of proliferation, migration, metastasis, and angiogenesis of breast cancer cells, induction of apoptosis and cell cycle arrest, and sensitization of breast cancer cells to radiotherapy and chemotherapy [29]. In specific terms, there is sufficient evidence from *in vitro*, animal, and human epidemiologic studies that specific vitamins, such as vitamin D3, folate, vitamin B6, and beta carotene, as well as dietary micronutrients like curcumin, piperine, sulforaphane, indole-3-carbinol quercetin, epigallocatechin gallate (EGCG), and omega-3 polyunsaturated fatty acids (PUFAs), show antitumor activity against breast cancer and have the potential to offer a natural strategy for breast cancer chemoprevention and reduce the risk of breast cancer recurrence [30]. Therefore, a supplement containing these micronutrients, using the safest form and dosage, should be investigated in future breast cancer chemoprevention studies.

## 17. VITAMIN D AND RISK OF BREAST CANCER

Most research on vitamin D has focused on colorectal and breast cancers. Sufficient levels of this vitamin at the time of diagnosis are associated with a better prognosis for breast cancer. Evidence associating serum 25(OH)D (either in serum or in the diet) with the development of breast cancer (BC) was recently assessed in a comprehensive review and meta-analysis, showing that 25(OH)D deficiency was directly related to breast cancer. Total vitamin D intake and supplementary vitamin D consumption, on the other hand, exhibited an inverse connection with this outcome [31]. Randomized clinical trials are warranted for further evidence from primary meta-analyses of observational studies.

## 18. FOLATE INTAKE AND RISK OF BREAST CANCER

Folic acid and folates are B vitamins. Foods naturally rich in folate are, for example, green leafy vegetables (spinach, broccoli, asparagus, lettuce), legumes (beans, peas), fruits (kiwi, strawberries, and oranges), and nuts (such as almonds and walnuts). As for foods of animal origin, liver and other offal have relatively high folate contents and some cheeses and eggs but should be consumed in limited and infrequent portions. It should also be kept in mind that food preparation, cooking, and storage processes can destroy much of the folate in food. These are water-soluble vitamins that are sensitive to heat, light, air, and acidity. When the greatest and lowest categories of folate consumption were examined, a recent dose-response meta-analysis of observational data found that folate intake was inversely associated with breast cancer risk, with folate intake having a linear association with breast cancer risk [32]. It is noteworthy that higher folate intake was correlated with lower breast cancer risk in premenopausal women, but not in postmenopausal women. However, the practical clinical significance of these associations requires further study, and additional folate supplementation should be carefully considered.

## 19. N-6 POLYUNSATURATED FATTY ACIDS AND RISK OF BREAST CANCER

`Omega 6 are polyunsaturated fats, and they are essential. In particular, their precursor (linoleic acid) cannot be synthesized by the body, and, therefore, must be taken with food. Omega 6 is proposed for several purposes, mainly to reduce cardiovascular risk, total and good cholesterol, increase good cholesterol, and prevent cancer. The inverse association between blood PUFAs n-6 levels and cancer is robust for breast cancer [17].

## 20. NUTRACEUTICALS AS ADJUVANTS TO PREVENT ENDOCRINE THERAPY-INDUCED HAIR LOSS IN BREAST CANCER PATIENTS

Endocrine therapy for breast cancer, such as tamoxifen and/or aromatase inhibitors, can cause endocrine therapy-induced hair loss. For some women, this is a serious side effect that can have a significant impact on their quality of life. Chemotherapy may be used to treat breast cancer in many women because it causes a considerable increase in free radicals and reactive oxygen species in the body. Eliminating 17-estradiol with aromatase inhibitors can exacerbate the situation because it can also act as an antioxidant. Supplements including vitamins and omega fatty acids are common intervention treatments; nevertheless, nutraceuticals such curcumin, ashwagandha, maca, annurca apple fruit, safflower, and ginseng do not encourage breast cancer cell growth. This could be due to tissue selectivity (selective estrogen receptor modulators (SERMs) having antagonistic characteristics in breast cancer cells) or a higher affinity for the estrogen receptor (ER). The best case scenario is that these compounds act as an antagonist in breast cancer cells while functioning as an agonist in hair follicles if they have SERM activity. Since the predominant ER in the human hair follicle is estrogen receptor beta (ERβ). In breast cancer cells, it is ERα, then their relative affinity for these two distinct receptors is also important. Furthermore, there is evidence showing that nutraceuticals such as curcumin, tocotrienols, kelp, ashwagandha, and resveratrol, in addition to exerting an antiproliferative effect on breast cancer cells, can also downregulate estrogen receptor alpha (ERα) while stabilizing antiproliferative ERβ, thereby altering the ERα:ERβ ratio. In addition, capsicum annuum extracted from chili peppers may also reduce human epidermis 2 (HER2) expression in breast cancer cells. As a consequence, women's usage of these nutraceuticals to enhance hair growth should not raise their risk of breast cancer. All of them have anti-inflammatory and antioxidant properties, which might be due to the fact that many of them are polyphenols. The hair follicle is susceptible to oxidative stress, and the action of the antioxidant

mechanism of these nutraceuticals may be the main driver of their stimulatory/protective influence [33, 34].

## 21. COLORECTAL CANCER

In Western nations, colorectal cancer (CRC) is one of the most frequent and fatal cancers. Its creation is a multistep process that spans more than 15 years, allowing for early identification and prevention. The high incidence and mortality rates highlight the need of prevention and screening, and preliminary data from several countries shows that screening will reduce CRC-related mortality rates. The prevention of CRC involves a healthy lifestyle and chemoprevention, which are important for individuals with a genetic predisposition and the general population. A recent review suggests that the following factors are associated with a lower incidence of CRC: magnesium, folate, high consumption of fruits and vegetables, fiber, and dairy products, whereas an increased incidence of CRC was observed with frequent consumption of alcohol or meat [35]. However, the level of evidence is moderate for β-carotene and selenium [35]. Some epidemiological studies have found an inverse correlation between high anthocyanin consumption and a low risk of colorectal cancer [36]. Anthocyanins/ anthocyanidins have a powerful electron-donating activity as a result of this structure, which can be described as an antioxidant feature. Anthocyanins may also help to prevent colon cancer by interfering with the cell cycle and causing anti-proliferation and apoptotic effects. Anthocyanin-induced autophagy is also indicated by the creation of cytoplasmic vacuoles in cells. Furthermore, a dose-response study shows that vitamin B2 intake is inversely related to the risk of CRC [37]. The inverse association may also exist between blood vitamin B2 concentration and CRC risk, suggesting the importance of vitamin B2 intake in CRC prevention [37]. A dose-response meta-analysis indicates that the level of circulating vitamin D in the blood is associated with a decreased risk of colorectal cancer in Asian countries. The strength of this association is similar to that in the Western population [38].

## 22. PROSTATE CANCER

Prostate cancer (PCa) represents one of the leading causes of cancer mortality among men in developed countries. Natural products have been widely researched for their anti-PCa properties, including tumor growth reduction, cell death induction, and metastasis and angiogenesis inhibition [39]. Furthermore, phytochemicals have been found in multiple studies to selectively target androgen receptor signaling as well as PCa stem cells. Many clinical investigations have been conducted to determine the efficacy of nutraceuticals in human patients, and the promising results obtained *in vitro* and preclinical models have been partially confirmed. In this area, more research is required.

## 23. PANCREATIC CANCER

A recent meta-analysis of observational studies found that vitamin intake can reduce the risk of pancreatic cancer, particularly vitamin D and vitamin B12 [40]. The mechanism of vitamin D would aid the penetration of drugs into the tumor, making them more effective. In addition, another review showed that the highest category of dietary zinc intake could significantly reduce the risk of pancreatic cancer, especially among American populations [41].

## 24. SPECIFIC DIETARY PATTERNS

### 24.1. Mediterranean Diet

The Mediterranean diet shows inverse associations with various types of cancer [42]. Many bioactive nutrients in the Mediterranean diet have been identified as protective factors against these types of diseases. The epigenome has been identified as the primary target of gene expression modulations related to these molecular nutrients. They can modify the epigenome and be incorporated into the "epigenetic diet," resulting in a diet that can be used therapeutically for health or for preventive purposes. Epigenetic therapy is a novel field in which nutraceuticals with low toxicity could be useful in cancer-preventive techniques. Recent breakthroughs in the understanding of the mechanisms of nutrigenomics, nutrigenetics, and nutraceuticals have led to the discovery of superfoods that can influence gene expression in a positive way. Nutraceuticals found in the Mediterranean diet can serve as epigenetic regulators and protective agents in tumor onset processes. Olive oil plays an essential role in the protective effect of the traditional Mediterranean Diet, and several epidemiological studies suggest that olive oil consumption prevents some cancers. Historically, the beneficial health effects of extra virgin olive oil (EVOO) intake were initially attributed to the high concentration of monounsaturated fatty acids. In contrast, many studies now show that phenolic compounds in olive oil have beneficial impacts on a variety of health-related indicators [43]. The phenolic compounds in EVOO are represented by phenolic alcohols, hydroxytyrosol and tyrosol, and secoiridoids, including oleocanthal, oleacein, oleuropein, and ligstroside [44]. Secoiridoids have antioxidant, anti-inflammatory, and antiproliferative properties and, therefore, exhibit anticancer activity [44]. Furthermore, data suggests that MD can increase the variety of the gut microbiota, and that a Mediterranean-style diet is linked to specific gut microbial traits [45]. Therefore, we can hypothesize that the gut microbiota of individuals following an MD can prevent the onset of chronic degenerative non-communicable diseases such as some types of cancer [45]. Controlled intervention studies on the composition and activity of the gut microbiota are needed to understand these correlations with dietary patterns.

## 25. FUNCTIONAL FOODS

Generally speaking, it is known that vegetables and fruits are protective against cancer development. We discuss specific functional foods in more depth here.

## 26. FERMENTED DAIRY FOODS

Fermented milk products or fermented dairy products, also known as cultured dairy foods, are dairy foods that have been fermented with lactic acid bacteria, such as Lactobacillus, Lactococcus, and Leuconostoc. Cultured buttermilk, sour cream, and yogurt are among the most common fermented dairy products in the Western world. Fermented dairy

products are high in nutrients and probiotics, which makes them promising for cancer prevention and treatment. In cohort studies, a recent meta-analysis looked at the link between fermented dairy consumption and cancer risk, finding statistical evidence of a considerably lower cancer risk linked with overall fermented dairy consumption [45]. Specifically, yogurt consumption was significantly correlated with reduced cancer risk in the comprehensive comparison and cohort studies. Fermented dairy consumption significantly reduced bladder, colorectal, and esophageal cancer in subgroup analysis by cancer type [46]. In stratified analyses, significantly reduced colorectal cancer risk was associated with cheese intake [46]. Yogurt consumption was significantly associated with a reduced risk of bladder cancer and colorectal cancer [46]. Notably, reports have shown that dietary probiotics such as kefir have great potential for cancer prevention and treatment [47]. Kefir is fermented milk made by incubating kefir grains with raw milk or water. Kefir grains are a mixture of yeasts and bacteria that live in a symbiotic association. Antibacterial, antifungal, anti-allergic and anti-inflammatory effects are some of the health benefits of kefir grains. In addition, it has been suggested that some of the bioactive compounds in kefir, such as polysaccharides and peptides, have great potential for inhibiting proliferation and inducing apoptosis in cancer cells. Many studies have revealed that kefir acts on several types of cancer, such as colorectal cancer, malignant T cells, breast cancer, and lung cancer [47].

## 27. RICE BRAN

Rice bran, a byproduct of rice milling, has been shown to contain a variety of phytochemicals, which are antioxidants in the diet. Several studies have indicated that rice bran consumption has an antioxidant impact, and some have even suggested that this effect may help prevent gastrointestinal cancer, owing to the antioxidative characteristics of the phytochemicals in rice bran [48]. Furthermore, these phytochemicals have been demonstrated to protect against cancer *via* oxidative stress mechanisms such as -catenin-mediated cell proliferation and inflammation [48].

## 28. CHILI PEPPER

Carotenoids, capsaicinoids, and vitamins are abundant health beneficial properties of hot pepper (genus Capsicum, family Solanaceae), an important horticultural crop traditionally used for seasoning food. Several studies have focused on the antioxidant, anti-inflammatory, and cancer-preventing effects of the carotenoids in chili peppers, and lutein and β-carotene, in particular, have demonstrated an inhibitory effect on gastric and prostate cancer risk [49]. Several studies have determined that pigments such as β-cryptoxanthin, neoxanthin, zeaxanthin capsanthin, capsorubin, and lutein can attenuate oncogene signaling, trigger cancer cell apoptosis, regulate cell cycle progression, dynamically modulate redox balance, inhibit tumor-specific angiogenesis, control tissue invasion and metastasis, modulate intercellular gap junction communications, and modulate drug resistance. The cytotoxic, genotoxic, and antiproliferative effects of carotenoids in cancer cells can be explained through several biological processes. Carotenoids may cause a pro-oxidative effect exclusively on cancer cells by generating and increasing the levels of ROS accumulation as a critical method to kill cancer cells [50] selectively. Inhibition of the phosphatidylinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway, as well as reduced activity and phosphorylation of mitogen-activated protein kinases (MAPKs) such as extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kina [49]. Inhibition of the pro-apoptotic B-cell lymphoma (Bcl-2) homologous antagonistic/killer 1 (Bak1), Bcl-2 associated death promoter (Bad), and Bcl-2 associated X protein (Bax) proteins is another approach. In addition, activation of the caspase cascade increases apoptosis [51, 52]. Carotenoids can also enhance the activity of tumor suppressor proteins: retinoid x receptor (RXR), peroxisome proliferator-activated receptor gamma (PPAR), peroxisome proliferator-activated receptor (PRAR), p21, p27, and p53, among others). They may lower the activity of cancer inducers nuclear factor kappa B (NF-kB), protein X-linked inhibitor of apoptosis (XIAP), survivin, matrix metalloproteinases (MMPs), S-phase kinase-associated protein 2 (Skp2), urokinase plasminogen activator (uPA), cell surface glycoprotein (CD44), chemokine receptor (CXCR4), and hypoxia-inducible factor-1α (HIF-1α) [50]. Finally, they can arrest the cell cycle by suppressing activation of the cyclin CDK complex, suppress metastasis through enhancing intercellular gap junction and E-cadherin communication, reduce angiogenesis by suppressing vascular endothelial growth factor activities, and reverse drug resistance through inhibition of ABC transporters [52, 53]. Although *in vitro* and *in vivo* studies on the chemoprotective action of carotenoids have shown promising progress, clinical trials have demonstrated a positive, negative, or nonpositive effect of carotenoids in the prevention or treatment of cancer [53].

## 29. DRAGON FRUIT

Dragon fruits are a valuable source of bioactive compounds, and those harvested in Israel revealed antioxidant properties and a higher total polyphenol and betacyanin content than those from Thailand [54]. The fruits examined from both origins showed significant cytotoxic activity toward colon and prostate cancer cells, with no toxic effect on normal cells.

## 30. SWEET CHERRIES

The accurate phytochemical composition and nutritional value of sweet cherries (Prunus avium L.) depend on the climatic region, cultivar, bio accessibility, and specific compounds' bioavailability [55]. However, sweet cherry extracts are highly enriched in several phenolic compounds with relevant bioactivity [55]. The results of several studies have expanded the action of sweet cherries to many cancer characteristics, particularly metabolic reprogramming. In particular, effects against oxidative stress, chronic inflammation, deregulated cell proliferation and apoptosis, invasion and metastasis, and metabolic alterations have been recognized. On this basis, sweet cherries can be considered a dietary supplement or cancer treatment.

## 31. CRANBERRY

Cranberries are rich in bioactive constituents reported to influence a variety of health benefits, ranging from improving immune function and decreasing infections to reducing cardiovascular disease. Studies have shown that cranberry and its components may exert anticancer properties. Current *in vitro* studies has indicated that cranberry and/or its components may act as chemo-preventive agents, decreasing cancer risk by inhibiting cell oxidation and inflammatory processes. Simultaneously, they may have chemotherapeutic effects by decreasing cell proliferation and angiogenesis, triggering cell apoptosis, and reducing cancer cells' capacity to penetrate and spread [56]. Limited *in vivo* studies have further documented potential antitumor activity [56]. On this basis, cranberry could be considered as a conglomerate of potential effective anticancer compounds.

## CONCLUSION

The use of nutraceuticals in cancer is being validated by a growing body of research. Innovative techniques that allow causal conclusions about biological pathways are progressively replacing the traditional broad scientific approach that linked specific phenotypic abnormalities to food habits. Researchers are looking at nutrigenetics and nutrigenomics to learn more about the interplay between the genome and diet. It is conceivable to conceive a notion of customized medicine that combines nutrition and health care by precisely analyzing the connection between individuals' genetic profiles and their food consumption. The list of nutrients with evidence in the scientific literature that may have an inhibitory impact on cancer growth is fairly long. *In vitro* and *in vivo* cancer suppression has been demonstrated with the use of these foods. More research is needed, however, to establish the parameters of patient administration. In various chemicals, there is still a knowledge gap in terms of causative p8999+roof, hence further clinical investigations are needed.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| ALA | = | Alpha-Linolenic Acid |
| DHA | = | Docosahexaenoic Acid |
| EPA | = | Eicosapentaenoic Acid |
| HBV | = | Hepatitis B Virus |
| HCC | = | Hepatocellular Carcinoma |
| HCV | = | Hepatitis C Virus |
| HIF-1 | = | Hypoxia-Inducible Factor-1 |
| NK | = | Natural Killer |
| PUFAs | = | Polyunsaturated Fatty Acids |

## CONSENT FOR PUBLICATION

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

Dr. Vincenzo Triggiani is the Associate Editor of the journal Endocrine, Metabolic & Immune Disorders-Drug Targets.

## ACKNOWLEDGEMENTS

Declared none.

## SUPPLEMENTARY MATERIALS

Supplementary material is available on the publisher's website along with the published article.

## REFERENCES

[1] Díaz, G.D.; Paraskeva, C.; Thomas, M.G.; Binderup, L.; Hague, A. Apoptosis is induced by the active metabolite of vitamin D3 and its analogue EB1089 in colorectal adenoma and carcinoma cells: Possible implications for prevention and therapy. *Cancer Res.*, **2000**, *60*(8), 2304-2312.
PMID: 10786699

[2] Scaglione-Sewell, B.A.; Bissonnette, M.; Skarosi, S.; Abraham, C.; Brasitus, T.A. A vitamin D3 analog induces a G1-phase arrest in CaCo-2 cells by inhibiting cdk2 and cdk6: Roles of cyclin E, p21Waf1, and p27Kip1. *Endocrinology*, **2000**, *141*(11), 3931-3939.
http://dx.doi.org/10.1210/endo.141.11.7782 PMID: 11089522

[3] Yuan, C.; Sato, K.; Hollis, B.W.; Zhang, S.; Niedzwiecki, D.; Ou, F.S.; Chang, I.W.; O'Neil, B.H.; Innocenti, F.; Lenz, H.J.; Blanke, C.D.; Goldberg, R.M.; Venook, A.P.; Mayer, R.J.; Fuchs, C.S.; Meyerhardt, J.A.; Ng, K. Plasma 25-hydroxyvitamin D levels and survival in patients with advanced or metastatic colorectal cancer: Findings from CALGB/SWOG 80405 (Alliance). *Clin. Cancer Res.*, **2019**, *25*(24), 7497-7505.
http://dx.doi.org/10.1158/1078-0432.CCR-19-0877
PMID: 31548349

[4] Kennel, K.A.; Drake, M.T. Vitamin D in the cancer patient. *Curr. Opin. Support. Palliat. Care*, **2013**, *7*(3), 272-277.
http://dx.doi.org/10.1097/SPC.0b013e3283640f74 PMID: 23912386

[5] Ng, K.; Nimeiri, H.S.; McCleary, N.J.; Abrams, T.A.; Yurgelun, M.B.; Cleary, J.M.; Rubinson, D.A.; Schrag, D.; Miksad, R.; Bullock, A.J.; Allen, J.; Zuckerman, D.; Chan, E.; Chan, J.A.; Wolpin, B.M.; Constantine, M.; Weckstein, D.J.; Faggen, M.A.; Thomas, C.A.; Kournioti, C.; Yuan, C.; Ganser, C.; Wilkinson, B.; Mackintosh, C.; Zheng, H.; Hollis, B.W.; Meyerhardt, J.A.; Fuchs, C.S. Effect of high-dose *vs* standard-dose vitamin D3 supplementation on progression-free survival among patients with advanced or metastatic colorectal cancer: The SUNSHINE randomized clinical trial. *JAMA*, **2019**, *321*(14), 1370-1379.
http://dx.doi.org/10.1001/jama.2019.2402 PMID: 30964527

[6] Alkan, A.; Köksoy, E.B. Vitamin D deficiency in cancer patients and predictors for screening (D-ONC study). *Curr. Probl. Cancer*, **2019**, *43*(5), 421-428.
http://dx.doi.org/10.1016/j.currproblcancer.2018.12.008 PMID: 30683325

[7] Chandler, P.D.; Chen, W.Y.; Ajala, O.N.; Hazra, A.; Cook, N.; Bubes, V.; Lee, I-M.; Giovannucci, E.L.; Willett, W.; Buring, J.E.; Manson, J.E. VITAL Research Group. Effect of Vitamin D3 supplements on development of advanced cancer. A secondary analysis of the VITAL randomized clinical trial. *JAMA Network Open*, **2020**, *3*(11), e2025850.

[8] Han, J.; Guo, X.; Yu, X.; Liu, S.; Cui, X.; Zhang, B.; Liang, H. 25-hydroxyvitamin D and total cancer incidence and mortality: A meta-analysis of prospective cohort studies. *Nutrients*, **2019**, *11*(10), E2295.
http://dx.doi.org/10.3390/nu11102295 PMID: 31561503

[9] Manson, J.E.; Cook, N.R.; Lee, I.M. VITAL Research Group. Vitamin D supplements and prevention of cancer and cardiovascular disease. *Engl J Med*, **2019**, *380*(1), 33-44.
http://dx.doi.org/10.1056/NEJMoa1809944

[10] Passarelli, M.N.; Karagas, M.R.; Mott, L.A.; Rees, J.R.; Barry, E.L.; Baron, J.A. Risk of keratinocyte carcinomas with vitamin D and calcium supplementation: A secondary analysis of a randomized clinical trial. *Am. J. Clin. Nutr.*, **2020**, *112*(6), 1532-1539. http://dx.doi.org/10.1093/ajcn/nqaa267 PMID: 33022713

[11] Pawlowska, E.; Szczepanska, J.; Blasiak, J. Pro- and antioxidant effects of vitamin C in cancer in correspondence to its dietary and pharmacological concentrations. *Oxid. Med. Cell Longev.*, **2019**, *2019*, 7286737. http://dx.doi.org/10.1155/2019/7286737

[12] Yang, C.S.; Luo, P.; Zeng, Z.; Wang, H.; Malafa, M.; Suh, N. Vitamin E and cancer prevention: Studies with different forms of tocopherols and tocotrienols. *Mol. Carcinog.*, **2020**, *59*(4), 365-389. http://dx.doi.org/10.1002/mc.23160 PMID: 32017273

[13] Zeng, Y.; Du, Q.; Zhang, Z.; Ma, J.; Han, L.; Wang, Y.; Yang, L.; Tao, N.; Qin, Z. Curcumin promotes cancer-associated fibroblasts apoptosis *via* ROS-mediated endoplasmic reticulum stress. *Arch. Biochem. Biophys.*, **2020**, *694*, 108613. http://dx.doi.org/10.1016/j.abb.2020.108613 PMID: 33010228

[14] Talib, W.H.; Alsayed, A.R.; Farhan, F.; Al Kury, L.T. Resveratrol and tumor microenvironment: Mechanistic basis and therapeutic targets. *Molecules*, **2020**, *25*(18), 4282. http://dx.doi.org/10.3390/molecules25184282 PMID: 32961987

[15] Weinberg, S.E.; Sun, L.Y.; Yang, A.L.; Liao, J.; Yang, G.Y. Overview of inositol and inositol phosphates on chemoprevention of colitis-induced carcinogenesis. *Molecules*, **2020**, *26*(1), 31. http://dx.doi.org/10.3390/molecules26010031 PMID: 33374769

[16] Puah, B.P.; Jalil, J.; Attiq, A.; Kamisah, Y. New insights into molecular mechanism behind anti-cancer activities of lycopene. *Molecules*, **2021**, *26*(13), 3888. http://dx.doi.org/10.3390/molecules26133888 PMID: 34202203

[17] Kim, Y.; Kim, J. N-6 polyunsaturated fatty acids and risk of cancer: Accumulating evidence from prospective studies. *Nutrients*, **2020**, *12*(9), 2523. http://dx.doi.org/10.3390/nu12092523 PMID: 32825393

[18] Lee, K.H.; Seong, H.J.; Kim, G.; Jeong, G.H.; Kim, J.Y.; Park, H.; Jung, E.; Kronbichler, A.; Eisenhut, M.; Stubbs, B.; Solmi, M.; Koyanagi, A.; Hong, S.H.; Dragioti, E.; de Rezende, L.F.M.; Jacob, L.; Keum, N.; van der Vliet, H.J.; Cho, E.; Veronese, N.; Grosso, G.; Ogino, S.; Song, M.; Radua, J.; Jung, S.J.; Thompson, T.; Jackson, S.E.; Smith, L.; Yang, L.; Oh, H.; Choi, E.K.; Shin, J.I.; Giovannucci, E.L.; Gamerith, G. Consumption of fish and omega-3 fatty acids and cancer risk: An umbrella review of meta-analyses of observational studies. *Adv. Nutr.*, **2020**, *11*(5), 1134-1149. http://dx.doi.org/10.1093/advances/nmaa055 PMID: 32488249

[19] Thilakarathna, W.P.D.W.; Rupasinghe, H.P.V.; Ridgway, N.D.; Thilakarathna, W.P.D.W. Mechanisms by which probiotic bacteria attenuate the risk of hepatocellular carcinoma. *Int. J. Mol. Sci.*, **2021**, *22*(5), 2606. http://dx.doi.org/10.3390/ijms22052606 PMID: 33807605

[20] Molska, M.; Reguła, J. Potential mechanisms of probiotics action in the prevention and treatment of colorectal cancer. *Nutrients*, **2019**, *11*(10), 2453. http://dx.doi.org/10.3390/nu11102453 PMID: 31615096

[21] Cruz, B.C.S.; Sarandy, M.M.; Messias, A.C.; Gonçalves, R.V.; Ferreira, C.L.L.F.; Peluzio, M.C.G. Preclinical and clinical relevance of probiotics and synbiotics in colorectal carcinogenesis: A systematic review. *Nutr. Rev.*, **2020**, *78*(8), 667-687. http://dx.doi.org/10.1093/nutrit/nuz087 PMID: 31917829

[22] Fong, W.; Li, Q.; Yu, J. Gut microbiota modulation: A novel strategy for prevention and treatment of colorectal cancer. *Oncogene*, **2020**, *39*(26), 4925-4943. http://dx.doi.org/10.1038/s41388-020-1341-1 PMID: 32514151

[23] Rodriguez-Arrastia, M.; Martinez-Ortigosa, A.; Rueda-Ruzafa, L.; Folch Ayora, A.; Ropero-Padilla, C.; Rodriguez-Arrastia, M. Probiotic supplements on oncology patients' treatment-related side effects: A systematic review of randomized controlled trials. *Int. J. Environ. Res. Public Health*, **2021**, *18*(8), 4265. http://dx.doi.org/10.3390/ijerph18084265 PMID: 33920572

[24] Devarajan, N.; Jayaraman, S.; Mahendra, J.; Venkatratnam, P.; Rajagopal, P.; Palaniappan, H.; Ganesan, S.K.; Devarajan, N. Berberine-A potent chemosensitizer and chemoprotector to conventional cancer therapies. *Phytother. Res.*, **2021**, *35*(6), 3059-3077. http://dx.doi.org/10.1002/ptr.7032 PMID: 33559280

[25] Mali, A.V.; Padhye, S.B.; Anant, S.; Hegde, M.V.; Kadam, S.S. Anticancer and antimetastatic potential of enterolactone: Clinical, preclinical and mechanistic perspectives. *Eur. J. Pharmacol.*, **2019**, *852*, 107-124. http://dx.doi.org/10.1016/j.ejphar.2019.02.022 PMID: 30771348

[26] Cutone, A.; Rosa, L.; Ianiro, G.; Lepanto, M.S.; Bonaccorsi di Patti, M.C.; Valenti, P.; Musci, G. Lactoferrin's anti-cancer properties: Safety, selectivity, and wide range of action. *Biomolecules*, **2020**, *10*(3), 456. http://dx.doi.org/10.3390/biom10030456

[27] O'Neill, E.J.; Termini, D.; Albano, A.; Tsiani, E. Anti-cancer properties of theaflavins. *Molecules*, **2021**, *26*(4), 987. http://dx.doi.org/10.3390/molecules26040987 PMID: 33668434

[28] Imran, M.; Rauf, A.; Shah, Z.A.; Saeed, F.; Imran, A.; Arshad, M.U.; Ahmad, B.; Bawazeer, S.; Atif, M.; Peters, D.G.; Mubarak, M.S. Chemo-preventive and therapeutic effect of the dietary flavonoid kaempferol: A comprehensive review. *Phytother. Res.*, **2019**, *33*(2), 263-275. http://dx.doi.org/10.1002/ptr.6227 PMID: 30402931

[29] Li, Y.; Li, S.; Meng, X.; Gan, R.Y.; Zhang, J.J.; Li, H.B. Dietary natural products for prevention and treatment of breast cancer. *Nutrients*, **2017**, *9*(7), 728. http://dx.doi.org/10.3390/nu9070728 PMID: 28698459

[30] Mokbel, K.; Mokbel, K. Chemoprevention of breast cancer with vitamins and micronutrients: A concise review. *In Vivo*, **2019**, *33*(4), 983-997. http://dx.doi.org/10.21873/invivo.11568 PMID: 31280187

[31] Hossain, S.; Beydoun, M.A.; Beydoun, H.A.; Chen, X.; Zonderman, A.B.; Wood, R.J. Vitamin D and breast cancer: A systematic review and meta-analysis of observational studies. *Clin. Nutr. ESPEN*, **2019**, *30*, 170-184. http://dx.doi.org/10.1016/j.clnesp.2018.12.085 PMID: 30904218

[32] Ren, X.; Xu, P.; Zhang, D.; Liu, K.; Song, D.; Zheng, Y.; Yang, S.; Li, N.; Hao, Q.; Wu, Y.; Zhai, Z.; Kang, H.; Dai, Z. Association of folate intake and plasma folate level with the risk of breast cancer: A dose-response meta-analysis of observational studies. *Aging (Albany NY)*, **2020**, *12*(21), 21355-21375. http://dx.doi.org/10.18632/aging.103881 PMID: 33146633

[33] Dell'Acqua, G; Richards, A; Thornton, MJ The potential role of nutraceuticals as an adjuvant in breast cancer patients to prevent hair loss induced by endocrine therapy. *Nutrients*, **2020**, *12*(11), 3537. http://dx.doi.org/10.3390/nu12113537

[34] Xie, M.; Liu, J.; Tsao, R.; Wang, Z.; Sun, B.; Wang, J. Whole grain consumption for the prevention and treatment of breast cancer. *Nutrients*, **2019**, *11*(8), 1769. http://dx.doi.org/10.3390/nu11081769 PMID: 31374888

[35] Chapelle, N.; Martel, M.; Toes-Zoutendijk, E.; Barkun, A.N.; Bardou, M. Recent advances in clinical practice: Colorectal cancer chemoprevention in the average-risk population. *Gut*, **2020**, *69*(12), 2244-2255. http://dx.doi.org/10.1136/gutjnl-2020-320990 PMID: 32989022

[36] Wang, X.; Yang, D.Y.; Yang, L.Q.; Zhao, W.Z.; Cai, L.Y.; Shi, H.P. Anthocyanin consumption and risk of colorectal cancer: A meta-analysis of observational studies. *J. Am. Coll. Nutr.*, **2019**, *38*(5), 470-477. http://dx.doi.org/10.1080/07315724.2018.1531084 PMID: 30589398

[37] Ben, S.; Du, M.; Ma, G.; Qu, J.; Zhu, L.; Chu, H.; Zhang, Z.; Wu, Y.; Gu, D.; Wang, M. Vitamin $B_2$ intake reduces the risk for colorectal cancer: A dose-response analysis. *Eur. J. Nutr.*, **2019**, *58*(4), 1591-1602. http://dx.doi.org/10.1007/s00394-018-1702-5 PMID: 29744609

[38] Zhang, L.; Zou, H.; Zhao, Y.; Hu, C.; Atanda, A.; Qin, X.; Jia, P.; Jiang, Y.; Qi, Z. Association between blood circulating vitamin D and colorectal cancer risk in Asian countries: A systematic review and dose-response meta-analysis. *BMJ Open*, **2019**, *9*(12), e030513. http://dx.doi.org/10.1136/bmjopen-2019-030513 PMID: 31874870

[39] Fontana, F.; Raimondi, M.; Marzagalli, M.; Di Domizio, A.; Limonta, P. Natural compounds in prostate cancer prevention and treatment: Mechanisms of action and molecular targets. *Cells*, **2020**, *9*(2), 460. http://dx.doi.org/10.3390/cells9020460 PMID: 32085497

[40] Liu, Y.; Wang, X.; Sun, X.; Lu, S.; Liu, S. Vitamin intake and pancreatic cancer risk reduction: A meta-analysis of observational studies. *Medicine (Baltimore)*, **2018**, *97*(13), e0114. http://dx.doi.org/10.1097/MD.0000000000010114 PMID: 29595633

[41] Li, L; Gai, X The association between dietary zinc intake and risk of pancreatic cancer: A meta-analysis. *Biosci Rep*, **2017**, *37*(3), BSR20170155. http://dx.doi.org/10.1042/BSR20170155

[42] Divella, R.; Daniele, A.; Savino, E.; Paradiso, A. Anticancer effects of nutraceuticals in the Mediterranean diet: An epigenetic diet model. *Cancer Genom. Proteom.*, **2020**, *17*(4), 335-350. http://dx.doi.org/10.21873/cgp.20193 PMID: 32576579

[43] Reboredo-Rodríguez, P.; Varela-López, A.; Forbes-Hernández, T.Y.; Gasparrini, M.; Afrin, S.; Cianciosi, D.; Zhang, J.; Manna, P.P.; Bompadre, S.; Quiles, J.L.; Battino, M.; Giampieri, F. Phenolic compounds isolated from olive oil as nutraceutical tools for the prevention and management of cancer and cardiovascular diseases. *Int. J. Mol. Sci.*, **2018**, *19*(8), 2305. http://dx.doi.org/10.3390/ijms19082305 PMID: 30082650

[44] Emma, M.R.; Augello, G.; Di Stefano, V.; Azzolina, A.; Giannitrapani, L.; Montalto, G.; Cervello, M.; Cusimano, A. Potential uses of olive oil secoiridoids for the prevention and treatment of cancer: A narrative review of preclinical studies. *Int. J. Mol. Sci.*, **2021**, *22*(3), 1234. http://dx.doi.org/10.3390/ijms22031234 PMID: 33513799

[45] Merra, G.; Noce, A.; Marrone, G.; Cintoni, M.; Tarsitano, M.G.; Capacci, A.; De Lorenzo, A. De Lorenzo. A. Influence of Mediterranean diet on human gut microbiota. *Nutrients*, **2020**, *13*(1), 7. http://dx.doi.org/10.3390/nu13010007 PMID: 33375042

[46] Zhang, K.; Dai, H.; Liang, W.; Zhang, L.; Deng, Z. Fermented dairy foods intake and risk of cancer. *Int. J. Cancer*, **2019**, *144*(9), 2099-2108. http://dx.doi.org/10.1002/ijc.31959 PMID: 30374967

[47] Sharifi, M.; Moridnia, A.; Mortazavi, D.; Salehi, M.; Bagheri, M.; Sheikhi, A. Kefir: A powerful probiotics with anticancer properties. *Med. Oncol.*, **2017**, *34*(11), 183. http://dx.doi.org/10.1007/s12032-017-1044-9 PMID: 28956261

[48] Law, B.M.H.; Waye, M.M.Y.; So, W.K.W.; Chair, S.Y. Hypotheses on the potential of rice bran intake to prevent gastrointestinal cancer through the modulation of oxidative stress. *Int. J. Mol. Sci.*, **2017**, *18*(7), 1352. http://dx.doi.org/10.3390/ijms18071352 PMID: 28672811

[49] Villa-Rivera, M.G.; Ochoa-Alejo, N. Chili pepper carotenoids: Nutraceutical properties and mechanisms of action. *Molecules*, **2020**, *25*(23), 5573. http://dx.doi.org/10.3390/molecules25235573 PMID: 33260997

[50] Shin, J.; Song, M.H.; Oh, J.W.; Keum, Y.S.; Saini, R.K. Pro-oxidant actions of carotenoids in triggering apoptosis of cancer cells: A review of emerging evidence. *Antioxidants*, **2020**, *9*(6), 532. http://dx.doi.org/10.3390/antiox9060532 PMID: 32560478

[51] Rowles, J.L., III; Erdman, J.W., Jr Carotenoids and their role in cancer prevention. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids*, **2020**, *1865*(11), 158613. http://dx.doi.org/10.1016/j.bbalip.2020.158613 PMID: 31935448

[52] Saini, R.K.; Keum, Y.S.; Daglia, M.; Rengasamy, K.R. Dietary carotenoids in cancer chemoprevention and chemotherapy: A review of emerging evidence. *Pharmacol. Res.*, **2020**, *157*, 104830. http://dx.doi.org/10.1016/j.phrs.2020.104830 PMID: 32344050

[53] Koklesova, L.; Liskova, A.; Samec, M.; Buhrmann, C.; Samuel, S.M.; Varghese, E.; Ashrafizadeh, M.; Najafi, M.; Shakibaei, M.; Büsselberg, D.; Giordano, F.A.; Golubnitschaja, O.; Kubatka, P. Carotenoids in cancer apoptosis-The road from bench to bedside and back. *Cancers (Basel)*, **2020**, *12*(9), 2425. http://dx.doi.org/10.3390/cancers12092425 PMID: 32859058

[54] Paśko, P.; Galanty, A.; Zagrodzki, P.; Luksirikul, P.; Barasch, D.; Nemirovski, A.; Gorinstein, S. Dragon fruits as a reservoir of natural polyphenolics with chemopreventive properties. *Molecules*, **2021**, *26*(8), 2158. http://dx.doi.org/10.3390/molecules26082158 PMID: 33918584

[55] Fonseca, L.R.S.; Silva, G.R.; Luís, Â.; Cardoso, H.J.; Correia, S.; Vaz, C.V.; Duarte, A.P.; Socorro, S. Sweet cherries as anti-cancer agents: From bioactive compounds to function. *Molecules*, **2021**, *26*(10), 2941. http://dx.doi.org/10.3390/molecules26102941 PMID: 34063349

[56] Mantzorou, M.; Zarros, A.; Vasios, G.; Theocharis, S.; Pavlidou, E.; Giaginis, C. Cranberry: A promising natural source of potential nutraceuticals with anticancer activity. *Anticancer. Agents Med. Chem.*, **2019**, *19*(14), 1672-1686. http://dx.doi.org/10.2174/1871520619666190704163301 PMID: 31272361