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

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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

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$_3$SeH), 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$_2$SeO$_4$), sodium selenite (Na$_2$SeO$_3$), selenide (Se^{-2}), diselenides (Se$_2$$^{-2}$), and selenocyanate (SeCN-). Organic forms include selenoesters (Se-(C = O)-OH), ethaselen ((1,2-[bis(1,2-benzisoselenazolone-3(2H)-ketone)]-ethane (1,2-BBSKE), methyl selenium (CH$_3$Se$^-$), 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].
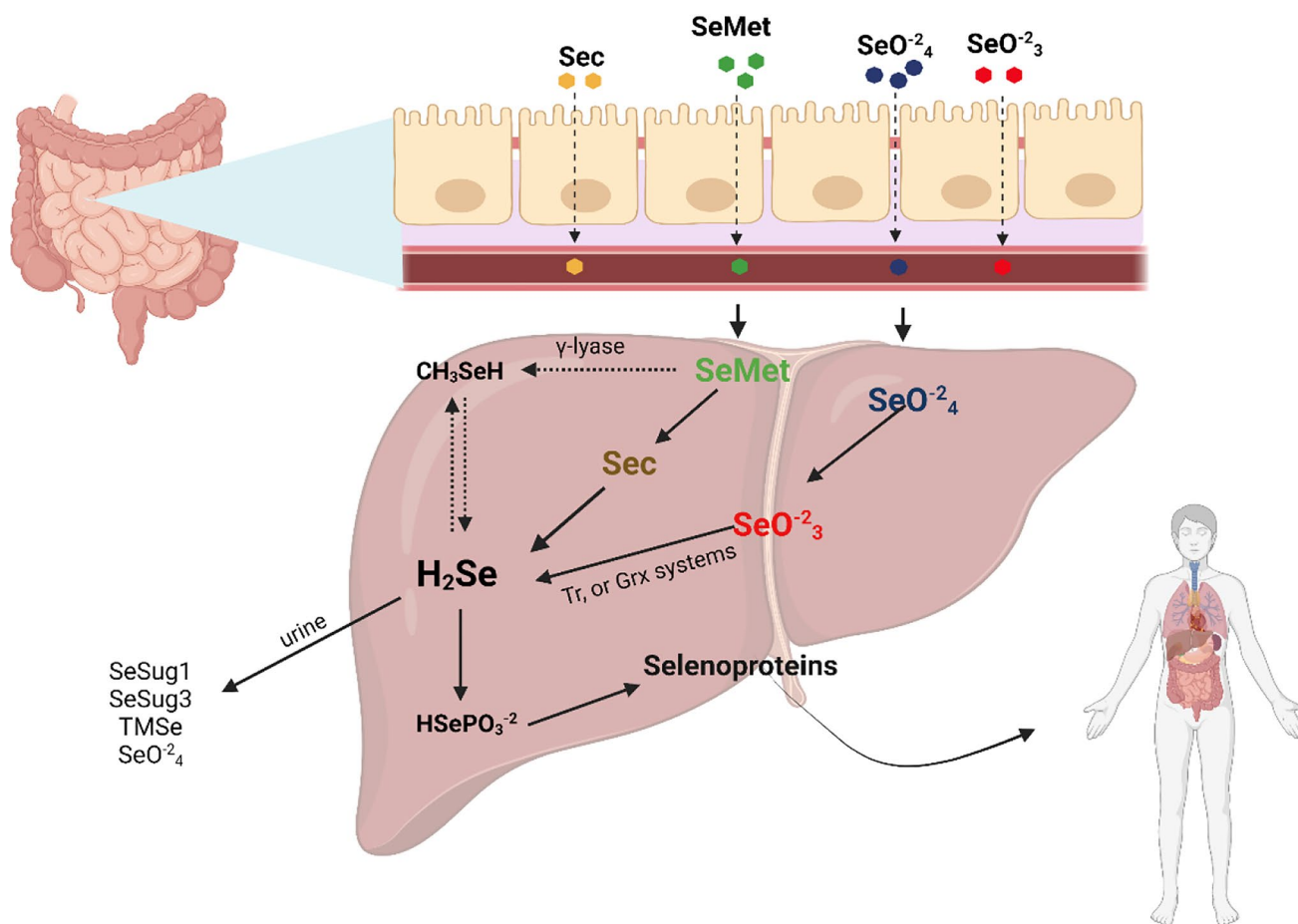
Fig. 1 ADME process of selenocompounds. Selenocompounds such as SeO2-3, SeO2-4, Sec, and SeMet are absorbed via the intestinal lumen, where they go directly to the blood vessels, which later are metabolized by the liver. Briefly, SeMet is generally converted to proteins and Sec, which can also be metabolized 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 selenocompounds 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
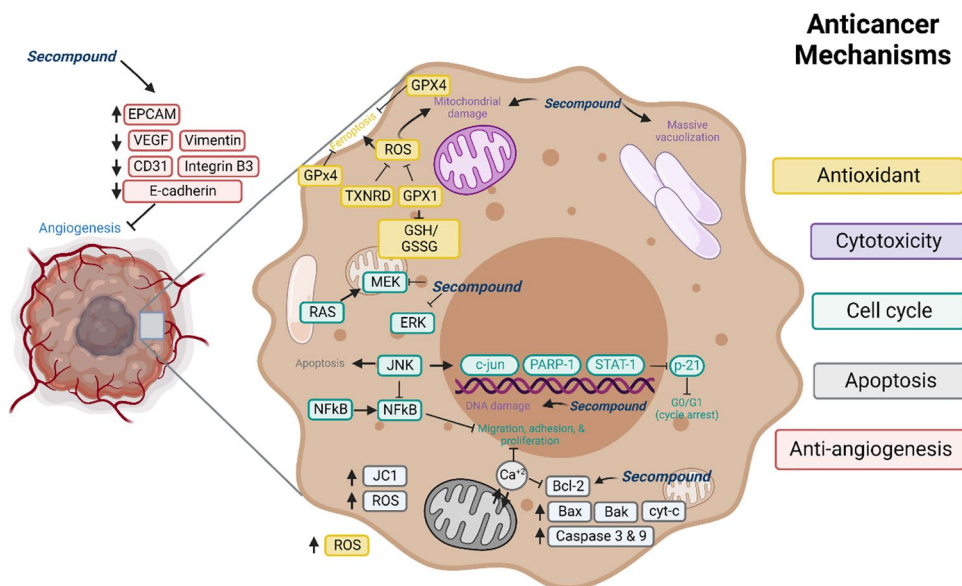
Antioxidant Mechanisms

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_3^{2-} 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_3^{2-}, 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_3^{2-} whereas for A375 cells were 6.6 μM for O_3SSe^{-2} and 4.7 μM for SeO_3^{2-}. 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_3^{2-}. These results showed that cytotoxicity effects could depend both on the chemical form of Se and the type of cells [88].

In addition, SeO_3^{2-} cytotoxicity was studied by Řezáčová et al. [91] in human bladder cancer cells (RT-112) with concentrations ranging from 0 to 100 μM SeO_3^{2-} at 24, 48, and 72 h of incubation. The cytotoxic effect of SeO_3^{2-} 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), Se-Met (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 selenocompounds 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 mm³, 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.

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].

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,

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 down-regulating 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$_2$SeO$_3$ 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.

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.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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