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Metabolism and Anticancer Mechanisms of Selocompounds: Comprehensive Review

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Abstract

Selenium (Se) is an essential micronutrient with several functions in cellular and molecular anticancer processes. There is evidence that Se depending on its chemical form and the dosage use could act as a modulator in some anticancer mechanisms. However, the metabolism of organic and inorganic forms of dietary selenium converges on the main pathways. Different selenocompounds have been reported to have crucial roles as chemopreventive agents, such as antioxidant activity, activation of apoptotic pathways, selective cytotoxicity, antiangiogenic effect, and cell cycle modulation. Nowadays, great interest has arisen to find therapies that could enhance the antitumor effects of different Se sources. Herein, different studies are reported related to the effects of combinatorial therapies, where Se is used in combination with proteins, polysaccharides, chemotherapeutic agents or as nanoparticles. Another important factor is the presence of single nucleotide polymorphisms in genes related to Se metabolism or selenoprotein synthesis which could prevent cancer. These studies and mechanisms show promising results in cancer therapies. This review aims to compile studies that have demonstrated the anticancer effects of Se at molecular levels and its potential to be used as chemopreventive and in cancer treatment.

Keywords Selenocompounds · Selenium metabolism · Anti-cancer mechanisms · Combinatorial therapies · Selenium-enriched foods

Introduction

Cancer is one of the most common causes of death worldwide. It has been estimated that every year, almost 20 million cases are reported, with approximately a 60% of mortality [1]. Among the diverse cancer treatments, the most common are the ones based on radiotherapy and chemotherapy [2, 3]. However, chemotherapeutics such as tegafur uracil (UFT), tegafur gimeracil oteracil potassium (S-1), 5-fluorouracil (5-FU), 5-FU + levofolinate calcium (l-LV), capecitabine (Cape), irinotecan hydrochloride hydrate (IRI), UFT + calcium folinate (LV), oxaliplatin (OX), and trifluridine/tipiracil hydrochloride (FTD/TPI) have shown to be highly cytotoxic, targeting both healthy and tumoral cells. These therapies lead to adverse or side effects such as nausea, diarrhea, headaches, alopecia, and liver damage [4, 5]. For that reason, the search for novel treatments with low or null cytotoxicity is of critical importance.

Se is an essential multifunctional micronutrient for humans that plays a crucial role as antioxidant through

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several enzymatic mechanisms of some: glutathione peroxidase (GPX), thioredoxin reductase (TXNRD), and iodothyronine deiodinases (DIO). Optimal concentrations of Se (~ 55 µg/day) are crucial for the regulation of the inflammation process, antioxidant response, thyroid hormones, immune system, and fertility control [6]. Se deficiency (< 20 µg/day) can lead to several pathologies such as muscle weakness and inflammation, fragile red blood cells, irregular skin coloration, heart muscle dysfunction, susceptibility to cancer, Kashin-Beck, and Keshan diseases. Supplementation with supra-nutritional levels (> 100 µg/day) of Se might decrease the risk of different sorts of cancers [7, 8]. In fact, Se received a qualified health claim in 2013 from the FDA that declares that Se reduces the risk of site-specific cancers. On the other hand, toxic concentrations (> 350 µg/day) can generate liver and kidney injury, blood clotting, heart and liver necrosis, hair and nail loss, nausea, and vomiting [9].

There is evidence that supplementation of hydrogen selenide (H2Se), methylselenol (CH_3SeH), selenodyglutation (GSSeSG), selenomethionine (SeMet), selenocysteine (Sec), Se-methylselenocysteine (SeMSC), and methylseleninic acid (MSeA) might decrease the risk of cancers [10–15]. Although several scientific investigations have studied the effects of selenocompounds as modulators, which means that these substances could stimulate or suppress the endogenous systems to help mechanisms that counteract cancer, it is not well understood how these compounds interact with other molecules and cellular components.

The chemopreventive effects of selenocompounds have been related to different molecular mechanisms, which can act simultaneously: antioxidant modulation [11, 15–18], selective cytotoxicity [19, 20], cell cycle arrest [21], activation of both intrinsic and extrinsic apoptotic pathways [22, 23], and reduced angiogenesis [12, 22, 24, 25]. Also, selenocompounds have demonstrated several anticancer outcomes in combination with chemotherapeutic agents and natural compounds. Specific pathways to an understanding of the interaction between Se with cellular and molecular factors in cancer development are proposed.

This work focuses on the study of the main metabolic pathways of the selenocompounds, their dietary sources, and anti-cancer molecular mechanisms. In addition, the effects of the combination of natural or chemotherapeutic compounds with Se on cancer are also described. Finally, current novel applications, such as the likely interplay of Se and gut microbiota and its relevance, are also discussed.

Selenocompounds and Their Sources

Selenocompound refers to any molecule that includes this mineral in its structure, commonly acting as a sulfur analog. Inorganic forms include elemental Se, H2Se, sodium selenate (Na_2SeO_4), sodium selenite (Na_2SeO_3), selenide (Se^{-2}), diselenides (Se_2^{-2}), and selenocyanate (SeCN-). Organic forms include selenoesters (Se-(C = O)-OH), ethaselen ((1,2-[bis(1,2-benzisoselenazolone-3(2H)-ketone)]-ethane (1,2-BBSKE), methyl selenium (CH_3Se^-), Se-aromatic containing molecules, and selenoamino acids like SeMSC, Sec, SeMet, selenoid glutathione (SDG), and MSeA [26, 27]. Also, Se can be found in the structure of selenoproteins like GPX1, GPX2, GPX3, GPX4, and GPX6; TXNRD1, TXNRD2, TXNRD3; DIO1, DIO2, DIO3; and selenoproteins H, I, K, M, N, O, P, R, S, T, V, and W [28, 29].

Humans can assimilate Se in both inorganic and organic molecules. However, Se assimilation is more efficient in the form of organic Se from various food sources, such as meat, seafood, kernels, and yeasts [30]. The chief natural Se food sources include Brazil nuts, chicken eggs, cow milk, red meats, and seafood [31–35] (Table 1). Other sources include Se-enriched foods, which have been purposely fortified in order to counteract dietary Se deficiency mainly due to the low bioavailability in agriculture soils [36]. Hence, the search for novel Se-enriched foods has been identified as an issue of interest [37]. This fortification relies on the Se absorption, accumulation, and biotransformation mechanisms, which depend mainly on genetics and plant species or organisms [38]. Se-biofortified *Brassica oleracea L.* var. gongylodes [39], spirulina [29], and yeast [37, 40] have been developed to meet the daily requirements of the population [29, 31, 37]. Lately, Se biofortification of crops like chickpea [41–43], rice [44], soybean [33], wheat [45], mushrooms (*Pleurotus ostreatus*) [46], and coffee [47] have been pointed out as novel ways of obtaining new sources of dietary Se. Recently, some processed foods such as yeast-leavened breads [48] have been produced to increase their Se content and antioxidant properties. The crop fertilization, the enrichment of flours at the end of the milling process, and the addition of Se to formulations have also come up as attractive and effective strategies to increase the dietary Se intake especially for Se-deficient populations such as China, New Zealand, Ukraine, Russia, Finland, and the USA [49, 50].

Se Absorption, Distribution, Metabolism, and Excretion Process

The nutritional availability of Se is highly dependent on its chemical form that affects its absorption, distribution, metabolism, and excretion (ADME) process rates (Fig. 1) [55].

Table 1 Natural and enriched Se food sources

Source of Se	Total Se concentration	Reference	Serving size	Se per serving size (μg)	Reference
Natural foods					
Brazil nut	~60 μg/g	[31]	28 g	1470–1680	[51]
Red meat (raw)	100–250 μg/g	[32]	65–85 g	6500–8500	[32]
Seafood	120–770 μg/g	[33]	35 g	4200	[52]
Cow milk	~0.008 μg/mL	[34]	240 mL	1.92	[34]
Chicken eggs	~0.02–0.04 μg/g	[35]	50 g	1.2–1.5	[35]
Enriched foods					
Yeast					
Se-enriched yeast	0.01 μg/g	[32, 37, 40]	20 g	0.2	[37]
Mushrooms					
Pleurotus ostreatus	25.9 μg/g	[46]	70 g	1800	[46]
Vegetables					
Brassica oleraceae	>0.0285 μg/g	[39]	150 g	4.2	[39]
Microalgae					
Spirulina	20 μg /mL	[29]	3 g	60	[29]
Kernels					
Chickpea	6.93 μg/g	[41–43]	120 g	830	[41]
Rice	0.337–0.533 μg/g	[44]	240 g	120	[53]
Soybean	2 μg/g	[38]	120 g	240	[38]
Wheat	0.27 μg/g	[45]	150 g	40	[45]
Coffee	1.86 μg/g	[47]	20 g	35	[47]
Enriched processed foods					
Bread	1.12 μg/g	[48]	28 g	32	[48]
Tortilla	0.651 μg/g	[54]	112.5 g	73.23	[54]

Absorption

Among the most important factors that affect the transport of Se species into the enterocytes are the presence of other Se species, the chemical structure, and the Se doses [56]. In this regard, inorganic forms, such as selenate (SeO^{2-}_4) and selenite (SeO^{2-}_3), are transported through paracellular and transcellular pathways, respectively. On the other hand, organic Se, such as Sec, SeMet, and SeMSC, are transported by transcellular pathways [57]. Leblondel et al. [58] suggested that SeMet shares a common absorption transport mechanism with its chemical analog, methionine (Met), while Sec and cysteine show different mechanisms. Nickel et al. [59] suggested the B^0 system as the dominant transport of other selenoamino acids.

Human studies indicate differences in the absorption of inorganic and organic forms of selenocompounds. Jäger et al. [60] and Jäger et al. [61] demonstrated in two different studies that after 2–3 h of oral administration of Na_2SeO_4 (50 μg Se), Na_2SeO_3 (200 μg Se), and selenized yeast (100 μg Se), the Se plasma concentration changed from 82.5 to 85.1 μg Se/L, 84.5 to 97.4 μg Se/L, and 89.5 to 92.1 μg Se/L, respectively. Even though the initial supplementation doses were different for each selenocompound, it was shown that Na_2SeO_3 was absorbed faster than Na_2SeO_4 and selenized yeast. Another study carried out by Di Dato et al. [62] with thirty healthy volunteers who were supplemented with SeMet (166 μg) for 14 days showed an accumulation of Se in serum. There was an increase of 32% of Se in serum concerning baseline values from 80 to 102 μg/L after 14 days. Thus, these results showed that prolonged SeMet intake of 166 μg/day could increase blood levels reaching normal circulating Se values [62].

Distribution

Once absorbed by the enterocytes, Se can follow three different routes: liver, lymphatic system, or plasma [63]. In plasma, Se is associated with plasma proteins and eventually is taken by the liver or by kidneys to be excreted [63]. In the liver, Se is used to synthesize selenoproteins, especially selenoprotein P (SELENOP). The main function of SELENOP is the transport of Se to the peripheral tissues. When SELENOP reaches the target tissues, it is degraded to obtain Sec and to be part of other selenocompounds [64, 65]. Regarding the lymphatic system, Se can travel into plasma or be taken up by the liver [63].

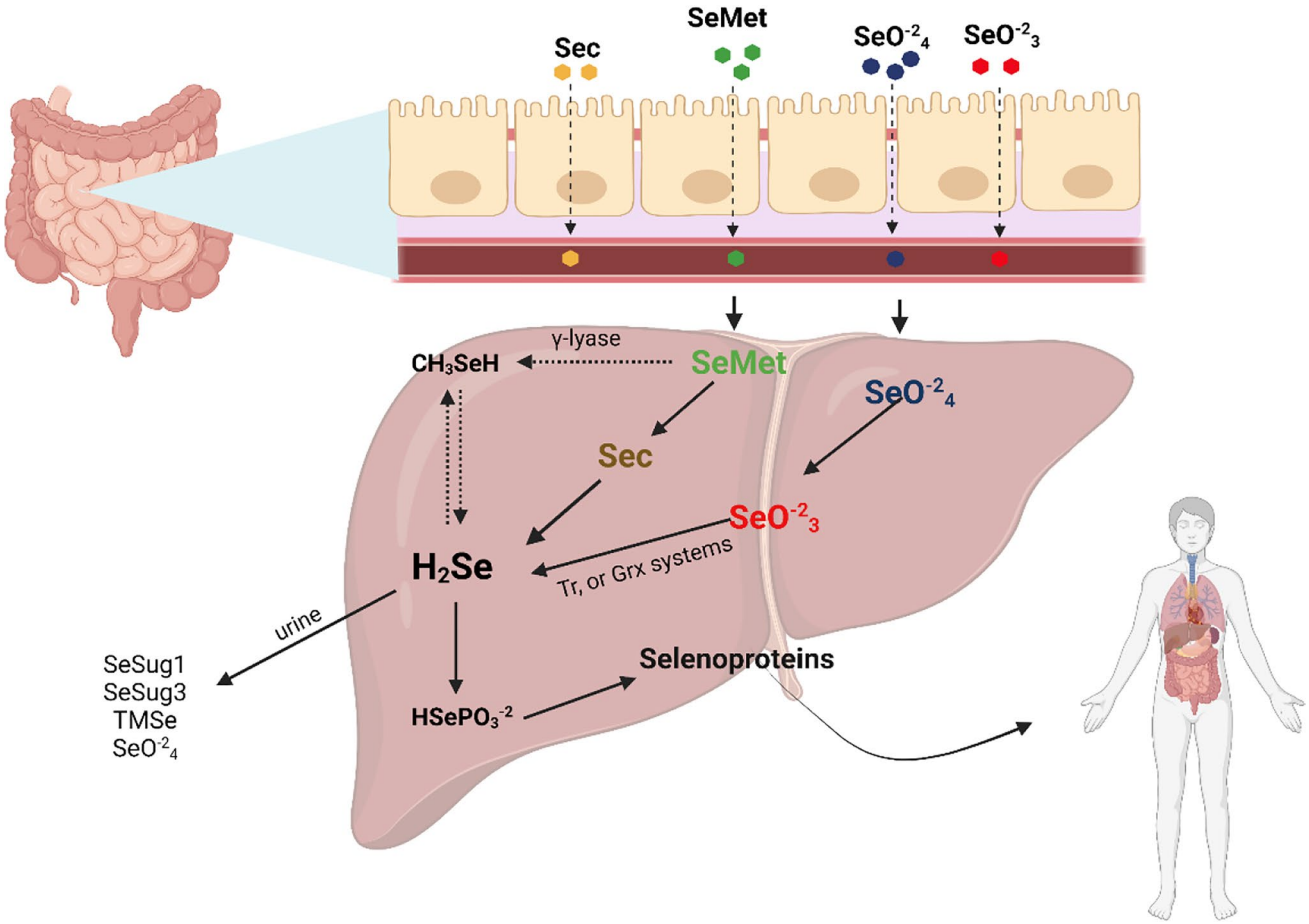

Fig. 1 ADME process of selenocompounds. Selenocompounds such as SeO2-3, SeO2-4, Sec, and SeMet are absorbed via the intestinal lumen, where they go directly to the blood vessels, which later are metabolized by the liver. Briefly, SeMet is generally converted to proteins and Sec, which can also be metabolized as selenoproteins. SeO2-4 is transformed into SeO2-3 with a later conversion to H2Se which can be excreted via breath as dimethyl selenide or via kidney as selenosugars, SeO2-4, and TMSe

Akahoshi et al. [66] reported the presence of Se in the brain, heart, liver, lung, kidney, pancreas, spleen, and testis of mice fed during 6 weeks with high amounts of SeMet (20 mg SeMet or 8.053 mg Se/kg diet). The organ with the highest content of Se was the liver (11 µg Se/g tissue) followed by the kidneys (7 µg Se/g tissue). Besides, the Se content of all organs was increased in a time-dependent manner [66].

Metabolism

Humans can retain selenoamino acids more efficiently than inorganic Se forms [67]. Thus, SeMet can be incorporated into proteins, or it can be metabolized to selenocompounds as H_2Se, an intermediary for selenoprotein production. H_2Se from SeMet can be generated by two reactions, one by a trans-sulfuration pathway to form Sec which is catabolized by Sec lyase [64, 68] or by CH_3SeH through the γ-lyase followed by demethylation reaction [69]. On the other hand, inorganic Se cannot be a part of building proteins. $SeO^{2-}{}_3$ or $SeO^{-2}{}_4$ are reduced to form H_2Se via thioredoxin (Trx) or glutaredoxin (Grx) systems [70] to generate selenoproteins or to be excreted. Once H_2Se is generated; selenoproteins can be synthesized after the activation of selenophosphate $(HSePO_3)^{-2}$ [49].

Takahashi et al. [71] reported the presence of a selenometabolite in bile after the supplementation of Na_2SeO_3, potassium selenocyanate (KSeCN), and SeMet in rats. The bile of Wistar rats was collected after 10 min of being injected with 0.2 mL of 50 mg Se/mL from Na_2SeO_3, SeCN, or SeMet. These selenocompounds were metabolized into selenodiglutathione (GSSeSG), as a common biliary selenometabolite. GSSeSG appeared after 10 min of Na_2SeO_3 and SeCN administration, while in treatments with SeMet, GSSeSG, it was detectable 20 min after administration. GSSeSG was synthesized from H_2Se which was formed through the ingestion of Na_2SeO_3, SeCN, and SeMet. GSSeSG in bile could be re-metabolized and eventually excreted (Fig. 1) [71].

Excretion

To avoid toxicity, the metabolized Se is subsequently excreted through urine, feces, and breath. The Se excretion depends on the chemical form and dosage and it could be found in urine as SeO^{-2}_4, selenosugars, or as trimethylselenonium ion (TMSe) [55, 72]. Kokarnig et al. [72] gave Se supplements to volunteers to evaluate total Se and selenocompound profiles in their urine. Five different selenocompounds (SeO^{2-}_4, SeO^{2-}_3, selenized yeast, SeMet, SeMSC) were ingested in capsules containing 200 µg of Se, except for selenized yeast containing 165 µg of Se. After SeO^{2-}_4 ingestion, the excreted Se was present as selenosugar 1 (SeSug 1) (14 ng Se mL^{-1}), selenosugar 3 (SeSug 3) (3.2 ng Se mL^{-1}), TMSe (0.13 ng Se mL^{-1}), and as intact SeO^{2-}_4 (0.67 ng Se mL^{-1}). SeSug 1, SeSug 3, and TMSe were detected after SeO^{2-}_3 ingestion at 8.5, 2.3, and 0.7 ng Se mL^{-1}, respectively. The same compounds, SeSug 1, SeSug 3, and TMSe, were found in subjects who consumed the selenized yeast at concentrations of 2.4, 0.85, and 0.10 ng Se mL^{-1}, respectively. In subjects supplemented with SeMet, SeSug 1 (5.3 ng Se mL^{-1}), SeSug 3 (2.4 ng Se mL^{-1}), SeMet (0.31 ng Se mL^{-1}), and TMSe (0.06 ng Se mL^{-1}) were detected. On the other hand, in the SeMSC group, SeSug 1 (20 ng Se mL^{-1}), SeSug 3 (1.4 ng Se mL^{-1}), SeMSC (1.1 ng Se mL^{-1}), and TMSe (0.07 ng Se mL^{-1}) were found in the urine after 24 h of ingestion. In all treatments, SeSug1 was the predominant excretion compound present in urine.

Similar results were reported by Takahashi et al. [55], who found that three selenocompounds, SeO^{-2}_4, SeSug1, and TMSe, in the urine of male Wistar rats when rats were intravenously administered with SeO^{-2}_4, SeO^{-2}_3, SeMet, SeMSC, and selenocystine at doses of 2 µg or 10 µg Se/0.2 mL/rat for each compounds. SeSug1 was the predominant compound in the urine of all treatments. SeSug1 and SeO^{-2}_4 were detected in rats fed with the SeO^{-2}_4 treatment. In addition, the dose is an important factor in the excretion rate. Results showed that the highest doses of SeO^{-2}_4 could not be metabolized and are excreted directly in the urine. Moreover, the levels of urinary SeSug1 originated from selenoamino acids were lower compared to those originating from SeO^{-2}_4 and SeO^{-2}_3 administration. These results could be related to the ability of the organism to retain selenoamino acids [55].

In other studies, the excretion levels of selenocompounds were identified and quantified in urine. The results demonstrated that 31.1%, 16.9%, and 11.8% of the initial dose administered of Na_2SeO_4, Na_2SeO_3, and selenized yeast, respectively, were excreted. Moreover, SeO^{2-}_4 was the main excreted metabolite after the administration of Na_2SeO_4 and SeSug1 of Na_2SeO_3 and selenized yeast administration [60, 61].

Cellular and Molecular Anticancer Mechanisms of Selenocompounds

Cancer evolves in three principal stages: precancerous, cancerous, and metastatic, with evidence demonstrating that selenocompunds act as modulators to counteract cancer in all phases [73]. Herein, this section will include a classification of anticancer molecular mechanisms on cancer models, as well as a relation among cellular, molecular, and genetic factors (Fig. 2).

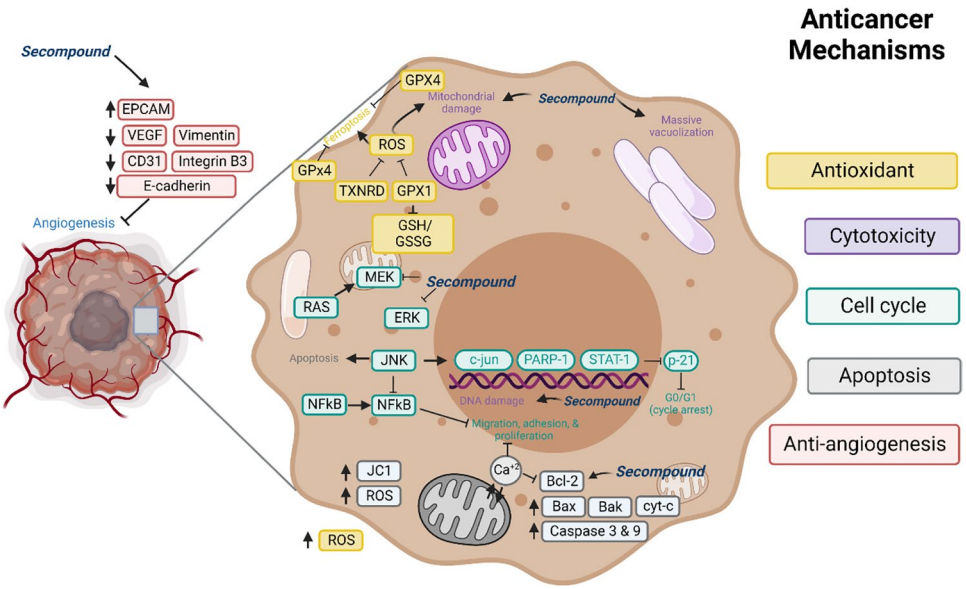

Fig. 2 Anticancer mechanisms that are carried out by the selenocompounds reviewed in this study. Antioxidant mechanism is colored in yellow, cytotoxicity in purple, arrest of cell cycle in green, apoptosis in gray, and anti-angiogenesis in red

Antioxidant Mechanisms

The oxidative stress due to high radical free content in the organism contributes to the risk of cancer in early stages. Se has one of the most significant key roles in the endogenous antioxidant defense mechanism. It is involved in the proper function of different enzymes and selenoproteins. Among the known 25 selenocysteine-containing proteins in humans, some of the most significant selenoproteins include TXNRD1, TXNRD2, and TXNRD3, GPX1, GPX2, GPX3, GPX4, and GPX6, DIO1, DIO2, and DIO3, which are needed to maintain cellular redox homeostasis [74]. These selenoproteins are an essential part of the intracellular redox system, reducing glutathione/oxidized glutathione (GSH/GSSG), and reactive oxygen/nitrogen species (ROS/RNS), avoiding cell damage.

The family of Se-dependent peroxidases includes GPX1, GPX2, GPX3, GPX4, and GPX6, in humans. GPX1 protects cells from oxidative damage by reduction of hydrogen peroxide and other organic peroxide forms. The single nucleotide polymorphisms (SNPs) in *GPX1* gene Pro198Leu (rs1050450) were shown to increase the risk of developing acute myeloid leukemia in a study conducted among the Romanian population [75]. The frequency of *GPX1* gene (Pro198Leu) was higher in patients with acute myeloid leukemia compared to healthy subjects, 83.3%, and 57.2%, respectively. Furthermore, the SNPs in *GPX1* gene were associated with a decrease in the antioxidant activity of the enzyme conferring an increased risk of cancer development. Choi et al. [76] demonstrated the effects of this polymorphism on the development of prostate cancer in two men's groups (smokers and asbestos-exposed). Also, Erdem et al. [77] showed a protective effect of Pro198Leu (rs1050450) polymorphism against prostate cancer development. Other studies conducted on esophageal cancer cell lines EC109 and EC9706 reported that high GPX1 enzymatic activity promoted the invasion and migration through enzyme matrix metalloproteinase-2 and urokinase-type plasminogen activator, which were key for tumor formation and metastasis [78].

In addition, colorectal cancer (CRC) cells were treated with cytokines and GPX2 enzymatic activity enhanced their anti-inflammatory mediators 15d-PGJ2 (15-deoxy-Δ12,14-prostaglandin J2) and IL-22 (interleukin-22), suggesting that GPX2 plays a relevant role in inflammation [79]. The overproduction of GPX3 protein has been linked to decrease tumor growth and metastasis of cervical and prostate cancers [80, 81]. In addition, GPX3 protein was able to enhance the sensitivity of ovarian adenocarcinoma cells to cisplatin [82]. Jia et al. [83] developed a full analysis of the selenoproteome linked to diverse cancers, finding a higher expression of antioxidant enzymes. The most relevant results showed that the *GPX3* gene was the most common and highly expressed in colon, esophagus, liver, lung, and stomach cancer cells. Results showed a notable increment in ROS activity during the cancerous phase and, by that, promoting an acute antioxidant response. On the other hand, *GPX4* gene expression that participates in the antioxidant protection of cell membrane lipids was overexpressed in liver cancer, resulting in an increase in tumor grade [84]. *GPX4* gene expression acts as an oncogene and inhibits ferroptosis in cancer cells; therefore, the anticancer effect of cisplatin can be enhanced by *GPX4* inhibition [85].

Some TXNRD proteins are key enzymes against cellular oxidative stress. In animal models, the inactivation of *TXNRD1* gene increased liver cancer risks in mice treated with carcinogenic diethylnitrosamine [86]. Another study with immunocompromised mice xenografted with colon cancer cells and fed diets rich in Se showed an increase in TXNRD1 and GPX1 enzymatic activity, both being related to the antioxidant protection of lipids and a significant reduction of tumor growth [23]. The role of selenoproteins in carcinogenesis has been documented in several studies, which have shown that the regulatory mechanisms are highly ambiguous, requiring further analysis on a large scale [87].

Selective Cytotoxicity

Several studies have focused on the role of selenocompounds as chemotherapeutic agents, because of their potential to exert higher cytotoxicity in cancer cells compared to healthy cells. However, Se cytotoxic activity depends on several factors, such as the chemical structure of the selenocompound [88], cell culture medium [89], extracellular microenvironment [90], cell line [88], presence of supplements such as amino acids in the medium [88], and treatment time [91].

The cytotoxicities of $SeO^{2-}{}_3$ and selenosulfate (O_3SSe^{-2}) were evaluated on human hepatoma (HepG2), malignant melanoma (A375), and urinary bladder carcinoma cells (T24) [88]. The results demonstrated that in HepG2 cells, O_3SSe^{-2} toxicity was higher than the exerted by $SeO^{2-}{}_3$, while in A375 and T24 cells, an opposite effect was found at 24 h of exposure. For HepG2 cells, the IC_{50} values were 13.8 μM for O_3SSe^{-2} and > 15 μM for $SeO^{2-}{}_3$ whereas for A375 cells were 6.6 μM for O_3SSe^{-2} and 4.7 μM for $SeO^{2-}{}_3$. On the other hand, the IC_{50} values for T24 cells were 6.9 μM for O_3SSe^{-2} and 3.5 μM for $SeO^{2-}{}_3$. These results showed that cytotoxicity effects could depend both on the chemical form of Se and the type of cells [88].

In addition, $SeO^{2-}{}_3$ cytotoxicity was studied by Řezáčová et al. [91] in human bladder cancer cells (RT-112) with concentrations ranging from 0 to 100 μM $SeO^{2-}{}_3$ at 24, 48, and 72 h of incubation. The cytotoxic effect of $SeO^{2-}{}_3$ at 24 h of exposure was detected with a concentration of 10 μM, while at 48–72 h, concentrations of 2.5 μM were the first to produce cytotoxic effects. Hence, lower doses were required to observe cytotoxic effects when the cells were incubated

for longer periods. Se cytotoxicity in this model was SeO^{2-}_3 dose-dependent. Cells treated with SeO^{2-}_3 showed morphological changes such as massive vacuolization and product of mitochondrial damage. Bladder cancer cells treated with 10 µM of SeO^{2-}_3 had an expression of the phosphorylated histone H2A.X as a marker of DNA damage. Besides, high activity of Poly[ADP-ribose]polymerase 1 (PARP-1) and c-Jun N-terminal kinase (JNK) in cells treated with SeO^{2-}_3 was found. PARP-1, associated with DNA fragmentation and JNK along with mitochondrial dysfunction, has been related to necroptosis cell death. These effects could be associated with the increase of ROS in bladder cancer cells as a product of oxidative stress produced by the changes of the intracellular redox environment of SeO^{2-}_3 [91]. The relationship between the excessive production of ROS by selenocompounds and cytotoxicity in cancer cells was also demonstrated by Wang et al. [90]. The presence of the antioxidant NAC (N-acetyl-L-cysteine) at high doses (5 mM) inhibited significantly the selenite (Na_2SeO_3)-induced ROS production and cytotoxicity in human breast cancer cells, demonstrating the key role of the redox effects among the different mechanisms that may be involved [90].

The Se binding protein (SBP1), which acts as a covalent-binding factor for Se, plays an essential role in protein degradation, intracellular transport, cell differentiation, motility, and redox modulation [92]. It was found that SBP1 regulates the extracellular form of reduced GSH, enhancing Se uptake with marked cytotoxicity effects in cancer cells [90]. Human breast cancer cells (MCF-7) with downregulated SBP1 were treated with Na_2SeO_3 (7.5 µM) for 24 h to evaluate the cytotoxicity. The results showed a decrease of Se concentration in the culture medium after the first 4 h to levels of 3 µM Se which led to cell death. This effect could be attributed to the knockdown of SBP1 that could increase reduced GSH levels of the extracellular medium, which is important to transform Na_2SeO_3 to H_2Se, an intermediate that can easily cross the cell membrane and is comparatively more toxic than Na_2SeO_3 [90].

On the other hand, Díaz [93] synthesized selenoesters to prove their cytotoxic and antiproliferative effects. Results showed that methyl selenoesters and Na_2SeO_3 directly affected histone modification, due to Se being implicated in oxygen and hypoxia conditions, and gene expression for migration and adhesion for malignant cells. Also, it downregulates the expression of human gene ITGB1, or β1-integrin (CD29), driving to low attraction to fibronectin and, by that, reducing the possibility of cancer diffusion.

Recently, nanoparticles have been studied because of their physical properties and their facility to embed molecules. Through the elaboration of nanoparticles, researchers have controlled drug release improving targeting and cellular bioavailability, reducing toxicity, and even degradation of the drug delivery vehicle [94, 95]. Seleno-nanoparticles (SeNPs) had been shown to have higher pro-oxidant properties than selenite and hyperaccumulation in cancer cells with potent therapeutic effects [96]. An interesting approach for SeNPs is their interaction with the redox system in cells. Employing an in vivo model (male Kunming mice) with xenografted hepatocarcinoma cells (H22 cells), a redox-based dynamic interaction between SeNPs and TXNRD enzymatic activity, generated ROS [96]. This simple-step reaction improved the triggering of redox cycling with oxygen to generate ROS, resulting in a strong pro-oxidant effect combined with an accumulation of SeNPs in the cancer cell lines [96].

SeNPs can also associate with other elements to enhance their activity. Reports by Li et al. [19] described that innovative Se-containing platinum-based nanoparticles (4 mM) showed selective cytotoxicity to both human hepatic L02 and HepG2 cells. The cytotoxicity was attributed to an abnormal increase in ROS levels, induced by a diminished level of reduced GSH. This also provoked a failure in mitochondrial membrane potential and relocation of cytochrome c (cyt c), eventually inducing apoptosis [19]. Similar findings were reported by Barbanete et al. [20] who developed selenite-doped hydroxyapatite nanoparticles loaded with a hydroxyapatite-binding anti-tumor platinum complex to investigate the proliferation of human prostate (PC3) or breast cancer cells (MDA MB-231) co-cultured with human bone marrow stem cells (hBMSc). Results highlight that platinum (80 µM) and Se (10 µM) released from the complex showed a selective cytotoxicity reduction of cell proliferation of cancer cells, without affecting the proliferation of hBMSc.

Cell Cycle Modulation

Selenocompounds have been reported to be involved in signaling pathways of the regulation of cell cycle arrest, cell proliferation, and migration. MSeA was shown to have better antitumor effects compared with SeMet and SeMSC in a human cervical carcinoma cell line (HeLa Cells). HeLa cells exposed to 3 µM of MSeA, SeMet, and SeMSC decreased levels of AKT by 55%, 45%, and 25%, respectively, compared with cells without treatment. Only MSeA showed decreased levels of MAP kinase-kinase (ERK) pathway with 65%. ERK and AKT signaling pathways have important functions in cell proliferation and migration [97].

For squamous esophageal cell carcinoma, evidence provided by Ahsan et al. [98] Na_2SeO_3, (1–100 µM), Se-(methyl) selenocysteine hydrochloride (10–100 µM), SeMet (10–100 µM), and MSeA (6 µM) demonstrated a protective result against DNA damage, suggesting a possible chemo-preventive effect. In addition, other effects showed a decreased inflammatory response, inhibition of cell proliferation and colony formation, and reduction of apoptotic-signal factors such as Ki-67 [98].

Recent investigations have shown that repression of selenoprotein H (SELENOH) diminishes cellular differentiation and enhances cell proliferation and migration, leading to higher tumor progression. In a nude-mouse model (C57BL/6 J and APC), knockdown cells of SELENOH also showed a faster cell cycle transition, making a favorable CRC tumor development [11]. On the other hand, high levels of SELENOH found in tumors and undifferentiated cells demonstrated an inhibitory influence on the progression of the S phase in CRC. This highlights the key role of SELENOH and the strong relationship between organic forms of Se supplementation (Se-enriched yeast + SeMet, 0.15 mg/kg daily) with the progression of CRC [11].

SELENOK is a critical component for the right activation and cell proliferation of the immune system [99]. Lower levels of SELENOK in lung adenocarcinoma were associated with poor survival, as this protein may regulate the growth and migration of lung cancer through calcium (Ca^{2+}) [99]. In this regard, high concentrations of SELENOK in three different choriocarcinoma cell lines (BeWo, JEG-3, and JAR) were shown to inhibit cell migration, adhesion, and proliferation; these effects were also related to optimal levels of Ca^{2+} influx to the interior of the cell [100].

In previous studies, SBP1 has been suggested as a potential biomarker in the prevention and treatment of breast cancer as its expression was reduced in breast cancer tissues compared to normal ones [101]. Ectopic expression of SBP1 attenuates the phosphorylation process of c-Jun and STAT1, which are linked to p21 transcription, ending in the G0/G1 cell cycle arrest [15]. Elhodaky et al. [102] reported that reduced levels of SBP1 in prostate cancer cells inhibited AMP-activated protein kinase (AMPK) and stimulated oxidative phosphorylation (OXPHOS) and tumor growth and progression at metastatic phase; the diminished levels of SBP1 were attributed to the binding of the transcriptional inhibitor hepatocyte nuclear factor-4 alpha (HNF4α).

The antitumor effects of Se-β-Lg were evaluated in an in vivo model in female mice inoculated with sarcoma cancer cells (S180) [103]. Mice administered with 150 µg/kg β-Lg, 100 µg/kg Se dioxide (SeO_2), and Se-β-Lg at concentrations of 50, 100, and 150 µg/kg, 15 days before and after tumor injection. The best results in the inhibition of growth tumor we found for was SeO_2 (53.05%), followed by Se-β-lg at 150 µg/kg (48.38%), while β-Lg showed a 21.51% tumor inhibition rate. The results indicated that Se-β-lg promotes apoptosis in S180 cells by blocking cell cycle in G0/G1 phase and inhibiting cell proliferation.

Activation of Apoptotic Pathways

The impact of selenocompunds on the activation of apoptosis is reviewed. Among the proteins involved in apoptotic responses, B-cell lymphoma 2 (Bcl-2) stands out. It promotes the survival of the cell by inhibiting pro-apoptotic responses, especially the expression of Bcl-2-like protein 4 (Bax) and Bcl-2 antagonist killer 1 (Bak), which trigger the permeabilization of mitochondrial membrane, releasing cyt c, and generating reactive oxygen species (ROS), initiating an apoptosis reaction [104].

Functional foods can be proposed as preventive and pro-apoptotic agents against cancer. For instance, Se-enriched chickpea sprouts (6.93 µg/g dw) induced the intrinsic apoptotic pathway in immunosuppressed mice by enhancing the expression of caspase-9 and by blocking Bcl-2 [23]. Besides, Bcl-2 expression was diminished considerably in Wistar male rats with CRC supplemented with Se-enriched *Saccharomyces cerevisiae* (5×10^8 CFU/mL with 10% of Na2SeO3). In addition, lower expressions of p53, a tumor suppressor factor increased with Se supplementation. Then, Se-enriched yeast could act as a preventive factor for the development of CRC [22]. SBP1 has also been linked to tumor-suppressive activity activating cyclin-dependent kinase inhibitor 1A (p21) expression throughout a tumor suppressor p53-independent mechanism in human bladder cancer [15]. Harmanci et al. [105] demonstrated that SeMet in doses of 500 and 1000 µM induced DNA fragmentation in glioblastoma multiforme cell line (GMS-10 and DBTRG-05MG) after 72 h incubation, leading to unchained apoptosis.

An important point of study for Se and its involvement in cancer development is the interaction between different apoptotic-related mechanisms; one of the major ones is the endoplasmic reticulum (ER) stress response. MSeA was evaluated by Lobb et al. [106], as a modulator for ER stress in malignant human blood cell lines, and THP1 monocytic leukemia cells (stressed with radiation, cytosine arabinoside, and doxorubicin chemotherapy). Intracellular proteins, such as binding immunoglobulin protein (GRP-78), phosphorylation of the eukaryotic initiation factor 2 (phospho-EIF2α), and X-Box binding protein 1 (XBP1), were indicators for Se-induced ER stress, which are directly related to ROS generation. Because of the ER stress response to MSeA supplementation (2.5, 5, and 15 µM), the cell acquires a more oxidized state which in turn leads to apoptosis and necrosis pathways [106]. Similar findings were published by Evans et al. [13] in a leukemia model employing SeMSC. In this study, ER stress was closely related to caspase 8 activity.

Ca^{2+} ions act primarily as second messengers in cancer physiology; specifically, an increase of these ions results in tumor progression by facilitating proliferation and metastasis of malignant cells [107]. Studies suggest that Se acts as a regulation factor in Ca^{2+} channels, more specifically in transient receptor potential, cationic channels (TRPCC). Ertilav et al. [108] reported that docetaxel (10 nM) in combination with elemental Se (1 µM) induced apoptosis in brain tumor cell line (DBTRG) by increasing mitochondrial membrane

depolarization factor (JC1) and ROS production, following a decrease in cell viability with an increment in Ca^{2+} flux by mammalian transient receptor potential melastatin (TRPM) activity.

Furthermore, Sakalli et al. [109] indicated that Na_2SeO_3 (200 nM) in combination with cisplatin (40 µM) decreased the accumulation of Ca^{2+} with activation of the transient receptor potential cation channel subfamily V member 1 (TRPV1), resulting in apoptosis for breast cancer (MCF-7) cells. The depolarization of mitochondria relies on the flux of Ca^{2+} ions, which is prevented by selenocompounds.

Recently, β-lactoglobulin (β-Lg) has been used as a possible treatment due to its anticancer activities in different cell lines. Zhao et al. [110] investigated the effect of a novel Se modification complex (Se-β-Lg) on hepatocellular carcinoma cell lines (HepG2 and Hep3B cells). Se-β-Lg was used at different concentrations (25–800 µg/mL) in HepG2 and Hep3B cells for 24–72 h, respectively. The study showed that Se-β-Lg induced apoptosis through the activation of cleaved caspase-8 and cleaved caspase-3 in HepG2 and Hep3B cells in a dose-dependent manner. In addition, the apoptosis of HepG2 and Hep3B cells could be triggered by cell cycle arrest. Additionally, Se-β-Lg in human breast cancer cells (MCF-7 and MDA-MB-231) showed apoptosis through the mitochondrial caspase-dependent apoptotic pathway and by cell cycle arrest. Furthermore, Se-β-Lg did not show toxic effects on normal human breast cells [111].

The antitumor activity of a Se polysaccharide from *Pleurotus ostreatus* (Se-POP-3) was evaluated in cancer liver (HepG2), breast cancer (MCF-7), and ovarian cancer (SKOV3) cells. Exposure of HepG2, MCF-7, and SKOV3 to 600 g/mL of Se-POP-3 for 24 h increased apoptosis levels by 39.53%, 39.46%, and 31.84%, respectively. Besides, it was measured that the metastatic effect of Se-POP-3 was dose-dependent inhibiting migration of cancer cells without any effect on the growth of normal cells [46]. In addition, it is also evaluated that the antitumor activity of another Se-enriched polysaccharide fraction (Se-POP-21) produced by *Pleurotus ostreatus* was also evaluated on different human cancer cell lines (A549, SKOV3, HepG2, and MCF-7). The results showed that Se-POP-21 reduced dose-dependently the viability of A549, SKOV3, HepG2, and MCF-7 cells and promoted apoptosis of A549 cells, without any effect on normal cells. Based on these studies, both compounds, Se-POP-21 and Se-POP-3, showed great potential as low-toxic antitumor drugs. Further studies are required for the development or use of these compounds as a chemotherapeutic agent [112].

Another protein combined with Se was ovalbumin, obtaining a complex that showed anticancer properties [113]. The anticancer effect of seleno-ovalbumin (Se-OVA) was evaluated in mice inoculated with H22 hepatoma cells; the study included a positive group (treatment with 5-FU at 20 mg/kg). Se-OVA (1.5 mg Se/kg) and positive groups showed lower tumor volume compared with the model or negative control group. The results showed a tumor inhibition rate of 48% for Se-OVA, while the treatment with 5-FU reported a 54% tumor inhibition. Even though the positive group had the lowest tumor weight and inhibition rate, the authors reported the death of two mice, which might be related to the side effects of 5-FU. Furthermore, Se-OVA showed an increase in the expression of Bax and cleaved-caspase 9 and a decrease in the expressions of Bcl-2 compared to the model group.

Besides, Se-OVA inhibits the proliferation of solid tumor cells by blocking the cell cycle in G0/G1 phase, and by activating apoptotic signals. Thus, Se-β-Lg and Se-OVA showed potential as antitumor agents and could have applications in food and drug industries as well as adjuvants in therapy cancer [103, 111].

On the other hand, mice xenografted with human breast cancer cells (MDA-MB-231) treated with Se-enriched *Pyracantha fortuneana* (Se-PFPs) at 100 or 400 (mg/kg/day) for 30 consecutive days showed anticancer effects by reduction of tumor volume. Control group (without Se-PFPs) and treatments with 100 or 400 Se-PFPs mg/kg/day had tumor volumes of 1366, 896, and 285 mm^3, respectively [114]. Besides, Se-PFPs did not show to have toxic effects in the mice, as there were no deaths during the study and inhibited the growth and induced apoptosis of triple negative breast cancer cells.

Antiangiogenic Effect

Angiogenesis plays a significant role in the progression of tumors. When a tumor develops the complete formation of blood vessels or vascularization is very difficult to control. There have been some investigations regarding the role of Se in this critical process of cancer biology, such as early and cancer development stages [115].

Se consumed in water was reported to reduce the concentration of vascular endothelial growth factor (VEGF) by 63% compared to the control group in an in vivo model of induced CRC mouse [12]. Additionally, improvement in caspase-3 expression, and malondialdehyde content was also reported, while there was a decrease in reduced GSH concentration. A study in men supplemented daily during 5 weeks with 300 µg Se in the form of selenized yeast regulated the expression of genes involved in cellular migration, invasion, remodeling, and immune responses. In addition, the supplementation upregulated the expression of epithelial markers, such as E-cadherin and epithelial cell adhesion molecule (EPCAM), while the mesenchymal markers vimentin and fibronectin were downregulated [21].

There have been several approaches to study the effects and mechanisms of Se-enriched yeast (> 10% of Na2SeO3)

administered to a rat model. Results revealed that Se significantly enhanced the expression of p53 in combination with a considerable reduction of angiogenic factor cluster of differentiation (CD31). This last factor is crucial for endothelial intercellular junctions in white blood cells and platelets [22]. Cai et al. [116] reported an angiogenic effect on human umbilical vein endothelial cells (HUVECs) with 2 µM of MSeA, with values ranging in moderate Se levels. The increment in adherence and the inhibition of cell migration and tube formation were the main effects of MSeA, leading to an impediment of sprouts of aortic rings for mice models and neoangiogenesis of chorioallantoic membrane for chick embryos. Additionally, downregulation and disordered clustering of integrin β3 and repression of phosphorylation of protein kinase B (PKB), nuclear factor of kappa light polypeptide gene enhancer in B-cell inhibitor, alpha (IκBα), and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) were achieved, leading to antiangiogenesis.

Lately, the development of SeNPs as antitumoral agents through biological methods has shown remarkable results [117]. In this regard, Rajkumar et al. [25] grew a strain of *Pseudomonas stutzeri* in the presence of 2 mM Na_2SeO_3 and observed the generation of phenazine carboxylic acid that promoted Se oxyanions to a reduced nanoparticle state, which showed high stability. These particles reduced cell migration and proliferation and significantly decreased angiogenesis in 30% of the cervical cancer cell line (HeLa) when administered at doses of 100 µg/mL [25].

To this regard, the chitosan oligosaccharide-conjugate Se (COS-Se) compound was analyzed as a functional food ingredient with anticancer properties [118]. Human gastric cancer cells (SGC-7901) were exposed to COS-Se at concentrations of 100, 200, 500, and 1000 µg/mL for 48 h. COS-Se had a cytotoxic effect in SGC-7901 cells in a dose-dependent manner. Besides, the anticancer effect of COS-Se was evaluated in nude mice transplanted with SGC-7901 cells. Mice were treated with COS-Se at doses of 50 and 100 mg/kg for 28 days. COS-Se showed a tumor inhibition rate of 29% and 33% at doses of 50 and 100 mg/kg, respectively. The authors declared that COS-Se reduced levels of CD34, matrix metalloproteinase-9, and vascular endothelial growth factor in nude mice [118].

Tables 2 and 3 show a summary of the anticancer mechanisms reported for selenocompounds, Se-enriched foods, and SENPs, in in vivo and in vitro models.

Combinatorial Therapies with Se

Table 4 summarizes some studies that have shown effective anticancer effects when chemotherapeutic agents were combined with Se. For cancer treatments, it has been used Se as a delivery method for doxorubicin, cisplatin, 5-FU, and ruthenium showing that Se enhanced from one to sixfold higher the uptake of chemotherapies for breast cancer cells (MCF-7). As a result, these strategies have recently shown a growing trend [122, 123].

Park et al. [124] investigated the combined effects of Se (10 µM) with docetaxel (DTX) at 500 pM on breast cancer cell line (MDA-MB-231) after 72 h of incubation. The combined strategy decreased cell growth (15%), increased apoptosis (63%), and enhanced cell cycle arrest compared to the control group. The same combination therapy (Se + DTX) was evaluated in glioblastoma cells (DBTRG). Ertilav et al. [108] exposed to 10 nM DTX for 10 h and subsequently exposed to 1 µM Se for 10 h. This combination effectively inhibited cell proliferation in DBTRG cells compared with the control group. These authors concluded that the DTX and Se treatment was better than DTX treatment alone [108].

Likewise, the combined therapy of Na_2SeO_3 (200 nM) and cisplatin (40 µM) was evaluated on breast cancer cells (MCF-7). After 72 h of incubation, the combined therapy showed a more effective apoptotic effect by the activation of caspases 3 and 9 [109]. Moreover, the combination of Se-containing molecules with cisplatin (EG-Se/Pt) increased the inhibition of T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma (Jurkat, Molt-4) cell viability compared to cisplatin alone in a dose- and time-dependent manner, inducing apoptosis and cell cycle arrest [125].

Another successful combination was the one reported by Wu et al. [126] who used Na_2SeO_3 (3 mg/kg) and Adriamycin prodrug Ac-Phe-Lys-PABCADM (PADM) (10 mg/kg) in an in vivo model. Nude mice were xenografted with gastric cancer cells (SGC-7901). The drug administration (Na_2SeO_3 + PADM) was given four times each 8 days during a total period of 40 days. The authors concluded that this combined therapy promoted apoptosis in gastric cancer xenografts by the elevation of proapoptotic proteins such as caspase 3, caspase 9, and p53.

Paclitaxel is another chemotherapeutic drug that combined with Se has shown anticancer effects in MCF-7 cells [127]. MCF-7 cells incubated with 50 µM Paclitaxel and 5 µM Na_2SeO_3 for 24 h showed an increase of ROS, and higher levels of caspases 9 and 3 compared with the treatment with only paclitaxel (50 µM). The combination of Se and paclitaxel in MCF-7 cells had synergistic effects especially in terms of increasing apoptosis of this specific cell line [127].

Selenium Status and Cancer Risk

Se status refers to the amount of biologically active selenium in the body resulting from the intake, retention, and metabolism of selenized compounds in the diet. It is an indicator of cancer risk and can be monitored measuring

Table 2 In vitro assay of selenocompounds with anticancer activity

Source of selenocompounds	Cell line	Dose	Main mechanisms	References
Na_2SeO_3	A375 and T24	4.7 µM and 3.5 µM	IC50 at 24 h, cytotoxic activity	[88]
Na_2SeO_3	RT-112	2.5 µM	At 48–72 h, cytotoxicity activity, DNA and mitochondrial damage. Necroptosis cell death	[92]
Na_2SeO_3	MCF-7	1 mol/L	At 48 h, SBP1 protein levels were reduced, ROS generation, apoptosis,	[90]
O_3SSe^{-2}	HepG2	13.8 µM	IC50 at 24 h, cytotoxicity activity	[88]
SeMet and SeMSC	HeLa	10 µM	Inhibited AKT signaling pathways and the migration	[97]
SeMet	GMS-10 and DBTRG-0 MG	50–1000 µM	DNA fragmentation and cell death	[105]
MSeA	HeLa cells	10 µM	Inhibited ERK and AKT signaling pathways and suppressed the cell proliferation and migration	[97]
MSeA	HUVECs	2 µM	Inhibits angiogenesis by downregulating integrin β3 signaling	[116]
MSeA	THP1	5 µM	DNA damage and ER stress	[106]
Se-β-Lg	Hep G2 and Hep 3B	500 µg/mL	Apoptosis and cell cycle arrest	[110]
Se-β-Lg	MCF-7 and MDA-MB-231	0–400 µg/mL	Increased the expression of cleaved-caspase-9 and cleaved-caspase-3 and cell cycle arrest	[111]
Se-enriched polysaccharide (Se. POP-3)	HepG2, MCF-7 and SKOV3	600 g/mL	Increased apoptosis, inhibiting migration of cancer cells	[46]
Se-enriched polysaccharide (Se-POP-21)	A549, SKOV3, HepG2, and MCF-7	600 g/mL	Reduced the viability and promoted apoptosis	[112]
SeNPs-apigenin	MCF-7 cell	1000 µM/mL	Increased the Cas-3 activity. Decreased the expression of Bcl2, induced apoptosis, and inhibition of cancer cell migration and invasion	[119]
Si-SeNPs-silymarin	AGS	20 mM (0.4–25.6 µg/ mL)	Induced expression of Bax/Bcl-2, cytochrome c, and cleavage of caspase proteins, mitochondria-mediated apoptosis	[120]
SeNPs-hydroxyapatite	MDAMB-2, PC3, and hBMSc	50 mg	Decrease proliferation and selectively cytotoxicity	[20]
SeNPs synthesized by *Pseudomonas stutzeri*	HeLa	100 µg/mL	Decrease of proliferative activity, cell migration and angiogenesis	[25]
Se-containing platinum	L02 HepG2	4 mM	Apoptosis by caspase activation and cyt c release	[19]

serum levels of Se and SELENOP. There is no linear relationship between Se status and cancer. Some studies suggest that the median level of plasma Se required for a significant reduction in cancer risk ranges from > 84 to 147 µg/L [128, 129]. For nearly two decades, it has been reported that the minimum Se intake required to achieve these plasma concentrations ranges from just below the RDA/RNI level to a total intake of about 140 µg/day from dietary Se [130]. In a nested case–control study of baseline serum Se levels and cancer risk with 19,573 females from Szczecin, Poland, there was evidence for an increased risk of cancer among women in the highest of Se levels (i.e., > 90 µg/L); this result suggests that the optimum serum level of Se in women from Poland should be between 70 and 90 µg/L [131]. The Nutritional Prevention of Cancer Trial evaluated Se supplementation as selenized yeast (200 µg/daily) during 6.4 years in 1312 participants from the southeastern United States. Se supplementation reduced total (37%) and prostate (67%) cancer incidence but was not significantly associated with lung and colorectal cancer incidence. Participants with

Table 3 In vivo assay of selenocompounds with anticancer activity

Source of selenocompounds	Administration	Dose	Assays	Main mechanisms	References
Sprouted chickpea flour with Se	Oral	2.29 µg of Se total/g diet	Immune-suppressed mice xenografted (HT-29 RFP)	Activation of the apoptotic intrinsic pathway, and antioxidant protection of lipids through GPX1 enzymatic activity	[23]
Selenized yeast	Gavage	1 mL of/day	Colorectal tumors induced with 1,2-dimethylhydrazine in Wistar rats	Decrease expression of the Bcl-2 Reduction of angiogenesis	[22]
Selenized yeast	Oral	300 µg/day	Placebo-controlled trial, Prostate cancer	Downregulated expression of genes involved in cellular migration, invasion, remodeling and immune responses. Inhibitory effect of epithelial-to-mesenchymal transition	[21]
Se-enriched Pyracantha fortuneana (Se-PFPs)	Oral	400 Se-PFPs mg/kg/day	mice xenografted with MDA-MB-231 cells	Arrest of the G2 phase cell. Caused apoptosis, increased p53, Bax, Puma and Noxa. Decreased Bcl2. Increased caspases 3/9 activity	[114]
Chitosan oligosaccharide-conjugated Se (COS-Se)	Oral	50 mg/kg diet	BALB/c-nu mice, xenografted with SGC-7901 cells	Inhibited proliferation and migration Reduced the levels of CD34, and matrix metalloproteinase-9	[118]
Se-β-Lg	Oral	150 µg/kg of body weight	Kunming mice, xenografted with S180 cells	Inhibition of cells proliferation and apoptosis by cell cycle arrest Improve immune functions	[103]
Se-OVA	Gavaged	1.5 mg Se/kg of body weight	Kunming mice, xenografted with H22 cells	Increase the expression of Bax and cleaved-caspase 9. Decrease of Bcl-2 expression. Block of the cell cycle and inhibit the proliferation of solid tumors	[113]
SeNPs with *Lactobacillus plantarum*	Oral	0.5 mL/day	Balb/c mice, xenografted with 4T1 cells	Antitumor immune response by the increase of IFN-γ production and natural killer cells	[121]
SeNPs (Na_2SeO_3 and GSH with bovine serum albumin)	Intraperitoneal injected	4 mg Se/kg of body weight	Male Kunming mice, xenografted with H22 cells	Increase of ROS and DNA damage	[96]
SeMet	Oral	0.15 mg/kg of body weight	Nude-mouse (C57BL/6 J and APC), xenografted with Caco-2 and HT-29	High expression of SELENOH, inhibition of the proliferation and G1/S phase	[11]
Se mineral	Oral	200 mg/L supplied in the drinking water	Colorectal tumors induced with 1,2-dimethylhydrazine in BALB/C Mice	Pro-oxidant, apoptotic and anti-angiogenic effects. Lower expression of CDX-2 and VEGF, and high caspase-3 expression	[12]

Table 4 In vitro studies of combination therapy with selenocompounds and chemotherapeutic agents

Selenocompounds and chemotherapeutic drugs	Incubation time	Type of cancer	Cell line	Therapeutic effect	Reference
DTX (500 pM) + Se (10 μM)	72 h	Breast	MDA-MB-231 MCF-7	Inhibits cell proliferation and increase apoptosis	[124]
DTX (10 nM) + Se (1 μM)	20 h	Brain/spine	DBTRG	Inhibits cell proliferation	[108]
Cisplatin (40 μM) + Na_2SeO_3 (200 nM)	48 h	Breast	MCF-7	Induce antitumor and apoptotic activity	[109]
EG-Se/Pt (5–100 μM)	72 h	Leukemia and lymphoma	Jurkat Molt-4	Inhibition of cell viability and increase of apoptosis	[125]
Paclitaxel (50 μM) + Na_2SeO_3 (5 μM)	24 h	Breast	MCF-7	Increase of ROS and apoptosis	[127]

DTX, docetaxel; *EG-Se/Pt*, Se-containing molecules with cisplatin; *Na_2SeO_3*, sodium selenite

baseline plasma Se concentrations in the lowest two tertiles (< 121.6 ng/mL) experienced reductions in total cancer incidence, whereas those in the highest tertile showed an elevated incidence [132]. Opposite results were reported in The Selenium and Vitamin E Cancer Prevention Trial, in which it was observed that 200 μg Se/daily had no effect on incidence of prostate cancer in a high-Se US population (136 μg/L) [133].

Single Nucleotide Polymorphisms on Selenoproteins

SNPs are genetic variations in the human genome, and some of them are associated with genetic susceptibility to cancer. These genetic variations could play an important role in shaping tumor environment, immune response, therefore, the response to chemotherapy, and other natural compounds [134]. The effects of SNPs in genes resulted in the regulation of DNA damage, cell cycle, metabolism, and immunity regulation, which are mechanisms associated with cancer progression and the therapy response [135]. It is known that the presence of genetic variations on Se metabolism can impact the synthesis of selenoproteins or have an influence on their biochemical functions [136]. For that reason, SNPs in Se metabolism have been investigated due to their relationship with the appearance of some diseases, such as cancer [136].

In this regard, the relationship between SNPs in the *SELENOS* gene and the susceptibility to gastric cancer was assessed in the Chinese population. The presence of two SNPs, rs34713741, and rs28665122 in the *SELENOS* gene was associated with a risk of that cancer. The study was made with 260 patients with gastric cancer and 278 healthy counterparts that served as controls. Only rs34713741 SNPs in *SELENOS* showed association with gastric cancer, while rs28665122 did not have differences of genotype frequencies between patients with cancer and the control group [137]. Recently, through a meta-analysis study, the *SELENOS* gene rs34713741 polymorphism has been associated with a higher risk of both gastric cancer and CRC [138]. The relationship of SNPs in selenoproteins genes with CRC development was also studied in the Iranian population. The SNPs analyzed were rs7579 and rs34713741 in *SELENOP* and *SELENOS* genes, respectively. No differences in selenoprotein gene SNPs between patients with CRC and controls were found, suggesting that these polymorphisms do not increase the risk of CRC cancer in the Iranian population [139]. Likewise, the risk of breast cancer in the Iranian population was associated with the presence of SNPs, rs5859, in the *SELENOF* gene. This was determined by studying 150 patients with histologically breast cancer and 200 healthy patients. Differences in the distribution of allele frequencies were found between healthy patients and those with breast cancer. Patients carrying AA and AG genotypes had a higher risk of breast cancer compared to counterparts with GG genotype; thus, SNPs rs5859 in the *SELENOF* gene may be associated with breast cancer [140].

In addition to the study of the relationship of the SNPs and the development of cancer, researchers have focused on the SNPs related to the metabolism of Se. This relationship could impact on Se status and therefore the Se response on aforementioned anticancer mechanisms. A study of genotyped volunteers that were supplemented for 6 weeks with 100 μg of Na_2SeO_3 per day. The results indicated that concentrations of Se in plasma, SELENOP, and GPX3 protein increased after supplementation. However, Se in plasma in supplemented volunteers depended on SELENOP genotype associated with gender and SNP 24,731. On the other hand, SNP 25,191 in *SELENOP* had an impact post-supplementation [141].

Se status or response to supplementation has been associated with SNPs, mainly in *SELENOP*, dimethylglycine dehydrogenase (*DMGDH*), *GPX1*, and *GPX4*. A study carried out with pregnant woman reported genetic variations in *DMGDH* (rs921943), *SELENOP* (rs3877899 and rs7579),

GPX1 (rs1050450), and *GPX4* (rs713041). The results showed that SNPs in *DMGDH* (rs921943) and *SELENOP* (rs3877899) were significantly associated with serum Se concentration [142].

More recently, Fedirko et al. [143] examined the association of SNPs related to the Se metabolism in the development of CRC. The study was developed with the collaboration of European patients with CRC (1420) and healthy patients (1421) that had suboptimal blood levels of Se (84.0–85.6 µg/L). The blood of each patient was analyzed in order to correlate the presence of SNPs that affect Se and selenoprotein metabolism with the development of CRC. The subsequent SNPs, rs17080528, rs11705137, rs4659382, rs2275129, and rs11111979 were found in selenoproteins genes, *GPX1*, *SELENOM*, *SELENON*, selenophosphate synthetase 1 (*SEPHS1*), and *TXNRD1*, respectively, which are involved in Se and selenoprotein transport, biosynthesis, and metabolism and their presence linked to the development of CRC [143]. On the other hand, SNPs were associated with selenoproteins genes that influenced the status of SELENOP favoring the development of CRC, such as *SELENON* (rs4659382, rs11247710, and rs2072749), and in *TXNRD1* (rs11111979). These selenoproteins and their genetic variations with antioxidant activity can have a great impact on carcinogenesis [143].

These outcomes could predict the behavior of biomarkers of Se status and thus susceptibility to disease such as cancer. Besides, knowing SNPs that affect the Se metabolism, it is possible to predict the response to supplementation, and thus the effect of Se on some diseases such as cancer. In addition, investigations should focus on finding the SNPs that affect some anticancer mechanisms in order to adjust Se supplements doses or the type of compound.

New Approaches: Insights About Gut Microbiota

The microbiome and the interplay with dietary habits are among the top factors that predispose mammals to cancer development. Microbiota influences Se forms and status, as it favors its biotransformation and selenoprotein expression. Colonization of germ-free mice induced the expression of different selenoproteins displaying a higher risk of Se deficiency when Se intake was limited [144]. Besides, Se can also modulate microbiota diversity and composition increasing the relative abundance of some health-promoting taxa such as *Christensenellaceae*, *Ruminococcaceae*, and *Lactobacillus*; furthermore, Se supplementation also lead to associations of specific bacteria taxa with plasma selenoproteins like GPX3, SELENOP, and selenoalbumine [145].

Different studies suggested that Se supplementation on gut health is associated with the gut microbiota. In this regard, fecal microbial transplant studies showed that Se protects the intestinal barrier function and immune responses [146]. The impact of gut microbiota on selenoproteins and other molecules linked to signaling pathways involved in oxidative stress, apoptosis, inflammation, and immune responses suggest a direct influence of Se and microbiota in the development of chronic diseases and cancer [147]. Se-enriched *Saccharomyces* reduces oxidative stress and inflammatory responses, protecting mice against pathological consequences associated with mucositis induced by 5-FU used in many types of cancer therapies [148].

Supranutritional levels of Se enhanced fermentation and the production of short-chain fatty acids, with a positive impact on epithelial and mucosal stability. In addition, the supplementation reduced inflammation and ultimately carcinoma development [146].

The administration of probiotics with Se has been proposed as an alternative in CRC treatments. For instance, the enrichment of SeNPs with *Lactobacillus plantarum* improved host immune response and life span of cancer-bearing mice [121]. Similar effects were also shown by the oral administration of SeNPs enriched with *Lactobacillus brevis*, which besides stimulating the immune response also reduced liver metastasis in a breast cancer mice model [149].

Knowing more about how microbiota interact and play an important role on Se status, response to supplementation, and metabolism could open a gap of other mechanisms that Se could act against some diseases such as cancer.

Conclusions and Future Approaches

In the last decade, Se has been the spotlight of micronutrient research because of its proven novel and complementary effects against cancer primarily due to its antioxidant and pro-apoptotic activities. Se toxicity remains a relevant topic, and therefore, scientists are looking for non-toxic ways of administration especially in terms of organic Se forms, which are comparatively less toxic and more bioavailable. Several in vitro studies have further advanced in the full understanding of the cellular and molecular pathways that Se undergoes, whereas in vivo investigations offer a new vision to elucidate its physiological roles. However, the need for novel and macro-scale clinical studies is critically important to fully grasp the synergism of different Se compounds with other treatments like chemotherapies. In addition, the latest innovations in genomics and the role of the microbiota in foods open new paths to improve the efficacy of Se-enriched products, placing this essential mineral as a crucial element for prolonging the average life of humans. The applicability of the different forms of Se recently investigated may offer new natural preventive or therapeutic strategies to improve

the quality of life for people that suffer from cancer or other diseases that exacerbate due to oxidative stress.

Author Contribution Dávila Vega and Gastelum Hernández wrote the main manuscript text. Serrano-Sandoval and Guardado-Félix structured the main topics, wrote, and revised the manuscript; Serna-Saldívar, Gutiérrez-Uribe, Milán-Carrillo, and Martínez-Cuesta reviewed the manuscript. All authors read and approved the final manuscript.

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Data Availability The data of this study will be made available from the corresponding author on reasonable request.

Declarations

Ethics Approval Not applicable.

Consent to Participate This article does not contain any studies with human participants or animals performed by any of the authors.

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References

1. World Health Organization, WHO (2021). Cancer today. https://gco.iarc.fr/today/home. Accessed January 21, 2021
2. Sommer J, Mahli A, Freese K, Schiergens TS, Kuecuekoktay FS, Teufel A, Thasler WR, Müller M (2017) Analysis of molecular mechanisms of 5-fluororacil-induced steatosis and inflammation *in vitro* and in mice. Oncotarget 8(8):13059–13072
3. Hashiguchi Y, Muro K, Saito Y (2020) Japanese society for cancer of the colon and rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol 25:1–42
4. Clemente A, Olias R (2017) Beneficial effects of legumes in gut health. Curr Opin Food Sci 14:32–36
5. Gao Y, Xiao X, Zhang C, Yu W, Guo W, Zhang Z, Li Z, Feng X (2017) Melatonin synergizes the chemotherapeutic effect of 5-fluorouracil in colon cancer by suppressing PI3K/AKT and NF-κB/iNOS signaling pathways. J Pineal Res 62:e12380
6. Garousi F (2017) The essentiality of selenium for humans, animals, and plants, and the role of selenium in plant metabolism and physiology. Acta Univ Sapientiae Aliment 10(1):75–90
7. Razaghi A, Poorebrahim M, Sarhan D, Björnstedt M (2021) Selenium stimulates the antitumour immunity: insights to future research. Eur J Cancer 155:256–267
8. Guo CH, Hsia S, Chung CH, Lin YC, Shih MY, Chen PC, Li Z (2021) Nutritional supplements in combination with chemotherapy or targeted therapy reduces tumor progression in mice bearing triple-negative breast cancer. J Nutr Biochem 87:108504
9. dos Reis AR, El-Ramady H, Santos EF, Gratão PL, Schomburg L (2017) Overview of Selenium deficiency and toxicity worldwide: affected areas, selenium-related health issues, and case studies. In: Pilon-Smits EAH et al (eds) Selenium in plants. Plant Ecophysiology 11:209–230
10. Lü J, Zhang J, Jiang C, Deng Y, Özten N, Bosland MC (2016) Cancer chemoprevention research with selenium in the post-SELECT era: promises and challenges. Nutr Cancer 68(1):1–17
11. Bertz M, Kühn K, Koeberle SC, Müller MF, Hoelzer D, Thies K, Kipp AP (2018) Selenoprotein H controls cell cycle progression and proliferation of human colorectal cancer cells. Free Radic Biol Med 127:98–107
12. Saeed M, Mohamed R, Amhed M (2019) The pro-oxidant, apoptotic and anti- angiogenic effects of selenium supplementation on colorectal tumors induced by 1,2- dimethylhydrazine in BALB/C Mice. Rep Biochem Mol Biol 8(3):215–226
13. Evans S, Jacobson G, Goodman H, Bird S, Jameson B (2020) Comparison of three oral selenium compounds in cancer patients: evaluation of differential pharmacodynamics effects in normal and malignant cells. J Trace Elem Med Biol 58:126446
14. Sonkusre P (2020) Specificity of biogenic selenium nanoparticles for prostate cancer therapy with reduced risk of toxicity: an i*n vitro* and *in vivo* study. Front Oncol 9:1541
15. Wang Y, Zhu W, Chen X (2020) Selenium-binding protein 1 transcriptionally activates p21 expression via p53-independent mechanism and its frequent reduction associates with poor prognosis in bladder cancer. J Transl Med 18(17):1–13
16. Hu T, Liang Y, Zhao G, Wu W, Li H, Guo Y (2019) Selenium biofortification and antioxidant activity in Cordyceps militaris supplied with selenate, selenite, or selenomethionine. Biol Trace Elem Res 187(2):553–561
17. Brzacki V, Mladenovic B, Dimic D, Jeremic L, Zivanovic D, Djukic D, Stojanovic N, Sokolovic D (2019) Comparison between the effects of selenomethionine and S-adenosylmethionine in preventing cholestasis-induced rat liver damage. Amino Acids 51:795–803
18. Marciel MP, Hoffmann PR (2019) Molecular mechanisms by which selenoprotein K regulates immunity and cancer. Biol Trace Elem Res 192(1):60–68
19. Li F, Li T, Han X, Zhuang H, Nie G, Xu H (2017) Nanomedicine assembled by coordinated selenium–platinum complexes can selectively induce cytotoxicity in cancer cells by targeting the glutathione antioxidant defense system. ACS Biomater Sci Eng 4(6):1954–1962
20. Barbanete A, Nadar RA, Degli-Esposti L, Palazzo B, Iafisco M, van den Beucken JJ, Margiotta N (2020) Platinum-loaded, selenium-doped hydroxyapatite nanoparticles selectively reduce proliferation of prostate and breast cancer cells co-cultured in the presence of stem cells. J Mater Chem 8(14):2792–2804
21. Kok DE, Kiemeney LA, Verhaegh GW, Schalken JA, Lin ENV, Sedelaar JP, Witjes JA, Hulsbergen-van de Kaa CA, van't Veer P, Kampman E (2017) A short-term intervention with selenium affects expression of genes implicated in the epithelial-to-mesenchymal transition in the prostate. Oncotarget 8:10565–10579
22. Abedi J, Saatloo MV, Nejati V, Hobbenaghi R, Tukmechi A, Nami Y, Khosroushahi AY (2018) Selenium-enriched Saccharomyces cerevisiae reduces the progression of colorectal cancer. Biol Trace Elem Res 185(2):424–432
23. Guardado-Félix D, Antunes-Ricardo M, Rocha-Pizaña MR, Martínez-Torres AM, Gutiérrez-Uribe JA, Serna Saldivar SO (2019) Chickpea (*Cicer arietinum L.*) sprouts containing supranutritional levels of selenium decrease tumor growth of colon cancer cells xenografted in immune-suppressed mice. J Funct Foods 56:73–84
24. Li W, Guo M, Liu Y, Mu W, Deng G, Li C, Qiu C (2016) Selenium induces an anti-tumor effect via inhibiting intratumoral

angiogenesis in a mouse model of transplanted canine mammary tumor cells. Biol Trace Elem Res 171(2):371–379
25. Rajkumar K, Mvs S, Koganti S, Burgula S (2020) Selenium nanoparticles synthesized using Pseudomonas stutzeri (MH191156) show antiproliferative and anti-angiogenic activity against aervical cancer cells. Int J Nanomed 15:4523–4540
26. Gandin V, Khalkar P, Braude J, Fernandes AP (2018) Organic selenium compounds as potential chemotherapeutic agents for improved cancer treatment. Free Radic Biol Med 127:80–97
27. Radomska D, Czarnomysy R, Radomski D, Bielawski K (2021) Selenium compounds as novel potential anticancer agents. Int J Mol Sci 22(3):1009
28. Avery JC, Hoffmann PR (2018) Selenium, selenoproteins, and immunity. Nutrients 10(9):1203
29. Fontagne-Dicharry S, Veron V, Larroquet L, Godin S, Wischhusen P, Aguirre P, Kaushik SJ (2020) Effect of selenium sources in plant-based diets on antioxidant status and oxidative stress-related parameters in rainbow trout juveniles under chronic stress exposure. Aquaculture 529:735684
30. Bizerea TO, Dezsi SG, Marginean O, Stroescu R, Rogobete A, Bizerea-Spiridon O, Ilie C (2018) The link between selenium, oxidative stress, and pregnancy-induced hypertensive disorders. Clin Lab 64(10):1593–1610
31. Tamires P, Thais A, Adriani D, Ângela C, Marina M, Thais C, João-Paulo T, Vanessa M (2020) Brazil nut prevents oxidative DNA damage in type 2 diabetes patients. Drug Chem Toxicol 18:1–7
32. Farzad R, Kuhn DD, Smith SA, O'Keefe SF, Hines IS, Bushman TJ, Stevens AM (2021) Effects of selenium-enriched prebiotic on the growth performance, innate immune response, oxidative enzyme activity and microbiome of rainbow trout (Oncorhynchus mykiss). Aquaculture 531:735980
33. Yamashita Y, Yamashita M, Iida H (2013) Selenium content in seafood in Japan. Nutrients 5(2):388–395
34. Zwierzchowski GA, Ametaj BN (2018) Minerals and heavy metals in the whole raw milk of dairy cows from different management systems and countries of origin: a meta-analytical study. J Agric Food Chem 66(26):6877–6888
35. Pilarczyk B, Tomza-Marciniak A, Pilarczyk R, Kuba J, Hendzel D, Udała J, Tarasewicz Z (2019) Eggs as a source of selenium in the human diet. J Food Compost Anal 78:19–23
36. Food and Agriculture Organization FAO (2001) Chapter 15: selenium. Last modified 2001. http://www.fao.org/3/Y2809E/y2809e0l.html. Accessed May 15, 2021
37. Mousaie A (2021) Dietary supranutritional supplementation of selenium-enriched yeast improves feed efficiency and blood antioxidant status of growing lambs reared under warm environmental condition. Trop Anim Health Prod 53(1):1–7
38. Dai H, Wei S, Twardowska I (2020) Biofortification of soybean (Glycine max L) with Se and Zn and enhancing its physiological functions by spiking these elements to soil during flowering phase. Sci Total Environ 740:139648
39. Golob A, Novak T, Maršić NK, Šircelj H, Stibilj V, Jerše A, Germ M (2020) Biofortification with selenium and iodine changes morphological properties of Brassica oleracea L. var. gongylodes and increases their contents in tubers. Plant Physiol Biochem 150:234–243
40. Ge J, Guo K, Zhang C, Talukder M, Lv M, Li JY, Li JL (2021) Comparison of nanoparticle-selenium, selenium-enriched yeast and sodium selenite on the alleviation of cadmium-induced inflammation via NF-kB/IκB pathway in heart. Sci Total Environ 773:145442
41. Guardado-Félix D, Serna-Saldivar SO, Cuevas-Rodríguez EO, Jacobo-Velázquez DA, Gutierréz-Uribe JA (2017) Effect of sodium selenite on isoflavonoid contents and antioxidant capacity of chickpea. Food Chem 226:69–74
42. Serrano-Sandoval SN, Guardado-Félix D, Gutiérrez-Uribe JA (2019) Changes in digestibility of proteins from chickpeas (Cicer arietinum L.) germinated in presence of selenium and antioxidant capacity of hydrolysates. Food Chem 285:290–295
43. Serrano-Sandoval SN, Guardado-Félix D, Gutiérrez-Uribe JA (2021) Deglycosilation of isoflavones in selenized germinated chickpea flours due to convection drying. LWT Food Sci Technol 153:112417
44. Ei H, Zheng HT, Farooq MU (2020) Impact of selenium, zinc and their interaction on key enzymes, grain yield, selenium, zinc concentrations, and seedling vigor of biofortified rice. Environ Sci Pollut Res 27:16940–16949
45. Islam MZ, Park BJ, Kang HM, Lee YT (2020) Influence of selenium biofortification on the bioactive compounds and antioxidant activity of wheat microgreen extract. Food Chem 309:125763
46. Zhang Y, Zhang Z, Liu H, Wang D, Wang J, Deng Z, Li T, He Y, Yang Y, Zhong S (2020) Physicochemical characterization and antitumor activity *in vitro* of a selenium polysaccharide from Pleurotus ostreatus. Int J Biol Macromol 165:2934–2946
47. de Brito MP, Tavanti RFR, Tavanti TR, Santos EF, Jalal A, Dos Reis AR (2021) Selenium biofortification enhances ROS scavenge system increasing yield of coffee plants. Ecotoxicol Environ Saf 209:111772
48. Guardado-Félix D, Lazo-Vélez MA, Pérez-Carrillo E, Panata-Saquicili DE, Serna-Saldívar SO (2020) Effect of partial replacement of wheat flour with sprouted chickpea flours with or without selenium on physicochemical, sensory, antioxidant and protein quality of yeast-leavened breads. LWT 129:109517
49. Lazo-Vélez MA, Chávez-Santoscoy A, Serna-Saldivar SO (2015) Selenium-enriched breads and their benefits in human nutrition and health as affected by agronomic, milling, and baking factors. Cereal Chem 92(2):134–144
50. Ligowe IS, Young SD, Ander EL, Kabambe V, Chilimba ADC, Bailey EH, Nalivata PC (2020) Selenium biofortification of crops on a Malawi Alfisol under conservation agriculture. Geoderma 369:114315
51 Lima W, Gavin C, Christina W, Ali FE, Mehdawi C, Elizabeth AH (2019) Selenium accumulation, speciation and localization in Brazil nuts (Bertholletia excelsa H.B.K). Plants 8:289
52. Ralston NV, Kaneko JJ, Raymond LJ (2019) Selenium health benefit values provide a reliable index of seafood benefits vs. risks. J Trace Elem Med Biol 55:50–57
53. Tangjaidee P, Xiang J, Yin H, Wen X, Quek SY (2019) Selenium, fibre, and protein enrichment of rice product: extrusion variables and product properties. Food Qual Saf 3(1):40–51
54. Guardado-Félix D, Pérez-Carrillo E, Heredia-Olea E, Serna-Saldivar SO (2022) Comparison of regular and selenium-enriched tortillas produced from sprouted corn kernels. Plant Foods Hum Nutr 77:226–232
55. Takahashi K, Suzuki N, Ogra Y (2018) Effect of administration route and dose on metabolism of nine bioselenocompounds. J Trace Elem Med Biol 49:113–118
56. Pick D, Degen C, Leiterer M, Jahreis G, Einax JW (2013) Transport of selenium species in Caco-2 cells: analytical approach employing the Ussing chamber technique and HPLC-ICP-MS. Microchem J 110:8–14
57. Gammelgaard B, Rasmussen LH, Gabel-Jensen C, Steffansen B (2011) Estimating intestinal absorption of inorganic and organic selenium compounds by in vitro flux and biotransformation studies in Caco-2 Cells and ICP-MS Detection. Biol Trace Elem Res 145(2):248–256
58. Leblondel G, Mauras Y, Cailleux A, Allain P (2001) Transport measurements across caco-2 monolayers of different organic and inorganic selenium: influence of sulfur compounds. Biol Trace Elem Res 83(3):191–206

59. Nickel A, Kottra G, Schmidt G, Danier J, Hofmann T, Daniel H (2009) Characteristics of transport of selenoamino acids by epithelial amino acid transporters. Chem Biol Interact 177(3):234–241
60. Jäger T, Drexler H, Göen T (2014) Human metabolism and renal excretion of selenium compounds after oral ingestion of sodium selenate dependent on trimethylselenium ion (TMSe) status. Arch Toxicol 90(1):149–158
61. Jäger T, Drexler H, Göen T (2015) Human metabolism and renal excretion of selenium compounds after oral ingestion of sodium selenite and selenized yeast dependent on the trimethylselenium ion (TMSe) status. Arch Toxicol 90:1069–1080
62. Di Dato C, Gianfrilli D, Greco E, Astolfi M, Canepari S, Lenzi A, Isidori A, Giannetta E (2017) Profiling of selenium absorption and accumulation in healthy subjects after prolonged l-selenomethionine supplementation. J Endocrinol Investig 40(11):1183–1190
63. Wastney ME, Combs GF, Canfield WK, Taylor PR, Patterson KY, Hill AD, Moler JE, Patterson BH (2011) A human model of selenium that integrates metabolism from selenite and selenomethionine. J Nutr 141(4):708–717
64. Seale LA, Ha HY, Hashimoto AC, Berry MJ (2018) Relationship between selenoprotein P and selenocysteine lyase: insights into selenium metabolism. Free Radic Biol Med 127:182–189
65. Zeng X, Zhang X, Fan B, Li Y, Jia X, Huang W, Liu J, Liu G (2019) Pharmacokinetics of sodium selenite in rat plasma and tissues after intragastric administration. Biol Trace Elem Res 119:494–501
66. Akahoshi N, Anan Y, Hashimoto Y, Tokoro N, Mizuno R, Hayashi S, Yamamoto S, Shimada K, Kamata S, Ishii I (2019) Dietary selenium deficiency or selenomethionine excess drastically alters organ selenium contents without altering the expression of most selenoproteins in mice. J Nutr Biochem 69:120–129
67. Ha HY, Alfulaij N, Berry MJ, Seale LA (2019) From selenium absorption to selenoprotein degradation. Biol Trace Elem Res 192:26–37
68. Lazard M, Dauplais M, Blanquet S, Plateau P (2015) Transsulfuration pathway seleno-amino acids are mediators of selenomethionine toxicity in Saccharomyces cerevisiae. J biol Chem 290(17):10741–10750
69. Brozmanová J, Mániková D, Vlčková V, Chovanec M (2010) Selenium: a double-edged sword for defense and offence in cancer. Arch Toxicol 84(12):919–938
70. Tobe R, Mihara H (2018) Delivery of selenium to selenophosphate synthetase for selenoprotein biosynthesis. Biochim Biophys Acta Gen Subj 1835 11:2433–2440
71. Takahashi K, Ogra Y (2020) Identification of the biliary selenium metabolite and the biological significance of selenium enterohepatic circulation. Metallomics 12:241–248
72. Kokarnig S, Tsirigotaki A, Wiesenhofer T, Lackner V, Francesconi KA, Pergantis SA, Kuehnelt D (2015) Concurrent quantitative HPLC–mass spectrometry profiling of small selenium species in human serum and urine after ingestion of selenium supplements. J Trace Elem Med Biol 29:83–90
73. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5):646–674
74. Silvestrini A, Mordente A, Martino G, Bruno C, Vergani E, Meucci E (2020) The role of selenium in oxidative stress and in nonthyroidal illness syndrome (NTIS): an overview. Curr Med Chem 27(3):423–449
75. Bănescu C, Iancu M, Trifa AP, Cândea M, Benedek-Lazar E, Moldovan VG, Dobreanu M (2016) From six gene polymorphisms of the antioxidant system, only GPX Pro198 Leu and GSTP1 Ile105Val modulate the risk of acute myeloid leukemia. Oxid Med Cell Longev 8:1–10
76. Choi JY, Neuhouser ML, Barnett M, Hudson M, Kristal AR, Thornquist M (2007) Polymorphisms in oxidative stress-related genes are not associated with prostate cancer risk in heavy smokers. Cancer Epidemiol Biomarkers Prev 16:1115–1120
77. Erdem O, Eken A, Akay C, Arsova-Sarafinovska Z, Matevska N, Suturkova L, Erten K, Özgök Y, Dimovski A, Sayal A, Aydin A (2012) Association of GPX1 polymorphism, GPX activity and prostate cancer risk. HET 31:24–31
78. Qian Q, Wang Q, Zhan P, Peng L, Wei SZ, Shi Y, Song Y (2010) The role of matrix metalloproteinase 2 on the survival of patients with non-small cell lung cancer: a systematic review with meta-analysis. Clin Cancer Investig J 28:661–669
79. Hiller E, Besselt K, Deubel S, Brigelius-Flohé R, Kipp AP (2015) GPx2 induction is mediated through STAT transcription factors during acute colitis. Inflamm Bowel Dis 21(9):2078–2089
80. Zhang X, Zheng Z, Yingji S, Kim H, Jin R, Renshu L, Lee DY, RohYang MR (2014) Downregulation of glutathione peroxidase 3 is associated with lymph node metastasis and prognosis in cervical cancer. Oncol Rep 31:2587–2592
81. Yu YP, Yu G, Tseng G (2007) Glutathione peroxidase 3, deleted or methylated in prostate cancer, suppresses prostate cancer growth and metastasis. Cancer Res 67:8043–8050
82. Saga Y, Ohwada M, Suzuki M (2008) Glutathione peroxidase 3 is a candidate mechanism of anticancer drug resistance of ovarian clear cell adenocarcinoma. Oncol Rep 20:1299–1303
83. Jia Y, Dai J, Zeng Z (2020) Potential relationship between the selenoproteome and cancer. Mol Oncol 13(6):83–89
84. Guerriero E, Capone F, Accardo M, Sorice A, Costantini M, Colonna G, Castello G, Costantini S (2015) GPX4 and GPX7 over-expression in human hepatocellular carcinoma tissues. Eur J Histochem 59:2535–2540
85. Zhang X, Sui S, Wang L, Li H, Zhang L, Xu S, Zheng X (2019) Inhibition of tumor propellant glutathione peroxidase 4 induces ferroptosis in cancer cells and enhances the anticancer effect of cisplatin. J Cell Physiol 235(4):3425–3437
86. Carlson BA, Yoo MH, Tobe R, Mueller C, Naranjo-Suarez S, Hoffmann VJ, Gladyshev VN, Hatfield DL (2012) Thioredoxin reductase 1 protects against chemically induced hepatocarcinogenesis via control of cellular redox homeostasis. Carcinogenesis 33:1806–1813
87. Varlamova EV, Cheremushkina IV (2016) Contribution of mammalian selenocysteine-containing proteins to carcinogenesis. J Trace Elem Med Biol 39:76–85
88. Hinrichsen S, Planer-Friedrich B (2016) Cytotoxic activity of selenosulfate versus selenite in tumor cells depends on cell line and presence of amino acids. Environ Sci Pollut Res 23(9):8349–8357
89. Arodin L, Wallenberg M, Jawad R, Danielsson O, Björnsted M (2019) The cell culture medium affects growth, phenotype expression, and the response to selenium cytotoxicity in A549 and HepG2 cells. Antioxidants 8(5):130
90. Wang Y, Fang W, Huang Y, Hu F, Wancai Y, Xiong B (2015) Reduction of selenium-binding protein 1 sensitizes cancer cells to selenite via elevating extracellular glutathione: a novel mechanism of cancer-specific cytotoxicity of selenite. Free Radic Biol Med 79:186–196
91. Řezáčová K, Čáňová K, Bezrouk A, Rudolf E (2016) Selenite induces DNA damage and specific mitochondrial degeneration in human bladder cancer cells. Toxicol In Vitro 32:105–114
92 Elhodaky M, Diamond AM (2018) Selenium-binding protein 1 in human health and disease. Int J Mol Sci 19(11):3437
93. Díaz N (2018) Design, synthesis and biological evaluation of novel methyl selenoesters as antiproliferative and cytotoxic agents. Tesis doctoral, Universidad de Navarra
94. Maiyo F, Singh M (2017) Selenium nanoparticles: potential in cancer gene and drug delivery. Nanomed J 12(9):1075–1089

95. Menon S, Ks SD, Santhiya R, Rajeshkumar S, Kumar V (2018) Selenium nanoparticles: a potent chemotherapeutic agent and an elucidation of its mechanism. Colloids Surf B 170:280–292
96. Zhao G, Wu X, Chen P, Zhang L, Yang CS, Zhang J (2018) Selenium nanoparticles are more efficient than sodium selenite in producing reactive oxygen species and hyper-accumulation of selenium nanoparticles in cancer cells generates potent therapeutic effects. Free Radic Biol Med 126:55–66
97. Sun L, Zhang J, Yang QSY, Liu Y, Wang Q, Han F, Huang Z (2017) Synergistic effects of SAM and selenium compounds on proliferation, migration and adhesion of HeLa cells. Anticancer Res 37:4433–4444
98. Ahsan A, Liu Z, Su R, Liu C, Liao X, Su M (2022) Potential chemotherapeutic effect of selenium for improved canceration of esophageal cancer. Int J Mol Sci. 23(10):5509
99. Marciel M, Khadka V, Deng Y, Kilicaslan P, Pham A, Bertino P (2018) Selenoprotein K deficiency inhibits melanoma by reducing calcium flux required for tumor growth and metastasis. Oncotarget 9(17):13407–13422
100. Li M, Cheng W, Nie T, Lai H, Hu X, Luo J, Li F, Li H (2018) Selenoprotein K mediates the proliferation, migration, and invasion of human choriocarcinoma cells by negatively regulating human chorionic gonadotropin expression via ERK, p38 MAPK, and Akt signaling pathway. Biol Trace Elem Res 184(1):47–59
101. Zhang S, Li F, Younes M, Liu H, Chen C, Yao Q (2013) Reduced selenium-binding protein 1 in breast cancer correlates with poor survival and resistance to the anti-proliferative effects of selenium. PLoS ONE 8(5):e63702
102. Elhodaky M, Hong LK, Kadkol S, Diamond AM (2020) Selenium-binding protein 1 alters energy metabolism in prostate cancer cells. Prostate 80(12):962–976
103. Sun S, Feng Y, Zhang Y, Ji H, Yu J, Liu A (2017) Antitumor and immunoregulatory activities of seleno-β-lactoglobulin on S180 tumor-bearing mice. Mol 23(1):46
104. Siddiqui WA, Ahad A, Ahsan H (2015) The mystery of BCL2 family: Bcl-2 proteins and apoptosis: an update. Arch Toxicol 89(3):289–317
105. Harmanci D, Erbayraktar Z, Sayin O, Guner GA (2017) In vitro effects of selenium on human glioblastoma multiforme cell lines: a preliminary study. Acta Clin Croat 56:48–57
106. Lobb R, Jacobson G, Cursons R, Jameson M (2018) The interaction of selenium with chemotherapy and radiation on normal and malignant human mononuclear blood cells. Int J Mol Sci 19(10):3167
107. Güzel KGU, Nazıroğlu M, Ceyhan D (2020) Bisphenol A-induced cell proliferation and mitochondrial oxidative stress are diminished via modulation of TRPV1 channel in estrogen positive breast cancer cell by selenium treatment. Biol Trace Elem Res 198:118–130
108. Ertilav K, Nazıroğlu M, Ataizi ZS, Braidy N (2019) Selenium enhances the apoptotic efficacy of docetaxel through activation of TRPM2 channel in DBTRG glioblastoma cells. Neurotox Res 35(4):797–808
109. Sakallı E, Nazıroğlu M, Çiğ B, Övey IS, Aslan-Koşar P (2016) Selenium potentiates the anticancer effect of cisplatin against oxidative stress and calcium ion signaling-induced intracellular toxicity in MCF-7 breast cancer cells: involvement of the TRPV1 channel. J Recept Signal Transduct Res 37(1):84–93
110. Zhao YY, Liu W, Wang D, Wu J, Shi Liu A (2018) Apoptosis and autophagy induction of Seleno-β-lactoglobulin (Se-β-Lg) on hepatocellular carcinoma cells lines. J Funct Foods 49:412–423
111. Xu X, Feng Y, Chen X, Wang Q, Meng T, Liu A (2019) Antitumor effects of seleno-β-lactoglobulin on human breast cancer MCF-7 and MDA-MB-231 cells in vitro. Toxicol In vitro 61:104607
112. Zhang ZY, Zhang H, Liu D, Wang Z, Deng T, Li Y, He Y, Zhong S (2021) A water-soluble selenium-enriched polysaccharide produced by *Pleurotus ostreatus*: purification, characterization, antioxidant and antitumor activities in vitro. Int J Biol Macromol 168:356–370
113. Sun N, Teng A, Zhao Y, Liu H, Tu J, Jia Q, Wang Q (2020) Immunological and anticancer activities of seleno-ovalbumin (Se-OVA) on H22-bearing mice. Int J Biol Macromol 163:657–665
114. Yuan C, Wang C, Wang J, Kumar V, Anwar F, Xiao F, Mushtaq G, Liu Y, Amjad K, Yuan D (2016) Inhibition on the growth of human MDA-MB-231 breast cancer cells *in vitro* and tumor growth in a mouse xenograft model by Se-containing polysaccharides from *Pyracantha fortuneana*. Nutr Res 36(11):1243–1254
115. Shashni B, Nishikawa Y, Nagasaki Y (2021) Management of tumor growth and angiogenesis in triple-negative breast cancer by using redox nanoparticles. Biomaterials 269:120645
116. Cai Z, Dong L, Song C, Zhang Y, Zhu C, Zhang Y, Li W (2017) Methylseleninic acid provided at nutritional selenium levels inhibits angiogenesis by down-regulating integrin β3 signaling. Sci Rep 7(1):1–13
117. Wadhwani SA, Shedbalkar UU, Singh R, Chopade BA (2016) Biogenic selenium nanoparticles: current status and future prospects. Appl Microbiol Biotechnol 100(6):2555–2566
118. Jiang Z, Chi J, Li H, Wang Y, Liu W, Han B (2020) Effect of chitosan oligosaccharide-conjugated selenium on improving immune function and blocking gastric cancer growth. Eur J Pharmacol 891:173673
119. Al-Otaibi AM, Al-Gebaly AS, Almeer R, Albasher G, Al-Qahtani WS, Abdel Moneim AE (2022) Potential of green-synthesized selenium nanoparticles using apigenin in human breast cancer MCF-7 cells. Environ Sci Pollut Res 1–10.
120. Mi XJ, Choi HS, Perumalsamy H, Shanmugam R, Thangavelu L, Balusamy SR, Kim YJ (2022) Biosynthesis and cytotoxic effect of silymarin-functionalized selenium nanoparticles induced autophagy mediated cellular apoptosis via downregulation of PI3K/Akt/mTOR pathway in gastric cancer. Phytomedicine 99:154014
121. Yazdi M, Mahdavi M, Kheradmand E, Shahverdi A (2012) The preventive oral supplementation of a selenium nanoparticle-enriched probiotic increases the immune response and lifespan of 4T1 breast cancer bearing mice. Arzneimittelforschung 62(11):525–531
122. Huang Y, He L, Liu W (2013) Selective cellular uptake and induction of apoptosis of cancer-targeted selenium nanoparticles. Biomaterials 34(29):7106–7116
123. Liu T, Zeng L, Jiang W, Fu Y, Zheng W, Chen T (2015) Rational design of cancer-targeted selenium nanoparticles to antagonize multidrug resistance in cancer cells. Nanomed J 11(4):947–958
124. Park SO, Yoo YB, Baek KJ, Yang J, Choi PC, Lee JH, Lee KR, Park KS (2015) Effects of combination therapy of docetaxel with selenium on the human breast cancer cell lines MDA-MB-231 and MCF-7. Ann Surg Treakt Res 88(2):55
125. Wu F, Cao W, Xu H, Zhu M, Wang J, Ke X (2017) Treatment with a selenium-platinum compound induced T-cell acute lymphoblastic leukemia/lymphoma cells apoptosis through the mitochondrial signaling pathway. Oncol Lett 13(3):1702–1710
126. Wu B, Ge J, Zixiong-Zhang Z, Huang C, Li X, Tan X, Fang X, Sun J (2019) Combination of sodium selenite and doxorubicin prodrug Ac-Phe-Lys-PABC-ADM affects gastric cancer cell apoptosis in xenografted mice. Biomed Res Int 2019:1–8
127. Guler Y, Ovey I-S (2020) Selenium enhances the TRPM2 mediated effect of paclitaxel on human breast cancer cells. Ann Med Res 27(4):1150–1156
128 Wei WQ, Abnet CC, Qiao YL, Dawsey SM, Dong ZW, Sun XD, Fan JH, Gunter EW, Taylor PR, Mark SD (2004) Prospective

study of serum selenium concentrations and esophageal and gastric cardia cancer, heart disease, stroke, and total death. Am J Clin Nutr 79:80–85
129. Nomura AM, Lee J, Stemmermann GN, Combs GF Jr (2000) Serum selenium and subsequent risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 9:883–887
130. Levander OA, Alfthan G, Arvilommi H, Gref CG, Huttunen JK, Kataja M, Koivistoinen P, Pikkarainen J (1983) Bioavailability of selenium to Finnish men as assessed by platelet glutathione peroxidise activity and other blood parameters. Am J Clin Nutr 37:887–897
131. Narod SA, Huzarski T, Jakubowska A (2019) Gronwald J, Cybulski C, Oszurek O, Debniak T, Jawoeska-Bieniek K, Lener M, Bialkowska K, Sukiennicki G, Muszynska M, Marcianiak W, Sun P, Kotsopoulos J, Lubinski J (2019) Serum selenium level and cancer risk: a nested case-control study. Hered Cancer Clin Pract 17:33
132. Duffi eld-Lillico AJ, Reid ME, Turnbull BW, Combs G, Slate E, Fischbach L, MArshall J, Clarck LC (2002) Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. Cancer Epidemiol Biomark Prev 11:630–639
133. Lippman SM, Klein EA, Goodman PJ et al (2009) Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the selenium and vitamin E Cancer Prevention Trial (SELECT). JAMA 301:39–51
134. Lim YW, Chen-Harris H, Mayba O, Lianoglou S, Wuster A, Bhangale T, Khan Z, Mariathasan S, Daemen A, Reeder J, Haverty P, Forrest W, Brauer M, Mellman I, Albert ML (2018) Germline genetic polymorphisms influence tumor gene expression and immune cell infiltration. Proc Natl Acad Sci 15(50):E11701–E11710
135. Deng N, Zhou H, Fan H, Yuan Y (2017) Single nucleotide polymorphisms and cancer susceptibility. Oncotarget 8(66):110635–110649
136. Méplan C (2017) Association of single nucleotide polymorphisms in selenoprotein genes with cancer risk. In: Chavatte L (eds) Selenoproteins. Methods Mol Biol 1661:313–324
137. Mao H, Cui R, Wang X (2015) Association analysis of selenoprotein S polymorphisms in chinese han with susceptibility to gastric cancer. Int J Clin Exp Med 8(7):10993–10999
138. Li J, Zhu Y, Zhou Y, Jiang H, Chen Z, Lu B (2020) The SELS rs34713741 Polymorphism is associated with susceptibility to colorectal cancer and gastric cancer: a meta-analysis. Genet Test Mol Biomarkers 24(12):835–844
139. Amini G, Salehi R, Asghar A, Kazemi M, Khosravi S (2019) Evaluation of SEPP1 and selenoprotein S gene polymorphisms (rs7579 and rs34713741) in relation to colorectal cancer susceptibility in subset of Iranian population: a case–control study. Adv Biomed 8:47
140. Mohammaddoust S, Salehi Z, Saedi H (2017) SEPP1 and SEP15 gene polymorphisms and susceptibility to breast cancer. Br J Biomed Sci 75(1):36–39
141. Méplan C, Crosley LK, Nicol F, Beckett GJ, Howie AF, Hill KE, Horgan G, Mathers JC, Arthur JR, Hesketh JE (2007) Genetic polymorphisms in the human selenoprotein P gene determine the response of selenoprotein markers to selenium supplementation in a gender-specific manner (the SELGEN study). FASEB J 21:3063–3074
142. Mao J, Vanderlelie JJ, Perkins AV, Redman CWG, Ahmadi KR, Rayman MP (2016) Genetic polymorphisms that affect selenium status and response to selenium supplementation in United Kingdom pregnant women. Am J Clin Nutr 103(1):100–106
143. Fedirko V, Jenab M, Méplan C, Jones JS, Zhu W, Schomburg L, Siddiq A, Hybsier S, Overvad K (2019) Association of selenoprotein and selenium pathway genotypes with risk of colorectal cancer and interaction with selenium status. Nutrients 11(4):935
144. Hrdina J, Banning A, Kipp A, Loh G, Blaut M, Brigelius-Flohé R (2009) The gastrointestinal microbiota affects the selenium status and selenoprotein expression in mice. J Nutr Biochem 20(8):638–648
145. Callejón-Leblic B, Selma-Royo M, Collado MC, Abril N, García-Barrera T (2021) Impact of antibiotic-induced depletion of gut microbiota and selenium supplementation on plasma selenoproteome and metal homeostasis in a mice model. J Agric Food Chem. 69(27):7652–7662
146. Zhai Q, Cen S, Li P, Tian F, Zhao J, Zhang H, Chen W (2018) Effects of dietary selenium supplementation on intestinal barrier and immune responses associated with its modulation of gut microbiota. Environ Sci Technol Lett. 5(12):724–30
147. Ferreira RLU, Sena-Evangelista KCM, De Azevedo EP, Pinheiro FI, Cobucci RN, Pedrosa LFC (2021) Selenium in human health and gut microflora: bioavailability of selenocompounds and relationship with diseases. Front Nutr 4(8):685317
148. Porto BAA, Monteiro CF, Souza ELS, Leocádio PCL, Alvarez-Leite JI, Genoroso SV, Cardoso VN, Almeida-Leite CM, Santos DA, Santos JRA (2019) Treatment with selenium-enriched Saccharomyces cerevisiae UFMG A-905 partially ameliorates mucositis induced by 5-fluorouracil in mice. Cancer Chemother Pharmacol 84(1):117–126
149. Yazdi MH, Mahdavi M, Setayesh N, Esfandyar M, Shahverdi AR (2013) Selenium nanoparticle-enriched Lactobacillus brevis causes more efficient immune responses in vivo and reduces the liver metastasis in metastatic form of mouse breast cancer. DARU J Pharm Sci 21(1):33–39