Micronutrient Food Supplements and Cancers

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Colorectal carcinogenesis is the second most common cause of mortality across all types of malignancies, followed by hepatic and stomach cancers. Chemotherapy and radiotherapy are key approaches to treating cancer patients, but these carry major concerns, such as a high risk of side effects, poor accessibility, and the non-selective nature of chemotherapeutics. A number of natural products have been identified as countering various forms of cancer with fewer side effects. The potential impact of vitamins and minerals on long-term health, cognition, healthy development, bone formation, and aging has been supported by experimental and epidemiological studies. Successful treatment may thus be highly influenced by the nutritional status of patients. An insufficient diet could lead to detrimental effects on immune status and tolerance to treatment, affecting the ability of chemotherapy to destroy cancerous cells.

1. Introduction

The World Health Organization (WHO) most recently reported cancer as a leading cause of death, with 10 million worldwide deaths in 2020. Of the various types of cancer, colon and rectum cancer was the second most common cause of death in 2020 with 935,000 deaths per year, followed by hepatic cancer (830,000 deaths) as third, and stomach cancer (769,000 deaths) as the fourth most common cause of mortality [1]. In addition to its negative health impact and increased mortality rate, the annual economic cost of cancer is also increasing significantly, estimated by the International Agency for Research on Cancer in 2010 to be US 1.16 trillion [2]. Adenocarcinoma is the most common type of gastric cancer, and the important factors associated with the incidence and prevalence of gastric cancers include an unhealthy diet, alcohol consumption, smoking, *Helicobacter pylori* infections, and pernicious anemia [3][4]. Risk factors associated with colorectal cancers include obesity, smoking, sedentary lifestyle, low fiber diets, red and processed meat, and inflammatory bowel disease (Crohn's disease and ulcerative colitis) [5][6][7]. Hepatic cancers, also known as hepatocellular carcinoma (HCC) or hepatoma, typically result from hepatitis B or C infections, cirrhosis, and chronic alcoholism [8][9]. Metabolic dysregulations such as nonalcoholic steatohepatitis and type 2 diabetes, probably aided by obesity, may also provide a road map for the pathogenesis of HCC [10][11].

Chemotherapy and radiotherapy, alone or in combination, have, for many years, been considered to be the key approaches for the treatment of patients with various types of cancer. However, conventional chemotherapies carry some major concerns that may outweigh their therapeutic benefits in certain cases, such as an increased incidence of side effects, poor accessibility to tumor tissues, and the non-selective nature of chemotherapeutic drugs [12][13]. Moreover, conventional chemotherapy is capable only of the fractional killing of cells, i.e., a number of cancerous cells die with each treatment, and thus repeated doses may be administered to effectively reduce the tumor size [14]. Fast-dividing cells, such as cells of the hematopoietic and gastrointestinal (GI) systems, are the most affected by chemotherapeutic drugs and are thus most prone to side effects. GI distress (nausea, vomiting, diarrhea, anorexia, constipation, and abdominal cramps) [15][16], alopecia [17], immunosuppression [18], myelosuppression [19], anemia [20], neutropenic enterocolitis [21], infertility [22], teratogenicity [22], secondary neoplasm [23], peripheral neuropathy [24][25], cognitive impairment [26], tumor lysis syndrome [24], and organ damage (cardiotoxicity, hepatotoxicity, nephrotoxicity, and ototoxicity) [25] are the adverse effects reported with antineoplastic agents.

Drug resistance is the main cause of treatment failure in cancer patients, the key mechanism of which is the potential efflux of cancerous cells, as these usually produce high amounts of efflux pumps such as p-glycoprotein [27]. Another mechanism responsible for drug resistance is gene amplification, which may lead to defective apoptotic pathways or the restoration of proliferative ability of cancerous cells. Mutations in genes that produce target proteins(tubulin) may result in the prevention of drugs from binding to target proteins [28]. The pharmacokinetic variability of cancer fighting drugs between patients is another concern that is difficult to deal with, and which may put clinicians in the challenging situation of choosing the right dose for the right patient to achieve an optimal therapeutic response [29]. In a randomized clinical

trial, 68% of patients with metastatic colorectal cancer were found to be underdosed and 17% were overdosed when treated with 5-fluorouracil [30].

The potential impact of vitamins and minerals on long term health, cognition, healthy development, bone mineralization, and aging has been supported by experimental, animal, and epidemiological studies. Billions of people are suffering from malnutrition and micronutrient deficiencies in low-income countries, though inadequate micronutrient status might also now be an issue in industrialized states [31]. Micronutrients have several health benefits, including bone formation, tissue maintenance, countering oxidative stress, serving as cofactors and coenzymes to certain enzymes, and the regulation and coordination of most bodily functions [32]. The success of treatment in the cancer recovery process may be highly influenced by the nutritional status of patients. An insufficient diet could possess detrimental effects on immune status, tolerance to treatment, and ability of chemotherapy to destroy cancerous cells. More importantly, mortality rates are almost 30% higher in malnourished cancer patients [33]. According to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, cancer patients who consume less than 60% of their daily energy requirements for 7–10 days cannot possibly have an adequate supply of micronutrients [33].

2. Micronutrients and Cancer: What We Need to Know?

In recent decades, most cancer patients have been taking vitamins and minerals such as vitamin D and selenium, with the aim of improving the effectiveness of the standard therapy and/or to decrease the undesirable side effects of the treatment together with the underlying disease [34]. Data collected from 2003 to 2010 within an Intergroup Phase III Breast Cancer Chemotherapy trial (S0221) revealed that 48% of patients were taking multivitamins, 34% were taking only calcium, 20% were receiving vitamins C and D, and omega-3 fatty acids, and 15% were supplementing with Vitamins B6, B9 and E [35]. However, there are justifiable concerns from an oncological point of view that taking dietary supplements during the course of cancer therapy may affect the efficacy of chemotherapy [35][36][37][38]. Thus, micronutrients must be selected appropriately, and should be taken at the right time so as not to reduce the effectiveness of cytoreductive therapy. Improved patient compliance, decreased frequency of adverse events, and lowered rates of treatment discontinuation have been evidenced in recent studies where selected micronutrients (vitamin D and selenium) and L-carnitine, were added to concurrent anticancer medications. An improved response to the cancer therapies has been noted, which improves the prognosis and patient's quality of life [39][40][41].

Cancer disease and therapy can influence the patient's nutritional status, which may exert a critical impact on the course of the disease, the efficacy of therapy and the risk of disease and/or treatment induced complications including fatigue, depression, impaired immunocompetence, and delayed wound healing. That is why laboratory-validated supplementation of micronutrients to cancer patients is now an important aspect in the concept of adjuvant and complementary oncological treatment, and therefore, in addition to the energy substrates (carbohydrates, proteins, and fats), it is important to ensure the optimal supplementation of immunostabilizing micronutrients [33]. Supplies of immunomodulatory and antioxidant micronutrients (Vitamin D and selenium) and vitamins with low storage capacity (Vitamin B1, C, B9 and K) are particularly critical in such patients [42][43][44][45][46][47]. Elevated markers of oxidative stress due to inadequate supplementation of antioxidant micronutrients [48][49] and increased risk of bleeding in association with zinc deficiency in cancer patients with poor nutritional status, have been evidenced [50].

Research is now equally focused on micronutrient supplementation and anticancer therapy, as micronutrient deficiencies are negative regulators of the course of malignant disease and the antitumor efficacy of treatment. Numerous studies have highlighted the potential role of micronutrient supplementation in improving the quality of life and the prognosis of cancer patients. A cohort study recruiting 1129 patients with lung cancer conducted by Jatoi et al., demonstrated a reduction in mortality rate of 26% in patients taking micronutrient preparations, in comparison to those not receiving such supplements. The mean survival of micronutrient supplementing and non-supplementing patients was 4.3 and 2 years, respectively [51].

Supplementation of patients with ovarian cancer (who were treated with cyclophosphamide and cisplatin) with multiple antioxidants (selenium 200 μg, vitamin C 800 mg, vitamin E 144 mg, β-carotene 60 mg, vitamin B2 18 mg, and vitamin B3 180 mg) every day for three months showed a significant improvement in the immune status of the patients, with decreased frequency of chemotherapy-induced adverse events. A significantly higher level of selenium, enhanced erythrocyte peroxidase activity, and higher leukocyte (neutrophils and granulocytes) count were observed in patients taking regular antioxidant supplements. Moreover, the incidence of chemotherapy-induced side effects including nausea, vomiting, anorexia, flatulence, abdominal pain, stomatitis, alopecia, malaise, and weakness were considerably lower in antioxidant receiving patients, compared to controls. In addition, cisplatin-induced neurotoxic symptoms occurred in one patient in the antioxidant group and two patients in the control group [52].

The clinical use of antioxidant supplements during cancer therapy is, however, still controversial and not fully justified, as the tumor reductive effects of some cytostatic agents and radiotherapy partially involve the formation of free radicals [37], though the extended list of cytostatic drugs in clinical practice nowadays do not primarily act through oxidative stress, such as antimetabolites (methotrexate), nitrogen mustard derivatives (cyclophosphamide), platinum complexes (cisplatin), vinca alkaloids (vinorelbine), anthracyclines (epirubicin), and taxanes (paclitaxel) [33]. If antioxidant nutrients interfere with the efficacy of standard anticancer therapy, then patients should not be allowed to take antioxidant supplements [33]. In contrast, antioxidants such as retinoids, vitamin C, vitamin E, and selenium have other essential metabolic functions in addition to radical scavenging properties, i.e., immunomodulation, apoptosis induction, and regulatory effects on cell proliferation and differentiation. It is possible that they may halt tumor growth through enhanced cell differentiation and apoptosis [53][54].

As recommended by the American Institute for Cancer Research (AICR), cancer patients with active chemotherapy and radiotherapy should not take micronutrient supplements containing antioxidants in a daily dose greater than the corresponding tolerable upper intake level. According to the same recommendation, the vitamin and mineral supplements can generally be regarded as safe in these patients if the daily doses are in the range of the recommended daily allowance (RDA) [55][56][57]. Following AICR recommendations for cancer prevention, all attempts to fulfill the needs of essential nutrients are to be exercised through dietary sources, before considering vitamin and mineral supplementation. Cancer patients should only be advised to take micronutrient supplements in case of nutritional problems and/or significant weight loss, and only to cover the basic supply of essential micronutrients. This approach will prevent a high-dose micronutrient intake and will compensate for potential nutrient deficiencies.

▍ 3. A Possible Link of Micronutrients with GI and Hepatic Cancers

Increasing evidence has suggested the important role of dietary habits and nutrient intake in the prevention of gastric malignancies. A report published by AICR and the World Cancer Research Fund (WCRF) indicates a possible decrease in the risk of gastric cancer with high consumption of fruits and non-starchy vegetables [58]. Certain micronutrients such as vitamins C and E, zinc, and iron have proven efficacy against *H. pylori* infections, and thus can be helpful in modulating the immune response while decreasing the risk of carcinogenesis [59][60]. The scientific data support the great contribution of microbial species to the development of cancers attributable to infectious agents [61], and thus it is also possible that micronutrients may influence the composition of gut microbiota that would have direct effects on *H. pylori*-induced disease states [62].

Plasma and dietary levels have been analyzed for several micronutrients, leading to the identification of retinol, vitamin C, and selected carotenoids among dietary components that may explain the protective role of fruits and vegetables against gastric carcinogenesis [63][64][65]. An Italian case control study showed the favorable effects of vitamin E, α-carotene, and β-carotene, and subsequently the detrimental effects of sodium intake even at intermediate levels, on gastric cancer [66]. Another hospital-based study displayed an inverse relation between gastric cancer and the high consumption of antioxidant vitamins (C, E and B3), potassium and iron, as well as with a low intake of sodium [67].

A large population-based case-control study conducted by Sun and colleagues demonstrated a lower risk of colorectal cancer with a dietary and supplementary intake of vitamin D, C, B2, B9, and calcium. Conversely, iron intake was associated with a higher risk of the disease (which may be due to provoking a chronic inflammation secondary to iron overload) [68]. More importantly, after exclusion of supplement users, the anticancer potential of vitamin D and calcium (i.e., from dietary sources only) remained significant. In a recent retrospective cohort study on 315 peri- and post-menopausal women undergoing colorectal and osteoporosis screening, serum vitamin D levels correlated with the presence and histological grading of colorectal adenomas. A total of 77 colorectal lesions were identified in 66 patients. Vitamin D insufficiency (<30 ng/mL) and deficiency (<20 ng/mL) were recognized in 79.4% and 35.2% of patients, respectively [69]. On the other hand, it should not be overlooked that abdominal irradiation in patients with gastrointestinal cancer can lead to bone loss and osteoporosis, thus increasing the risk of fracture of the vertebrae exposed to rays. Therefore, in conjunction with therapeutic abdominal irradiation, the advisability of adopting a calcium and vitamin D supplementation should be considered and weighed both as a complementary anti-cancer therapy and for the prevention of osteoporosis and consequent bone fractures [70]. A large 17-cohort study involving 5706 colorectal cancer patients and 7107 control participants with a wide range of circulating 25(OH)D showed that higher circulating 25(OH)D was related to a significantly lower risk of colorectal cancer in women and to a lower (but not significantly so) risk in men, with an optimal 25(OH)D concentration for colorectal cancer risk reduction of 75–100 nmol/L [71].

Since the liver is extensively involved in the metabolism of a wide range of xenobiotics, it is thus more prone to oxidative damage. An adequate consumption of antioxidant nutrients could decrease the markers of oxidative stress, which would

protect hepatocytes from associated injuries [72]. Hepatic disorders could possess a profound impact on the nutritional state of patients, including vitamins and minerals, and micronutrient deficiencies may impair metabolic processes at the biochemical and cellular level, and thus could further worsen the clinical situation of the patients even before physical and clinical alterations are seen. Evaluation of the micronutrient status in all patients with chronic and advanced liver diseases is an essential part of a comprehensive nutrition assessment, as optimization of the metabolic state is crucial to prevent disease progression to liver cirrhosis and HCC. Thus, early intervention with micronutrient supplementation could be a fruitful approach to improve clinical outcomes and patients' quality of life [73][74]. Patients with hepatic disorders are usually predisposed to the development of hepatic cancer. Zinc and vitamin D deficiency, and elevated serum levels of copper are considered to be among the risk factors for HCC [75][76][77]. Most of the patients with HCC have underlying cirrhosis, and are inherently at increased risk for micronutrient deficiencies [78].

The role of individual micronutrients in countering GI and hepatic carcinogenesis is described below. **Table 1** presented the selected micronutrients supported by their Recommended Dietary Allowance (RDA) levels and dietary sources.

Table 1. Selected micronutrients associated with GI and hepatic cancers.

Micronutrients	Underlined Cancer Types	RDA	Dietary Sources	References
Vitamin D	Colorectal cancer, HCC	15 µg	Egg yolks, tuna, salmon, sardines, mushrooms, cow's milk, soy milk, orange juice, and fortified foods.	[32][79][80][81]
Vitamin A	Gastric cancer, Colorectal cancer, HCC	900 µg	Liver (animals and fishes) and egg yolk. Provitamin A carotenoids obtained from plant sources including deep green, yellow and orange fruits and vegetables such as carrots, spinach, broccoli, mangoes, turnips, and sweet potatoes.	[32][65][79][82][83]
Vitamin E	Upper GI cancers, Colon cancer, HCC	15 mg	Vegetable oils (cotton seed oil, wheat germ oil, corn germ oil, and peanut oil). All green plants contain some concentration of tocopherol but some green leafy vegetables and rose hips contain more than wheat germ.	[32][79][82][83][84]
Vitamin C	Intestinal metaplasia, HCC	90 mg	Fruits (especially citrus fruits) and vegetables (especially peppers andpotatoes).	[32][85][86][87]

Micronutrients	Underlined Cancer Types	RDA	Dietary Sources	References
Zinc	Esophageal tumors, Gastric cancers, Colon cancer, HCC	11 mg	Oysters, red meat, nuts, whole grains, poultry, and dairy products.	[32][88][89][90][91]
Selenium	Colon cancer, HCC	0.055 mg	Brazil nuts, seafoods, meats, grains, dairy products, eggs, and organ meats.	[32][92][93]

4. Molecular Mechanisms of Micronutrients

Micronutrient intake is linked to a reduced risk of disorders such as cardiovascular disease, cancer, neuronal dysfunction, and cataracts [94]. An individual who consumes high amounts of vitamin C, barriers, citrus fruits, and tomatoes has a decreased incidence of proliferation and mutation [95]. Micronutrients exert anti-cancer action by the following underlying molecular mechanisms.

4.1. Antioxidant Effects

Vegetables and fruits are reported as promising antioxidant agents due to their micronutrients [96][97][98][99]. Epidemiological investigations find it challenging to delineate the effects of dietary antioxidants from the impact of many essential vitamins and dietary ingredients, although scientific proof of the nutritional benefits of ascorbic acid and vitamin D as antioxidants is emerging. Hydroxyl radicals, hydrogen peroxides, and superoxides are oxidative metabolites produced by metabolic pathways and radiation. Inappropriate intake of dietary antioxidants such as vitamin E and vitamin C can exacerbate radiation exposure [100][101][102]. Oxidative stress damages DNA and genetic material, which contributes to the development of aging and degenerative disorders including cancer [103]. With the progression of aging, oxidative lesions pile up in proteins and DNA [104]. DNA is oxidized by metabolites such as aldehyde and malondialdehyde generated from the metabolism of lipids. These metabolites assemble in proteins and DNA with developing age. The release of oxidants by phagocytic cells, as well as the resulting inflammation, is a potential provenance of NO that ultimately leads to cardiac disorders and carcinomas [105]. These free radicals contribute to the genetic mutation of DNA which leads to neoplasm and necrotic damage to cells [106].

The antioxidant micronutrients reported in vegetables have curative effects against GI and lung cancers [97][107]. The administration of micronutrients including beta-carotene, vitamin E, and vitamin C in patients suffering from oxidative damage to DNA has led to significant recovery. In China, a clinical study on cancer progression has reported that the supplementation of beta-carotene, selenium, and vitamin E markedly improved the condition of cancer patients [108][109]. Since gamma-tocopherol is a strong nucleophile, it binds electrophilic mutagens that reach the cell membrane. Glutathione is a strong nucleophile and antioxidant present in the soluble portion of the cell. Alpha-tocopherol and gamma-tocopherol act as a nucleophile and an antioxidant in the cell membrane, respectively. Alpha-tocopherol neutralizes electrophile mutagens such as NO. Alpha-tocopherol combines with NO and forms nitro–alpha-tocopherol complexes which recover the oxidative damage to proteins and DNA in cancer patients [110][111].

Vitamin D supports the antioxidant response via activating cellular signals which are responsible for the reduction of thioredoxin. Vitamin D also induces the expression of superoxide dismutase as well as downregulating levels of glutathione via elevating the levels of glucose-6-phosphate dehydrogenase [112]. Vitamin C, a potent antioxidant, is reported to be a potential replenisher of other antioxidants such as vitamin E throughout the body [113]. Ascorbic acid decreases free radicals, unstable nitrogen, oxygen, sulfur, and hydrogen atoms. Studies have shown that vitamin C preserves plasma lipids from peroxidative devastation caused by aqueous peroxyl radicals in human plasma [114]. In both in vivo and in vitro studies, higher doses of vitamin C have shown anticancer activity on tumor cells, thus presenting vitamin C as a pro-oxidative drug that inhibits hydrogen peroxide development in tissues, rather than merely serving as a radical scavenger [115][116]. Ascorbic acid is being studied to see whether, via reducing the harmful effects of free radicals through its antioxidant activity, it might hopefully avoid or postpone the onset of some chronic disorders such as cancer,

wherein oxidative damage is a major factor. Vitamin E and vitamin C, the most important lipid-soluble antioxidants, may be effective. Vitamin C inhibits the synthesis of nitrosamines (carcinogens) via the reduction of nitrates [117][118]. **Figure 1** highlights the potential antioxidant mechanisms of micronutrients.
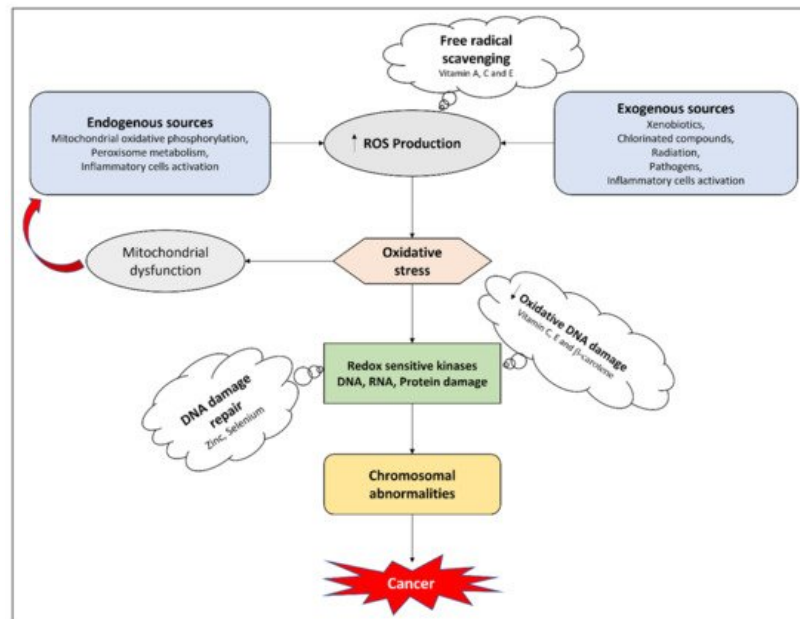

Figure 1. Potential mechanisms of micronutrients in countering oxidative stress. Increase (↑); decrease (↓).

4.2. Apoptosis Targeting

Different selenium species such as selenocysteine (SC), selenite (SeO_3^{-2}), and selenium dioxide (SeO_2) trigger apoptosis in cancer cells by causing morphological and phenotypic modifications that are characteristic of apoptosis. The apoptotic molecular mechanism induced by selenium remains unclear. However, the apoptotic pathway induced by selenium is modulated by the synthesis of reactive oxygen species (ROS) [119][120]. ROS regulate the p53 activation pathway [121] [122].Selenocysteine is involved in the initiation of the p53 pathway via protein phosphorylation of serine 15, 20, and 392 regions of p53. Moreover, upregulation of ROS is essential as the glutathione treatment decreases the phosphorylating process of p53 and thus prevents the apoptosis activated by SC. The mitochondrial dysfunction is activated by SC through segmentation of mitochondria, leading to loss of membrane potential which in turn results in the activation of the p53 pathway [123]. The activation of p53 upregulates the expression of Bcl-2−associated death promoter protein (BADP), tumor suppressor protein phosphatase and tensin homolog (PTEN), and Bcl-2−associated x gene (BAX) [124][125].

Researchers have reported that selenium causes the downregulation of B-cell lymphoma-extra-large and B-cell lymphoma-2 cells (anti-apoptotic proteins). The supplementation of selenium markedly elevated the mRNA levels of PTEN and p53 [119]. The elevated levels of BAX, BADP and the discharge of apoptotic mitochondrial proteins such as cytochrome C cause the aggregation of apoptosome, which leads to the activation of caspase-9 [124]. Caspase-9 provides the initiation step in the activation of caspase-3, 6 and 7 (downstream executioners). The downstreaming of the caspase cascade causes the cleavage of PRAP [126][127]. Researchers have established that selenium stimulates caspase-3,7 and 9 and in turn cleaves the PARP. The mRNA levels of caspase-3 and 9 are also found to be elevated with the supplementation of SeO_3 [123].

Vitamin D is reported to have an apoptosis targeting effect via the regulation of anti-apoptotic mediators, suppressing BCL, BCL-XL and overexpressing BADP, BAX [128]. Calciferol has been reported in an in vitro assay to activate the p53 signaling pathway. Researchers have also established that vitamin D is involved in the elevation of BCl-2 genes (a pro-apoptotic protein). Apoptosis was induced by vitamin D administration in rat glioma cells via the upregulation of p53 and fragmentation of DNA [129].

Selenium and derived compounds are presented as a model for apoptosis targeting in cancer in **Figure 2**.
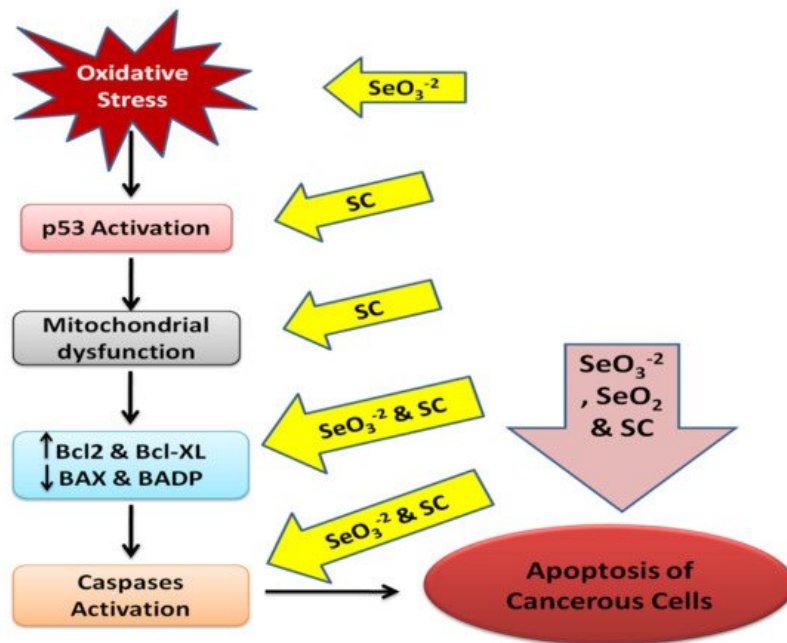
Figure 2. Selenium and derived compounds as a model for apoptosis targeting in cancer. Selenocysteine (SC), selenite (SeO_3^{-2}), and selenium dioxide (SeO_2) act on different pathways of the apoptosis of cancerous cells via activating p53, caspase-9, Bcl 2, and inhibiting Bcl-2−associated x gene (BAX). Increase (↑); decrease (↓).

4.3. Anti-Proliferative Mechanisms

Oncogenesis progresses through the three main steps of initiation, promotion, and proliferation. In the initiation step, cells at the tumor site develop somatic mutations that are transferred via ensuing mitosis cycles, resulting in progeny with gene expression defects that affect cell proliferation [130]. Promotion and proliferation occur due to the deregulation of cells, genetic abnormalities, and mutagenic promotion by further carcinogen exposure. Metastasis of cancerous cells leads to malignancy [131].

The pro-differentiating and anti-proliferating effects of micronutrients such as vitamin D have a prominent role in the prevention of malignancies [132][133]. Cell cycle modulation is regulated by an intricate system of connected regulators that instigate cellular proliferation. This regulation is controlled by cyclin proteins and their associated enzymes (cyclin-dependent kinases and cyclin-dependent kinase inhibitors). Malignancy takes place if the proliferation of neoplastic cells exceeds cell apoptosis (the molecular and biochemical signaling pathway for controlled cell death). The fact that several cancer drugs cause tumor regression by activating apoptosis highlights the importance of apoptosis in cancer-based scientific research [134]. The anti-proliferative function of vitamin D in malignant cells is based on cell-cycle disruption. Vitamin D inhibits cell growth by repressing a variety of important molecules concerned with cell cycle regulation. Treatment of MCF-7 cell lines in human breast cancer with vitamin D was found to suppress c-Myc, a recognized proto-oncogene involved in cell cycle regulation [135][136]. Vitamin D may thus enhance the activity of oncogene antagonists by suppressing the expression of certain oncogenes [137][138]. The G1 phase of the cell cycle was interrupted in ovarian carcinoma cells when supplemented with vitamin D via downregulating the cyclin-dependent kinase 2/cyclin E [139]. Vitamin D supplementation arrested the G0 and G1 phases of the cell cycle via inhibiting cyclin-dependent kinase 2 activity [140].

4.4. Anti-Angiogenic Effects

Angiogenesis is the synthesis of blood vessels in cancerous and normal cells. Endothelial cell proliferation and blood vessel development are hallmarks of pathological angiogenesis. Angiogenesis plays a key role in the metastasis and invasion of the neoplasm. Furthermore, circulating endothelial progenitor cells play a function in the formation of the blood vessels, and bone marrow-derived endothelial cell proliferation is connected to a number of tumors [141]. Since the expanding tumor mass requires an increased oxygen supply, neo-angiogenesis is a requirement for cancer progression in the tumor microenvironment. Hypoxia is frequently induced by tumor development, which facilitates hypoxia-inducible factor-1-dependent angiogenesis which is crucial for cancer development [142]. In many cancer cell lines, vitamin D has shown a suppressive effect on neo-angiogenesis. When vitamin D was added to an androgen-insensitive prostate cancer cell line, their proliferation was markedly reduced in hypoxic and normoxia conditions (similar to the ones in tumor cells). In breast cancer cell lines, vitamin D has shown inhibitory effects on vascular endothelial growth factor secretion. Moreover, it was reported that vitamin D inhibits angiogenesis via downregulating glucose transporter-1 and endothelin-1

which are necessary for neo-angiogenesis. HIF-1 translation and transcription are substantially downregulated in this molecular pathway [143].

Peyman and his coauthors established that excessive doses of ascorbic acid are involved in cancer prevention via suppressing the synthesis of blood vessels [144]. Mikirova et al., reported that a high dose of vitamin C modifies the metabolic activity of endothelial progenitor cells via lowering the ATPs level, thus inhibiting the proliferation of endothelial cells and the synthesis of blood vessels. Moreover, they established that a high dose of ascorbic acid prevents the synthesis of nitric oxide, which is a key agent in cancerous angiogenesis. Flavin adenine dinucleotide (FAD) and nicotinamide adenine dinucleotide phosphate are involved in the synthesis of nitric oxide. Thus, it is assumed that higher doses of vitamins alter the oxidation–reduction environment of the cancerous cells and thus nitric oxide synthesis is reduced by the production of peroxynitrite [145].

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