



# Toxicology and pharmacology of synthetic organoselenium compounds: an update

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## Abstract

Here, we addressed the pharmacology and toxicology of synthetic organoselenium compounds and some naturally occurring organoselenium amino acids. The use of selenium as a tool in organic synthesis and as a pharmacological agent goes back to the middle of the nineteenth and the beginning of the twentieth centuries. The rediscovery of ebselen and its investigation in clinical trials have motivated the search for new organoselenium molecules with pharmacological properties. Although ebselen and diselenides have some overlapping pharmacological properties, their molecular targets are not identical. However, they have similar anti-inflammatory and antioxidant activities, possibly, via activation of transcription factors, regulating the expression of antioxidant genes. In short, our knowledge about the pharmacological properties of simple organoselenium compounds is still elusive. However, contrary to our early expectations that they could imitate selenoproteins, organoselenium compounds seem to have non-specific modulatory activation of antioxidant pathways and specific inhibitory effects in some thiol-containing proteins. The thiol-oxidizing properties of organoselenium compounds are considered the molecular basis of their chronic toxicity; however, the acute use of organoselenium compounds as inhibitors of specific thiol-containing enzymes can be of therapeutic significance. In summary, the outcomes of the clinical trials of ebselen as a mimetic of lithium or as an inhibitor of SARS-CoV-2 proteases will be important to the field of organoselenium synthesis. The development of computational techniques that could predict rational modifications in the structure of organoselenium compounds to increase their specificity is required to construct a library of thiol-modifying agents with selectivity toward specific target proteins.

**Keywords** Ebselen · Selenium · Diselenides · Toxicology · Pharmacology · Thiol

## Introduction

In this review, we shall cover toxicological and pharmacological effects, in which organoselenium compounds are involved, but the effects of inorganic compounds will not be addressed here. The review mostly discusses recent literature, starting from 2011 until the end of 2020; however, some earlier studies are cited when needed. Method data for this review were sourced from online Web of Science database. The deadline for data search was August 2020; no

data were excluded based on language or publication origin. Since, it is not possible to cite all of the findings that have taken place, we apologize to those whose work has been omitted.

The chemical structures of representative organoselenium compounds which will be discussed in this review are shown in Scheme 1.

## A brief history of selenium: an element with two faces

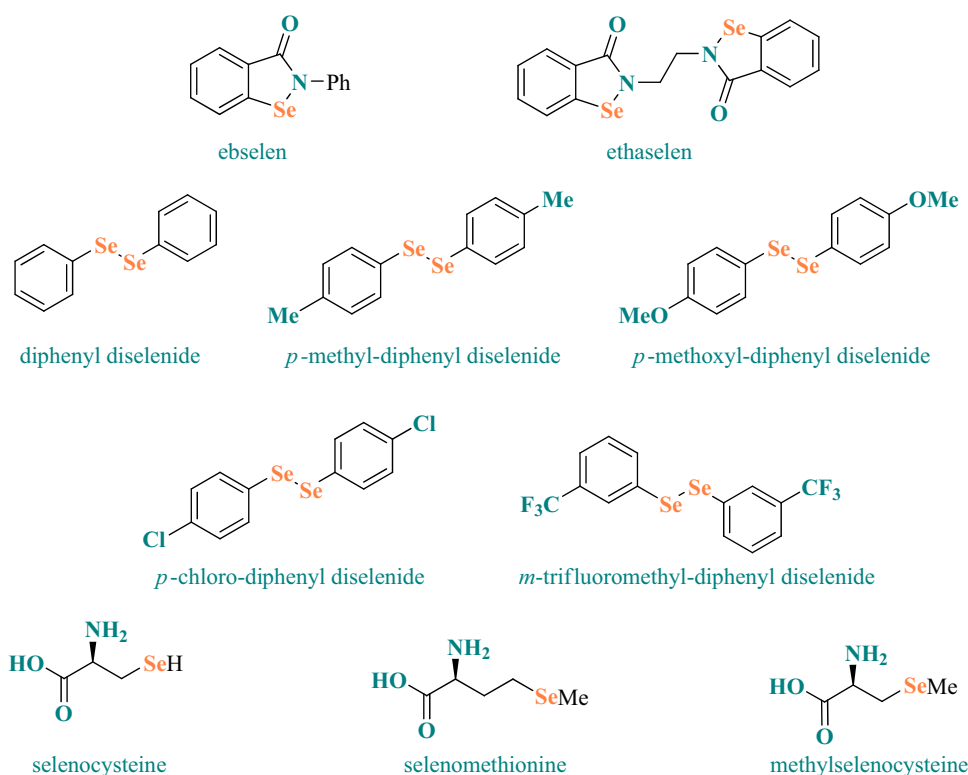
Since its discovery about 200 years ago, selenium has been attracting the interest of chemists and biologists. Soon after its isolation by Jacobs Berzelius, in 1817, selenium was used in organic synthesis and investigated as a potentially toxic or beneficial agent both in animals (including humans) and plants (Levine 1915, 1925; Martin 1936; Rocha et al. 2017; Smith 1941; Weil 1915). One of the first therapeutic uses of selenium was in the treatment of cancer and reports about

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**Scheme 1** Chemical structures of representative organoselenium compounds discussed in this review



the beneficial effects of elemental selenium in the treatment of inoperable carcinoma can be found in clinical studies published at the beginning of the twentieth century (Freeman 1922; Watson-Williams 1919; Weil 1915). In sharp contrast, the lethal effect of a single injection of selenite in one human patient with cancer can also be found in the literature, cited in Weil (1915). Subsequently, selenium was rarely used in cancer treatment in humans, possibly because its effectiveness in clinical studies was inconsistent (Weil 1915). In addition, the toxicity of selenium became notorious in farm and experimental animals exposed to high levels of the element (Levine 1915, 1925; Painter 1941; Smith 1941). In short, the early history of the element selenium in biology has been marked by the contrast between its toxic and beneficial effects.

The importance of selenium to mammals started to be defined in 1957 when Schwartz and Foltz demonstrated that selenite and selenate could prevent liver necrosis caused by feeding a vitamin E-deficient diet to rats. Though the classical paper of Schwartz and Foltz did not establish dietary essentiality to selenium in rats, it gave the first demonstration that selenium could mitigate the deficiency of an essential vitamin (Schwarz and Foltz 1957). The explanation on how vitamin E and selenium have partial overlapping nutritional and biochemical protective effects in mammals was deciphered only in 1985, when the phospholipid hydroperoxide glutathione peroxidase (GPx4) was characterized as a selenium enzyme (Ursini et al. 1985). GPx4 is involved in

the degradation of phospholipid hydroperoxides in biomembranes of mammalian cells, and consequently, it protects cell membranes from lipid peroxidation up-stream to vitamin E. Vitamin E scavenges phospholipid hydroperoxyl radicals directly, whereas GPx4 decreases the concentration of phospholipid peroxides that can generate the reactive peroxyl radicals. It is noteworthy that the selenium atom of the selenol ( $-SeH$ ) group of GPx4 interacts directly with lipid peroxides in biomembranes, whereas vitamin E interacts with lipid peroxide radicals.

The first discovered biochemical role of selenium was its presence as an integral part of the enzyme glutathione peroxidase (Flohe et al. 1973; Rotruck et al. 1973). The accurate molecular role played by selenium in mammalian cell biochemistry was elucidated in 1978, when the chemical nature of selenium, in the active site of rat liver glutathione peroxidase, was deciphered (Forstrom et al. 1978). The studies of Cone with bacteria (Cone et al. 1976) and Forstrom with rodents (Forstrom et al. 1978) introduced in the chemistry of life a new amino acid and a new functional group: the selenocysteine and the selenol group. They are analogs of the amino acid cysteine and its functional thiol group. The essentiality of selenocysteine and its selenol group in the biochemistry and physiology of mammalian cells will be presented in the next section: selenium physiology: selenium as a component of selenoproteins.

Adequate selenium intake has also been indicated to be critical to proper immune function and decrease the risk of

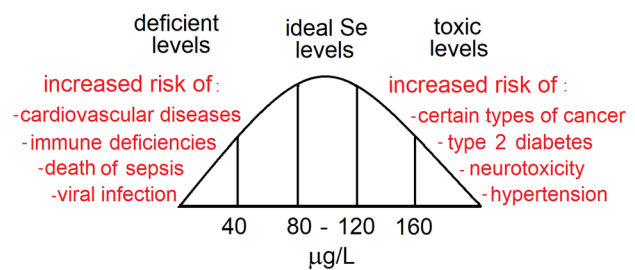
cardiovascular diseases (Avery and Hoffmann 2018; Huang et al. 2012; Kuria et al. 2020; Qian et al. 2019; Rayman 2012). Furthermore, beneficial effects of appropriate blood selenium levels as a factor against virus infections (particularly HIV and, more, recently against SARS-CoV-2) and sepsis severity have also frequently appeared in the literature (Aggarwal et al. 2016; Alhazzani et al. 2013; Guillin et al. 2019; Heller et al. 2020; Mertens et al. 2015; Moghaddam et al. 2020; Rayman 2012; Zhang et al. 2020b, c). However, negative and contradictory results can also be found in the literature (Bloos et al. 2016; Kamwesiga et al. 2015; Shivakoti et al. 2014; Stone et al. 2010). However, it is still elusive if selenium has specific direct role in such complex physiological, immunological, and pathological responses or if selenoproteins modulate indirectly the inflammatory and other responses by modulating the redox state of the body.

The influence of selenium supplementation as a potential anticarcinogenic agent was studied in a large epidemiological study in USA. The SELECT study compared the supplementation of selenium (as selenomethionine) and vitamin E in the incidence of prostate cancer. However, the study was interrupted before planned, because the data, contrary to the expectation, have not indicated potential beneficial effects of selenium or vitamin E. Despite the negative outcomes of SELECT (Dunn et al. 2010; Klein et al. 2011; Lippman et al. 2009; Nicastro and Dunn 2013), the potential use of selenium in cancer prevention or treatment is still a matter of debate (Chapelle et al. 2020; Vinceti et al. 2018). Several experimental studies have indicated the potential anti-cancer properties of inorganic and organic forms of selenium (Álvarez-Pérez et al. 2018; Gandin et al. 2018; Gopalakrishna et al. 2018; Krasowska et al. 2019; Ruberte et al. 2019; Sanmartín et al. 2012; Sharma and Amin 2013; Spengler et al. 2019; Steinbrenner et al. 2013; Tan et al. 2019). Some clinical studies have also demonstrated that selenite can have beneficial effects by itself or decrease some toxic effects of radiotherapy in cancer patients (Brodin et al. 2015; Han et al. 2019; Handa et al. 2020; Knox et al. 2019; Muecke et al. 2014). More recently, ethaselen (a derivative of ebselen) was described to have pharmacological effects against lung cancer cell lines and is now recruiting patients for clinical trials for lung cancer treatment (Tan et al. 2019; Zheng et al. 2017b).

The supranutritional intake of selenium has been linked with increased risk of developing type 2 diabetes, advanced prostate cancer, hypertension, dyslipidemia, and neurodegenerative diseases (amyotrophic lateral sclerosis (ALS), early onset dementia, and Parkinson Disease) (Adani et al. 2020a, b; Bastola et al. 2020; Loomba et al. 2020; Vinceti et al. 2018, 2019a, b; Wu et al. 2018; Yarmolinsky et al. 2018). In accordance with epidemiological studies, the intake of supranutritional levels of selenium, which were associated with an overexpression of two selenoenzymes

[glutathione peroxidase 1 (GPx1) and methionine sulfoxide reductase (MsrB1)] has been shown to cause hyperinsulinemia and insulin resistance in mice (Labunskyy et al. 2011). The detrimental effects of selenium in glucose homeostasis have been attributed to deregulation of cell redox balance (reductive stress). In contrast, the insufficient synthesis of selenoproteins by overexpressing a mutant selenocysteine t-RNA caused glucose intolerance and diabetes-like phenotype in mice (Labunskyy et al. 2011).

Concerning ALS, it seems that the speciation of selenium (e.g., selenite or selenate vs organic forms) can determine the neurotoxicity of selenium in humans (Vinceti et al. 2019b). Accordingly, Vinceti and collaborators have recently demonstrated that the speciation of selenium in the cerebrospinal fluid of patients with mild cognitive deficits predicted the risk of progression to Alzheimer's disease, with selenate ( $\text{Se}^{+6}$ ) increasing the risk significantly (Vinceti et al. 2017). Thus, in relation to cancer and other degenerative diseases, the role of selenium seems to have a U inverted shape curve with a relatively narrow range of selenium for the optimum physiological effects (Fig. 1). Another point that is highly critical and little explored is the speciation of selenium as a



**Fig. 1** U inverted shaped curve for selenium levels in humans. Low selenium status can increase the risk of immunological malfunctioning, cardiovascular diseases, sepsis severity, virus infection, and cognitive deficits. High levels of blood selenium can be associated with an increased risk of developing certain types of cancer (e.g., melanoma and prostate cancer), hypertension, type 2 diabetes, and neurodegenerative diseases (e.g., ALS and Alzheimer's Dementia). In the figure, the ideal levels of selenium were arbitrarily based on the optimal blood activity of glutathione peroxidase (see below). Selenium plays important physiological functions as a part of 25 selenoproteins in humans. At least one half of them are important oxidoreductases (e.g., 5 glutathione peroxidases (GPxs1-4 and 6); 3 thioredoxin reductases (TrxRs), which are involved in the regeneration of reduced thioredoxin (Trx); methionine sulfoxide reductase, which reduces oxidized methionine sulfoxide to methionine in proteins, 3 deiodinases (DIOs) that are involved in the metabolism of thyroid hormones (T3 and T4); selenophosphate synthetase and several selenoproteins without a clear-defined molecular role in cell physiology). The ideal physiological levels of selenium are not known, but for the blood GPx maximal activity, a level of selenium around  $100 \mu\text{g L}^{-1}$  is required (Rea et al. 1979; Thomson et al. 1977, 1982). However, how blood GPx activity can predict the whole-body selenoproteins adequate physiological activity is unknown. There is also epidemiological evidence, suggesting that above  $120 \mu\text{g L}^{-1}$ , selenium can start to facilitate the installation of pathological conditions (Bastola et al. 2020)

determinant of its toxic effects. Of particular toxicological importance, recent data have indicated that high levels of cationic selenium (e.g., selenate) in the cerebrospinal fluid of patients with mild cognitive impairment increases the risk of conversion from mild cognitive impairment to Alzheimer's Disease (Vinceti et al. 2017).

In this review, we will emphasize the potential pharmacology and toxicology of synthetic organoselenium compounds and some naturally occurring organoselenium amino acids (e.g., selenomethionine). The use of selenium as an important tool in organic synthesis and as a pharmacological agent goes back to the middle of the nineteenth and the beginning of the twentieth centuries. Notably, the rediscovery of ebselen (which was originally synthesized in 1924) and its investigation in several clinical trials in different types of human pathologies have motivated the search for new selenium-containing molecules with pharmacological properties (Masaki et al. 2016a; Ogawa et al. 1999; Saito et al. 1998; Singh et al. 2016; Yamaguchi et al. 1998). One point that has further stimulated the search for novel organoselenium compounds is the successive failures of ebselen or its low effectiveness as therapeutic agent (Beckman et al. 2016; Kil et al. 2017; Masaki et al. 2016a; Ogawa et al. 1999; Saito et al. 1998; Yamaguchi et al. 1998).

However, here, we have to emphasize that ebselen is still under clinical trials to treat bipolar disorder (Sharpley et al. 2020a) and has been registered for two clinical trials with moderate and severe COVID-19 patients (Haritha et al. 2020). Besides, ethaselen, an ebselen derivative, is in the recruiting phase of a clinical trial to treat lung cancer. The compound has been effective in a pre-clinical trial in human non-small cell lung cancer models (Ye et al. 2017; Zheng et al. 2017b, 2019b). In short, though ebselen has not been approved to treat a specific disease, its safety in humans has been an indication that organoselenium compounds can be promising therapeutic agents.

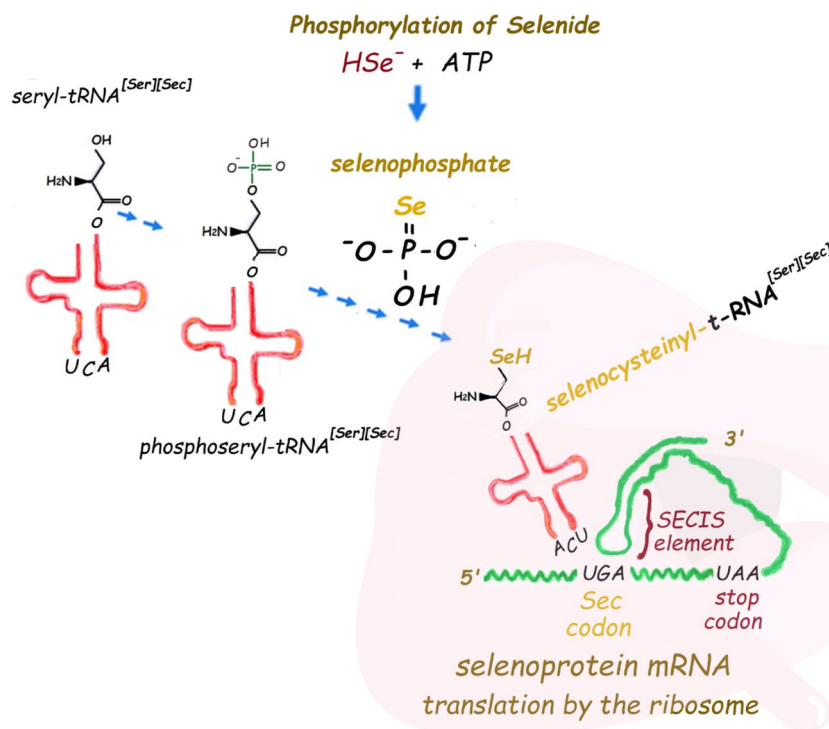
### Physiological chemistry of selenium: selenium as component of selenoproteins

The physiological chemistry of selenium in animals is played almost exclusively by the selenocysteinyl residue(s) found in a few types of selenoproteins. Selenocysteine is an analogue of cysteine and serine. The human genome codifies 25 selenoproteins that have usually only one residue of selenocysteine (Sec); the exception is the selenoprotein P that has near 10 s residues (for a brief description of selenoproteins function, see the legend of Fig. 1). The incorporation of selenium into the seryl-carbon skeleton is complex and occurs at the level of the transfer RNA (t-RNA[Ser]Sec) (in a process named co-translational incorporation of Sec in its t-RNA and then in the selenoproteins) (for reviews, see Hatfield et al. 2014; Labunskyy et al. 2014). This t-RNA[Ser]

Sec is first loaded with a seryl residue by the action of a seryl t-RNA synthetase and metabolized to phosphoseryl-t-RNA[Ser]Sec by the enzyme seryl-t-RNA[Ser][Sec] kinase (PSTK). Then, selenophosphate donates, via the reaction catalyzed by the enzyme selenocysteine synthase (SepSecS), the selenium atom to form the selenol group in the place of the phosphorylated OH group of serine (Fig. 2). The incorporation of the selenium atom in an organic moiety requires four enzymatic steps, including the binding of serine to the t-RNA[Ser]Sec, the phosphorylation of loaded seryl residue, the synthesis of selenophosphate by the reaction of HSe- (selenide) with ATP (a reaction catalyzed by the selenoenzyme selenophosphate synthetase), and the incorporation of selenophosphate in the place of the phosphorylated OH group of serine. For details about the incorporation of selenium in the serine skeleton, see the reviews (Hatfield et al. 2014; Labunskyy et al. 2014; Serrão et al. 2018).

The entire process requires several steps, protein factors, e.g., the Sec-t-RNA[Ser]Sec dedicated translation elongation factor (EFSec), SECIS-binding protein 2 (SBP2 or SECISBP2), ribosomal protein eL30, translation initiation factor 4A3 (eIF4A3), nucleolin, Secp43 or t-RNA selenocysteine 1-associated protein 1 (TRNAUIAP) and SepSecS, the specific RNA sequences (the selenocysteine insertion sequence or SECIS elements), and the t-RNA[Ser]Sec. The machinery utilized in the synthesis of selenoproteins interprets the stop codon UGA as selenocysteine only when it is present within the RNA sequences of the selenoproteins. The key players here are the SECIS elements, which in vertebrates are non-coding RNA regions adjacent to the selenoprotein sequence, and selenocysteine-t-RNA (Bulteau and Chavatte 2015; Howard and Copeland 2019; Serrão et al. 2018; Simonović and Puppala 2018).

As briefly commented in the previous paragraph, the existence of these SECIS elements forming a stem-loop-stem-loop structure with near 100 nucleotides in the 3'-untranslated region of human 25 selenoprotein mRNAs is indispensable for the proper insertion of Sec in the selenoproteins. In fact, the stem-loop-stem-loop forming the SECIS bends or kinks itself toward the UGA codon inside the selenoprotein sequence and, inside of the ribosome, SECIS interacts with the t-RNA loaded with Sec and with protein factors described just above, allowing the release of the transporter and the incorporation of selenocysteine in the nascent polypeptide. For reviews about the molecular players in the noncanonical incorporation of Sec at UGA codon in selenoproteins (i.e., about the recoding of UGA), see (Bulteau and Chavatte 2015; Howard and Copeland 2019; Simonović and Puppala 2018). The selenocysteinyl residue, specifically its selenol group, is the softest of the nucleophile centers found in biomolecules. Accordingly, several selenoproteins are oxidoreductases enzymes, where the -SeH (-Se<sup>-</sup>) of the selenocysteine participates in the catalysis.



**Fig. 2** Incorporation of selenide in the phosphoseryl-t-RNA[Ser]Sec and synthesis of selenocysteinyl-t-RNA[Ser]Sec after the reaction of selenophosphate with the phosphorylated hydroxyl group of serine-loaded t-RNA[Ser]Sec. Selenocysteine is released from the t-RNA when the ribosome reads the UGA codon inside the mRNA sequence of a selenoprotein. The recoding of UGA codon to selenocysteine depends on the SECIS elements (which in mammals is a non-cod-

ing mRNA forming a stem-loop structure that kinks to interact with the t-RNA). The translation of the in-frame UGA codons inside the genes of selenoproteins also requires several protein factors that are not indicated in the figure (for more details, consult the text or the reviews Bulteau and Chavatte 2015; Howard and Copeland 2019; Simonović and Puppala 2018)

The well-characterized selenoproteins include glutathione peroxidase isoforms (e.g., GPx1 and GPx4); thioredoxin reductase isoforms (TrxR1, TrxR2, TrxR3), iodothyronine deiodinases (DIO1, DIO2, and DIO3), methionine sulfoxide reductase B (MsrB), selenophosphate synthetase, and selenoprotein P. There are a group of endoplasmic reticulum-resident selenoproteins which the molecular roles are still elusive (Pitts and Hoffmann 2018; Addinsall et al. 2018; Gennadyevna 2020; Pitts and Hoffmann 2018). In addition to DIO2, selenoproteins K, M, N, S, T, and selenoprotein 15 kDa are found in the endoplasmic reticulum, where they appear to be involved in the regulation of  $Ca^{2+}$  levels, protein folding, inflammatory processes, and oxidative stress (Addinsall et al. 2018; Gennadyevna 2020; Pitts and Hoffmann 2018; Pothion et al. 2020; Shchedrina et al. 2010).

As commented above, the physiological chemistry of selenium seems to be played almost exclusively by the  $-SeH$  group of selenoproteins. Recently, it was demonstrated that selenocysteine can be incorporated in the uncoupling protein (UCP1) in the place of cysteine (Jedrychowski et al. 2020). The process is not a random incorporation of selenocysteine, but occurs in a specific cysteinyl residue (Cys253).

The incorporation of selenocysteine is expected to occur via its t-RNA[Ser][Sec], because selenocysteine does not exist as a free amino acid in the presence of oxygen and water. However, the reasons why a cysteine codon can interact with the t-RNA[Ser][Sec] are unknown. Despite this, the data published by Jedrychowski and collaborators may open a new role for selenium as a modulator of the cysteine physiological function, via specific incorporation of selenocysteine in the place of specific cysteinyl residue in a small portion of synthesized thiol-containing proteins (for instance, for replacement of Cys 253 in UCP1, about 1.5% of this position was loaded with Sec) (Jedrychowski et al. 2020).

## Toxicity of organoselenium compounds

### Interaction of selenium with thiols

Herein, we will emphasize the biochemistry of interaction of organoselenium compounds with thiols from molecules of biological significance and their implications, without highlighting the pathophysiological processes associated

with high levels of selenium. Among the organoselenium compounds, we will address primarily selenides and diselenides, such as ebselen, diphenyl diselenide, and some derivatives of them.

The molecular mechanisms involved in selenium toxicity are not completely elucidated; however, the interaction of inorganic and organic selenium with low- and high-molecular-weight thiols plays a central role in their toxicity. This evidence was first reported to inorganic forms, in which classical experiments showed the effectiveness of selenite in oxidizing sulfhydryl groups, producing disulfides and an unstable intermediary containing  $-S-Se-S-$  bonds (Ganther 1968; Painter 1941; Tsen and Tappel 1958). Afterward, studies demonstrated that the oxidation of thiols, such as glutathione (GSH) and cysteine, by selenite produced the radical superoxide (Seko et al. 1989; Spallholz 1994). To date, the oxidation of thiols has also been the basis to explain the toxicity of a variety of organoselenium compounds (Barbosa et al. 2017; Nogueira and Rocha 2011; Prigol et al. 2012) and mounting evidence has pointed out that reactive species (RS) formation contributes for the toxicity of many compounds (Nogueira and Rocha 2011; Prigol et al. 2012). In effect, the occurrence of oxidative stress and related phenomena has been highlighted in numerous *in vitro* and *in vivo* studies with organoselenium compounds. Interestingly, the increased production of RS accompanied by cell viability loss, DNA damage, and apoptosis are considered important pro-oxidant effects elicited by some organoselenium compounds against cancer cells, virus, and fungal pathogens (Álvarez-Pérez et al. 2018; Chen et al. 2020; Sies and Parnham 2020; Thangamani et al. 2017). It is important to mention here that the thiol oxidation may also subsidize the antioxidant effects of some selenium compounds via activation of antioxidant gene expression.

Therefore, the systematic study of oxidation of sulfhydryl groups from biological thiol-containing molecules by organoselenium compounds has facilitated the identification of potential “molecular targets” that might support both selenium pro-oxidative and antioxidant effects. In this context, we will cite here some *in vitro* and *in silico* (computational) studies toward specific interactions of some organoselenium compounds with proteins containing vicinal thiol groups, which are more efficiently oxidized than monothiol molecules.

### In vitro molecular toxicity of organoselenium compounds

Although the molecular mechanisms involved in toxicity of organoselenium compounds are still not completely understood, the interaction with thiols is pointed out as a key phenomenon. Similar to inorganic selenium molecules, the interaction of the sulfur atom from thiols with the selenium

atom from organoselenium compounds ( $S^{IV}Se$ ) can lead to the formation of a selenenyl–sulfide bond ( $S-Se$ ), an adduct able to impair the activity of sulfhydryl enzymes. In fact, the toxic effects of several selenides and diselenides have been related to their potential in disrupting the activity of thiol-containing enzymes via oxidation of cysteinyl residues (Barbosa et al. 1998; Chaudiere et al. 1992; Galant et al. 2017, 2020; Nogueira and Rocha 2011; Quispe et al. 2019; Yu et al. 2017).

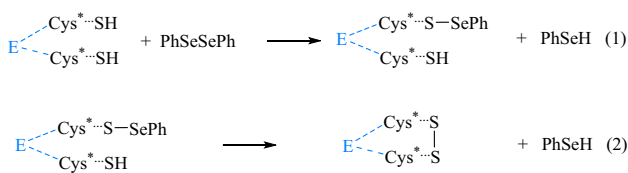
Focusing on diphenyl diselenide and its derivatives, the more precise findings include mainly those toward the enzyme  $\delta$ -aminolevulinic acid dehydratase ( $\delta$ -ALA-D).  $\delta$ -ALA-D catalyzes the condensation of two molecules of 5-aminolevulinic acid to porphobilinogen, a monopyrrole precursor of prosthetic group heme, and due to its sulfhydryl nature, it has been commonly used in toxicological researches as an indicator of toxicity caused by pro-oxidant agents (Chaudiere et al. 1992; Ecker et al. 2018; Klimaczewski et al. 2018; Rocha et al. 2012c).

The active site of  $\delta$ -ALA-D possesses three cysteine residues coordinated with  $Zn^{2+}$ , which prevent the formation of disulfide bridges between the sulfhydryl groups. The proximity of the cysteine groups in the active site renders to enzyme a high sensitivity to oxidation (Nogara et al. 2020; Rocha et al. 2012c; Saraiva et al. 2012).

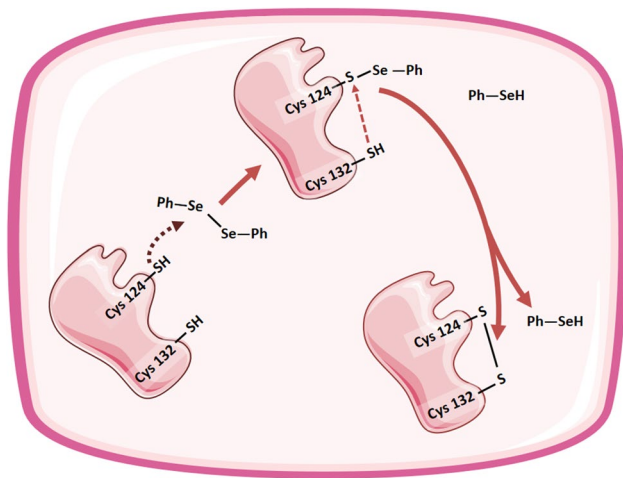
The first studies demonstrating the diphenyl diselenide potential inhibitory on  $\delta$ -ALAD were carried out comparing the animal and plant enzymes (Barbosa et al. 1998; Farina et al. 2002). These findings revealed that diphenyl diselenide inhibited the activity from the animal enzyme, but not from the plant, in which the active site has aspartic acid instead of cysteine residues and the metal  $Mg^{2+}$  in the place of  $Zn^{2+}$ . Since that, various other diphenyl diselenide derivatives were reported as inhibitors of the enzyme from different sources, as well (Nogueira and Rocha 2011; Nogueira et al. 2004; Rocha et al. 2012a, b, c).

In general, the mechanism by which diphenyl diselenide and its derivatives inhibit the  $\delta$ -ALA-D activity involves two steps of cysteine oxidation: (1) the first oxidation involves the attack of the selenium atom from diphenyl diselenide by the most reactive cysteinyl residue to yield the intermediate ( $E-S-SePh$ ); and (2) the attack of the second more nucleophilic cysteinyl residue to the  $S-Se-$  bond of the intermediate ( $E-S-SePh$ ), generating the oxidized enzyme ( $E-(S-S)$ ) and two molecules of selenol ( $PhSeH$ ) (Scheme 2) (Rocha et al. 2012c; Saraiva et al. 2012).

By docking analyses, the cysteine 124 residue from the active site of the enzyme was identified as the nucleophilic center that initiates the attack on the  $Se-Se$  bond from diselenides, forming an  $E-S-SePh$  as intermediate. The vicinal cysteine 132 residue was identified as responsible for the subsequent attack to the  $S-Se$  bond, resulting in the formation of the disulfide bond between cysteines 124 and 132



**Scheme 2** Molecular mechanism of oxidation of  $\delta$ -ALAD catalytic thiols by diphenyl diselenide



**Fig. 3** Additional proposed molecular mechanism showing the oxidation of catalytic cysteine (cys) 124 and 132 from human  $\delta$ -ALAD by diphenyl diselenide, obtained by *in silico* studies (Nogara et al. 2020; Saraiva et al. 2012)

from  $\delta$ -ALA-D. Along with diphenyl diselenide, these interactions were also shown *in silico* for *p*-chloro-, *p*-methoxy-, and *m*-trifluoromethyl diselenide derivatives (Saraiva et al. 2012) (Fig. 3).

A very recent docking study was performed with sources of  $\delta$ -ALA-D enzyme from *Homo sapiens* (Hs $\delta$ -AlaD), *Drosophila melanogaster* (Dm $\delta$ -AlaD), and *Cucumis sativus* (Cs $\delta$ -AlaD), and the results corroborated the previous findings and provided more information about the mechanism of action (Nogara et al. 2020). Nogara and collaborators also reported the interaction of diphenyl diselenide with the cysteine residues from Hs $\delta$ -AlaD and Dm $\delta$ -AlaD, but not with Cs $\delta$ -AlaD (a non-thiol protein). In the Hs $\delta$ -AlaD active site, they found that the selenium atoms of diphenyl diselenide interacted with the carboxylic group of aspartate 120 and the Zn<sup>2+</sup> ion, besides the thiolate group from cysteine 124. In the Dm $\delta$ -AlaD, selenium atoms interacted with arginine 205, proline 212, phenylalanine 204, tyrosine 20, and arginine 217 via H bond, and with the cysteine 122. Interestingly, they found that the diphenyl diselenide putative metabolite, phenylselenenic acid, as well as other oxidized organoselenium forms presented similar binding pose,

interacting with the cysteine 124 and 122 residues from the active site from Hs $\delta$ -AlaD and Dm $\delta$ -AlaD, respectively (Nogara et al. 2020).

Because organoselenium compounds are highly prone to suffer a nucleophilic attack by cysteinyl residues, the activity of other sulfhydryl enzymes has been usually carried out to test the *in vitro* pro-oxidant potential of novel organochalcogens. Among them, the enzymes Na<sup>+</sup>, K<sup>+</sup>ATPase and lactate dehydrogenase (LDH) have been investigated (Chagas et al. 2013a; Kade et al. 2009; Lugokenski et al. 2011). In addition to diphenyl diselenide, herein, we highlighted the toxicological studies showing the inhibitory effects of ebselelen, 4-(4-fluorophenylseleno)-3-phenylisoquinoline), chloro (4-(4-chlorophenylseleno)-3-phenylisoquinoline), trifluoro (4-(3-trifluoromethylphenylseleno)-3-phenylisoquinoline), and bis(phenylimidazoselenazoly) diselenide on  $\delta$ -ALA-D and Na<sup>+</sup>, K<sup>+</sup>ATPase activities from rat tissues (Chagas et al. 2015; Sampaio et al. 2017a).

Recently, the activities of both enzymes were also used for screening the toxicity of novel zidovudine (AZT)-based selenides on human erythrocytes. Among 5'-phenylseleno-, *p*-chloro-, *p*-methyl-AZT derivatives, the *p*-methyl substituted AZT-derivative was the least toxic and did not cause  $\delta$ -ALA-D and Na<sup>+</sup>, K<sup>+</sup>ATPase inhibition, thiol depletion, and eryptosis; whereas the 5'-phenylseleno- and *p*-chloro-derivatives inhibited both  $\delta$ -ALA-D and Na<sup>+</sup>, K<sup>+</sup>ATPase activities, causing thiol depletion, and eryptosis (Ecker et al. 2018).

Regarding the oxidation of thiols from low-molecular-weight compounds, increasing evidence indicates that the oxidation rate seems to be dependent on pH and independent of thiol group pKa. At pH 7.4, cysteine and dithiothreitol were more reactive with diphenyl diselenide, whereas 2,3-dimercapto-1-propanesulfonic acid, GSH, and dimercaptosuccinic acid exhibited a low reactivity (Hassan and Rocha 2012).

### Organoselenium compounds: thiol depletion, reactive species overproduction, and mitochondrial dysfunction

As mentioned before, some organoselenium compounds may exhibit strong electrophilic activity, forming selenenyl-sulfide bonds with the cysteinyl residues from non-protein and protein thiols. Therefore, the activity of several protein families, including antioxidant enzymes as well as the GSH cell levels can be affected, and represent one of the main mechanisms by which organoselenium compounds modulate a wide spectrum of related biological processes. Among them, we highlighted herein those associated with oxidative stress, in which thiol depletion, RS overproduction, DNA damage, and mitochondrial dysfunctions are usually pointed out as key end-points.

Although ebselen and diphenyl diselenide are well recognized as antioxidant active agents, both compounds may exacerbate the production of RS at relatively high concentrations in vitro. In a range from 10 to 50  $\mu\text{M}$ , ebselen and diphenyl diselenide induced RS overproduction, accompanied by loss of viability, and DNA damage in human white cells (Bueno et al. 2018; Caeran Bueno et al. 2013). Similarly, ebselen caused an increase in RS levels, viability loss, -SH oxidation, and calcium dyshomeostasis in cultured astrocytes (Santofimia-Castano et al. 2013, 2016).

It is important to note that depletion of thiols accompanied by the increase in RS production has been suggested as possible mechanisms involved in the action of ebselen, diphenyl diselenide, and its derivatives against a diversity of fungal pathogens (Bueno Rosseti et al. 2014; Jaromin et al. 2018; Ngo et al. 2016; Rosseti et al. 2015; Thangamani et al. 2017).

In line with this, a study toward *Saccharomyces cerevisiae* showed that the deleterious effects of diphenyl diselenide on growth, size, and membrane permeability were followed by a marked RS overproduction at the highest concentration tested (10  $\mu\text{M}$ ) (Galant et al. 2017). Diphenyl diselenide and its dicholesteroyl diselenide derivative were genotoxic and mutagenic to *S. cerevisiae*, and these effects were associated with oxidative damage, because *N*-acetylcysteine partially reversed the toxicity of these compounds (de Oliveira et al. 2014).

Toxicological studies have indicated that mitochondria are potential targets for pro-oxidant action of selenides and diselenides, including ebselen and diphenyl diselenide. In general, the deleterious effects are demonstrated at concentrations ranging from 10 to 100  $\mu\text{M}$ . One of the first studies that simultaneously evaluated the effect of ebselen and diphenyl diselenide on mitochondria demonstrated that both compounds caused mitochondrial depolarization and swelling, effects that were associated with thiol oxidation, given that dithiotreitol prevented them (Puntel et al. 2010). In an extension of this study, using renal and hepatic mitochondria, ebselen and diphenyl diselenide inhibited the activity of complex I and II, without changing the complex III and IV. These effects were reversed by GSH and then related to the oxidation of critical thiol groups from mitochondrial complexes I and II (Puntel et al. 2013).

In the rat liver mitochondria, a recent study investigated diphenyl diselenide derivatives containing *o*-methoxy and *p*-methyl groups substituted in the aryl (25–100  $\mu\text{M}$ ) and revealed that only the compound containing the *p*-methyl group affected the mitochondrial membrane potential and decreased the State III respiration from 25  $\mu\text{M}$  (Stefanello et al. 2020). Mitochondria from rat hippocampal astrocytes exposed to ebselen at a concentration of 100  $\mu\text{M}$  showed disturbances in the membrane potential and calcium levels

along with RS overproduction (Santofimia-Castano et al. 2013).

As the mitochondria are highly sensitive to redox status, pro-oxidant agents can disrupt mitochondrial homeostasis and trigger cell death via apoptosis. As stated above, diphenyl diselenide and ebselen induced in vitro deleterious effects on mitochondria that could elicit apoptosis. However, some in vitro findings show that exposure of healthy cells to both compounds did not culminate with apoptosis. In fact, human leukocytes exposed to diphenyl diselenide and ebselen, ranging from 10 to 50  $\mu\text{M}$ , presented changes in mRNA expression of antioxidant enzymes, such as catalase, superoxide dismutase, and glutathione peroxidase, and increase in RS production, but did not undergo apoptosis (Caeran Bueno et al. 2013). Accordingly, exposure of rat hippocampal astrocytes to ebselen (10–100  $\mu\text{M}$ ) caused viability loss, endoplasmic reticulum, and mitochondrial stress, without changing the activity of caspase-3, an apoptosis activation marker (Santofimia-Castaño et al. 2016; Santofimia-Castano et al. 2013).

On the other hand, the activation of death signaling by many organoselenium compounds toward unhealthy cells and pathogens has driven studies on the synthesis and screening for anti-cancer, anti-viral, and anti-fungal applications (these will be further addressed in detail at the pharmacological section).

### In vivo toxicity of organoselenium compounds

Although diphenyl diselenide and ebselen are recognized as compounds with low toxicity in vivo, at high doses, they can elicit toxic effects, which vary a lot according to the species, exposure time, and route of administration. As demonstrated in vitro, mechanistically, the in vivo toxicity of ebselen, diphenyl diselenide, and its derivatives has been associated with oxidative events, including thiol depletion, lipid peroxidation, and inhibition of sulfhydryl enzymes, such as  $\delta$ -ALA-D,  $\text{Na}^+$ ,  $\text{K}^+$  ATPase, and LDH (Nogueira and Rocha 2011; Nogueira et al. 2004). To date, the toxicological implications from acute and chronic exposures to organoselenium compounds on mammalian models have not been extensively reported in the literature. Therefore, we will also include here some findings found in non-mammalian models. Table 1 summarizes the acute and chronic effects of some organoselenium compounds.

#### Acute exposure

In rodents, the toxicity of diphenyl diselenide and ebselen varies depending on the route of administration, age, and species (Table 1). After acute administration by the intraperitoneal (i.p) route, diphenyl diselenide was more toxic to mice than rats (Meotti et al. 2003). On the other hand, the



**Table 1** Effects of acute and chronic treatments with diphenyl diselenide, ebselen, and selenomethionine

Acute exposure			Chronic exposure	
Species	Treatments	Effects	Treatments	Effects
Mice	Diphenyl diselenide			
	210 $\mu\text{mol kg}^{-1}$ (i.p) <sup>a</sup>	Mortality		
	150 $\mu\text{mol.kg}^{-1}$ (i.p)	↑ PTZ-induced seizure		
	10 $\text{mg kg}^{-1}$ (i.p)	Stereotypy		
	Ebselen			
	340 $\mu\text{mol kg}^{-1}$ (i.p) <sup>a</sup>	Mortality		
Selenomethionine			Selenomethionine	
	~ 8 $\text{mg kg}^{-1}$ (i.p) <sup>a</sup>	Mortality	0.2 and 2 $\text{mg g}^{-1}$ (p.o)	↑Liver
	8 $\text{mg Se kg}^{-1}$ (i.p)	Hepatic lipid peroxidation	50 days	Lipoperoxidation Arsenic-induced
Rats	Diphenyl diselenide		Diphenyl diselenide	
	1200 $\mu\text{mol kg}^{-1}$ (i.p) <sup>a</sup>	Mortality	1 $\text{mg kg}^{-1}$ (i.p)	↑Hg deposition
	10 $\text{mg kg}^{-1}$ (i.p)	Anxiety	21 days	In liver and brain
	50 to 500 $\text{mg kg}^{-1}$ (i.g)	Seizures, brain lipid peroxidation in pups	Ebselen	
			10 $\text{mg kg}^{-1}$ (s.c)	Hepatic lipoperoxidation
			21 days	In suckling
			Selenomethionine	
			1.2–1.8 $\text{mg kg}^{-1}$	↓Weight
			(p.o)	Liver and
			13 weeks	pancreas damage
Ebselen				
	400 $\mu\text{mol kg}^{-1}$ (i.p) <sup>a</sup>	Mortality		
	Selenomethionine			
Selenomethionine				
	~4 $\text{mg kg}^{-1}$ (i.p) <sup>a</sup>	Mortality		
1 $\text{mg kg}^{-1}$ (i.p)	Pancreatic damage			
Rabbits	Diphenyl diselenide			
	500 $\text{mmol kg}^{-1}$ (i.p)	Mortality, hepatotoxicity, and brain oxidative stress		
Fly <sup>b</sup>			Diphenyl diselenide	
			0.5–2 $\mu\text{M}$ (p.o)	Developmental delay
			10 days	
Fish			1–10 $\mu\text{M}$ (p.o)	↑Hg toxicity in adult
			3 days	
			Diphenyl diselenide	
			5 ppm (p.o)	↓weight
			60 days	Oxidative damage
				<i>Silver catfish</i> and <i>Cyprinius carpo</i>
Selenomethionine			Selenomethionine	
			10–30 $\mu\text{g g}^{-1}$ (p.o)	Behavioral changes, cardiac dysfunctions
			90 days	In adult Zebrafish
			30–60 $\mu\text{g g}^{-1}$ (p.o)	Cognitive impairment, brain oxidative stress
			30 days	In adult Zebrafish
			100 $\mu\text{g L}^{-1}$ (p.o)	Embryonic teratogenesis
		48 hpf	in Zebrafish	
		30–60 $\mu\text{g g}^{-1}$ (p.o)	Growth retard, mortality, hematological	
		30 days	disturbances in	
			juvenile <i>Steelhead trout</i>	
Lambs	Selenomethionine			
	1–8 $\text{mg/kg}$ (p.o)	Tachypnea, myocardial necrosis, pulmonary edema		

<sup>a</sup>LD<sub>50</sub> the dose of a test substance that is lethal for 50% of the animals, *hpf* hours post-fertilization, *PTZ* pentylenetetrazol, *Fly<sup>b</sup>* *Drosophila melanogaster*

i.p. administration of diphenyl diselenide-loaded nanocapsules ( $50\text{--}1000\ \mu\text{mol kg}^{-1}$ ) did not cause overt toxicity or death in mice (Stefanello et al. 2015a). The  $\text{LD}_{50}$  values for ebselen were very similar when intraperitoneally injected in mice and rats (Meotti et al. 2003).

Diphenyl diselenide was also toxic to rabbits, when administered by the i.p route at a dose of  $500\ \mu\text{mol kg}^{-1}$  caused mortality, hepatotoxicity, and disruption of brain redox status (Stralioetto et al. 2010).

By subcutaneous (s.c) and intragastric (i.g) routes, diphenyl diselenide usually exhibited lower toxicity than that observed after i.p administration. Acute intragastric or subcutaneous administration of diphenyl diselenide did not cause overt toxicity or death in rats and mice (da Luz Fiuza et al. 2015; Meinerz et al. 2014; Meotti et al. 2003; Wilhelm et al. 2009b).

By the intravenous route, sheep treated with a single dose of diphenyl diselenide ( $6\ \mu\text{mol kg}^{-1}$ ) did not have any overt sign of toxicity until the end of observational period, namely 37 days (Leal et al. 2018).

Especially toward central symptoms from acute treatments, the first investigations demonstrated that an i.p administration of diphenyl diselenide increased the pentilentetrazole-induced seizure in mice (Table 1), but not in rats (Brito et al. 2006). Regarding the age of animals, diphenyl diselenide administered by s.c or i.g route did not cause seizures in adult rats or mice; however, in 12-day-old rat pups, oral acute treatment induced seizure episodes (Table 1) (Prigol et al. 2007). Diphenyl diselenide acutely administered at the dose of  $10\ \text{mg kg}^{-1}$  induced stereotypy in mice and anxiety-like behavior in rats, manifestations that were related to the inhibition of the brain monoamino oxidase (MAO-B) activity and increased levels of pro-inflammatory marker tumor necrosis factor  $\alpha$  (TNF), respectively (Figueira et al. 2015; Yamakawa et al. 2020).

In non-mammalian models, some findings showed that the acute treatment of zebrafish with diphenyl diselenide and diphenyl diselenide-loaded nanocapsules, at concentrations ranging from  $0.1$  to  $2\ \mu\text{M}$ , did not cause behavioral impairments and/or oxidative stress (Ferreira et al. 2019b; Ibrahim et al. 2014b).

### Chronic exposure

The toxic effects elicited by diphenyl diselenide from chronic treatments also vary in relation to the organisms (Table 1). Most of chronic protocols have applied dietary diphenyl diselenide, which have revealed that the long-term intake is relatively safe for several species. Evidence has been found to suggest that dietary diphenyl diselenide, from  $1$  to  $3\ \text{ppm}$ , was relatively secure for rats, rabbits, and some fish species after months of exposure, without eliciting either systemic or central signals of toxicity (Baldissera et al.

2020a; Barbosa et al. 2008; de Bem et al. 2006; dos Santos et al. 2020). However, the intake of high concentrations for a long time may culminate with toxic effects in fish. In fact, *Silver catfish* and *Cyprinius carpio* fed with  $5\ \text{ppm}$  diphenyl diselenide, for 60 days, had reduction in the weight and body length, and also showed increased lipid peroxidation in the liver, brain, and muscle (Menezes et al. 2014, 2016).

Here, we highlight that diphenyl diselenide chronic treatment (Table 1) did not induce toxicity in rats, but enhanced the Hg accumulation in the liver and brain as well as potentiated motor deficits and body-weight loss caused by methylmercury (MeHg) (Dalla Corte et al. 2013).

In vivo chronic toxicity data with ebselen are scarcer than diphenyl diselenide, but there is evidence that chronic subcutaneous administration of the compound ( $10\ \text{mg/kg}$ , for 21 days) to suckling rats culminated with lipid peroxidation and non-protein thiol depletion in the liver (Farina et al. 2004).

In invertebrates, literature brings some findings from *D. melanogaster* as an organism model to study toxicology and pharmacology of dietary diphenyl diselenide. Accordingly, the toxicity of dietary diphenyl diselenide was dependent on sex of *D. melanogaster* both in relation to total body thiol depletion and disruption in the mRNA expression of the antioxidant enzymes like catalase, superoxide dismutase, and glutathione *S* transferase (Occai et al. 2018).

Leão and collaborators exposed flies to diphenyl diselenide during both developmental and adult phases. Dietary diphenyl diselenide, ranging from  $0.5$  to  $2\ \mu\text{M}$ , affected the normal developmental success of *D. melanogaster* and also enhanced the toxicity of MeHg on development. In adult flies, diphenyl diselenide ( $1$  to  $10\ \mu\text{M}$ ) did not induce toxic effects, but increased the toxicity of MeHg on climbing ability and survival of individuals (Leão et al. 2018).

Moreover, diphenyl diselenide and MeHg co-exposure increased the Hg levels in the flies, an effect that was related to the formation of a less excretable complex between the selenium from the organoselenium and Hg. Accordingly, the same group had already demonstrated that diphenyl diselenide and MeHg co-exposure had increased the Hg content in the brain and liver of rodents (Dalla Corte et al. 2016, 2013). In flies and rats, the reduced intermediate of diphenyl diselenide (phenylselenol or selenophenol) may have reacted with MeHg to form a  $\text{PhSe-HgMe}$  complex. This complex possibly facilitated the break of  $-\text{C-Se-}$  and  $-\text{Hg-C-}$  bonds, releasing the insoluble  $\text{HgSe}$  salt (Madabeni et al. 2020).

**In vivo toxicity of diphenyl diselenide derivatives and other organoselenium compounds** Similar to diphenyl diselenide, the toxic profile of diselenide derivatives varies depending on the species and administration route, and, in general, the intragastric and subcutaneous administrations were reported to be safer than intraperitoneal. For mice, the intragastric

LD<sub>50</sub> for diselenide derivatives, *p*-chloro and *p*-methoxyl substituted diselenides, was found to be > 1 mmol kg<sup>-1</sup>. For *m*-trifluoromethyl and benzylamino derivatives, the LD<sub>50</sub> was estimated to be > 0.62 and 350 mg kg<sup>-1</sup>, respectively (Ibrahim et al. 2019; Savegnago et al. 2009).

The intragastric administration of *p*-methoxyl-substituted diselenide-nanoencapsulated (25 mg kg<sup>-1</sup>, 7 days) did not cause any alteration in hematological and oxidative damage markers, and enhanced the selenium levels in the blood, kidney, and liver of mice (Sari et al. 2017).

By the subcutaneous route, *p*-chloro diselenide derivative (1000 μmol kg<sup>-1</sup>) did not induce overt sign of toxicity in mice and reduced the toxicity of HgCl<sub>2</sub> on the liver and kidney, as indicated by the restoration of δ-ALA-D, Na<sup>+</sup>, K<sup>+</sup> ATPase, and lipid peroxidation to normal levels (de Freitas et al. 2012).

In rats, 2,2'-dithienyl diselenide derivative, at doses of 50 and 100 mg kg<sup>-1</sup>, caused systemic toxicity after intragastric administration, such as weight body loss, hepatotoxicity, inhibition of δ-ALA-D activity, lipid peroxidation, and death (Chagas et al. 2013a).

Acute intraperitoneal administration of vinyl chalcogenide 3-methyl-1-phenyl-2-(phenylseleno)oct-2-en-1-one, at doses of 125–500 μg kg<sup>-1</sup>, was toxic to rats, increasing plasma alanine aminotransferase and causing hematological and behavioral changes. The compound also increased lipid and protein oxidation in the brain (de Andrade et al. 2014; dos Santos et al. 2012). Likewise, rats exposed chronically to this vinyl chalcogenide (i.p., 30 days), in addition to cause behavioral alterations, increased brain lipid and protein oxidation, thiol depletion, liver, and renal damage (Medeiros et al. 2012; Mello et al. 2012).

3,3'-Diselenodipropionic acid (DSePA), a synthetic derivative of selenocystine, has been extensively investigated as an antioxidant and radioprotective agent. The acute oral toxicity of DSePA is low in mice (LD<sub>50</sub> ~ 200 mg kg<sup>-1</sup>) and rat (LD<sub>50</sub> ~ 25 mg kg<sup>-1</sup>) when compared with its parent compound selenocystine and other organoselenium commonly used as a nutritional supplement, including methylselenocysteine and selenomethionine (Kunwar et al. 2018, 2020; Yang and Jia 2014). The mechanisms involved in the toxicity of DSePA have not been studied in detail, but considering its structure and its LD<sub>50</sub> for rodents (which is greater than selenocystine); we can predict that its toxicity will be mediated by oxidation of thiol groups of critical target proteins. Although the acute *in vivo* toxicity of DSePA in mice has been described to be low in relation to selenocystine, we have to bear in mind the extreme sensitivity of humans to the toxic effects of selenocystine (Weisberger and Suhrland 1956). This aspect is important in view of the structural similarity of DSePA with selenocystine.

Regarding the *in vivo* toxicity of naturally occurring organoselenium compounds, we included here some

toxicological studies published in the last decade with selenomethionine, methylselenocysteine, and selenocystine, in which the findings with selenomethionine were the most prevalent (Table 1). Selenomethionine can be metabolized to selenide and provided selenium to be incorporated into selenoproteins. However, depending on the species, selenomethionine levels exceeding 0.2 ppm can become toxic (Schrauzer 2003).

Human cases of acute and/or chronic selenomethionine poisoning are rare, but, recently, a fatal case of occupational acute intoxication with this powdered amino acid was reported. After trying to open a sealed bag-container, the L-selenomethionine powder blew out back onto 30 years-old man. Selenomethionine contaminated his skin and clothes, and was also inhaled. A few hours after the contamination (about 5 h), the man died, and just before dying, he had abnormal blood pH (7.01), oxygen saturation (75%), glucose (17 mg 100 mL<sup>-1</sup>), bicarbonate (12 mEq L<sup>-1</sup>), urea (14 mg dL<sup>-1</sup>), creatinine (1.51 mg 100 mL<sup>-1</sup>), 11 mg L<sup>-1</sup> of selenium (normal levels below 0.16 mg.L<sup>-1</sup>), and urine selenium levels of 25 mg L<sup>-1</sup> (normal levels below 0.2 mg L<sup>-1</sup>) (Spiller et al. 2020).

In an experimental animal model, lambs orally administered with a single dose of selenium as selenomethionine (ranging from ~ 1 to 8 mg of Se kg<sup>-1</sup>) developed tachypnea, whose severity and time to recovery were dose-dependent. Histopathologic alterations were also observed in the animals exposed to the higher doses, including myocardial necrosis, pulmonary edema, and hemorrhage (Tiwary et al. 2006).

In rats, the *i.p.* LD<sub>50</sub> of selenomethionine was estimated to be ~ 4 mg Se kg<sup>-1</sup>, whereas for mice ~ 8 mg Se kg<sup>-1</sup> (Schrauzer 2003). Indeed, rats intravenously injected, at a bolus dose of 1.0 mg Se kg<sup>-1</sup> as selenomethionine, accumulated selenium preferably in the pancreas and had a significant increase in the serum amylase levels, a key marker of pancreatic damage.

The chronic toxicity of selenomethionine is considered lower than inorganic selenium forms, and often is reported in animals fed with too high levels. Rats fed for 8 weeks with selenomethionine (16 ppm of Se) did not develop signs of toxicity, whereas the same amount of selenium as sodium selenite produced hepatotoxicity, cardiotoxicity, and splenomegaly (Schrauzer 2003).

Oral administration of 0.5 and 1.0 mg selenomethionine, for 13 weeks, did not also induce toxic effects in rats. However, higher concentrations (1.2 and 1.8 mg Se kg<sup>-1</sup> body weight.day<sup>-1</sup>) caused weight loss, liver, and pancreas damage and decreased food consumption (Schrauzer 2003).

In a mouse model, the supplementation of sufficient and excess levels of selenomethionine (0.2 and 2 mg Se<sup>-1</sup> kg<sup>-1</sup>, respectively), for 50 days, improved the basal immunological parameters impaired by arsenic intoxication, but the

two doses increased the hepatic lipid peroxidation arsenic-induced (Rodríguez-Sosa et al. 2013).

In non-mammalian models, most of the literature about the toxicity of selenomethionine intake is in fish. In zebrafish, chronic exposure to elevated dietary selenomethionine (from 10 to 30  $\mu\text{g g}^{-1}$ ) has been associated with impairments in behavioral performance, aerobic metabolic capacity, and energy homeostasis (McPhee and Janz 2014). These adverse effects were correlated with the negative impact of chronic dietary selenomethionine on cardiac function, because zebrafish exposed to similar concentrations had a marked decrease in the ventricular contractile rate, stroke volume, and cardiac output, as well as disruption in the mRNA expression of cardiac remodeling enzymes (Pettem et al. 2017).

Adult zebrafish exposed to selenomethionine  $\sim 30$  and 60  $\mu\text{g g}^{-1}$  of diet developed learning impairment, which was associated with oxidative stress and altered brain mRNA expression of dopaminergic system components (Naderi et al. 2017).

Chronic exposure of adult zebrafish to selenomethionine (34.1  $\mu\text{g g}^{-1}$ ; 90 days) also displayed changes in social learning via dysregulation of key genes of the serotonergic pathway (Attaran et al. 2020).

In zebrafish embryos, selenomethionine at 100  $\mu\text{g L}^{-1}$  induced significant deformities (lordosis and craniofacial malformation), which were partially attributed to oxidative stress, since N-acetylcysteine reduced the teratogenic signals (Arnold et al. 2016).

A study performed with steelhead trout in the juvenile stage fed on  $\sim 8, 15, 30,$  and 60  $\mu\text{g Se g}^{-1}$  diet in the form of selenomethionine, for 4 weeks, revealed that Se accumulated in a dose-dependent manner in all tissues. Moreover, the diets with selenomethionine at 30  $\mu\text{g g}^{-1}$  or higher arrested growth and increased mortality and hematological disturbances (Lee et al. 2019).

## Pharmacology of organoselenium compounds

The coronavirus COVID-19 pandemic, caused by the worldwide spread of new SARS-CoV-2, has dominated the work of researchers in an unprecedented global effort to lead to the rapid discovery of drugs with the clinical potential to fighting this new infectious disease for which no specific drugs or vaccines are available (Roser et al. 2020).

Since the nutritional essentiality of selenium as a trace element for human health has been demonstrated (Schwarz and Foltz 1957), the multifaceted aspects of this nutrient have attracted worldwide clinical and research interest (Allingstrup and Afshari 2015; Navarro-Alarcon and Cabrera-Vique 2008; Oldfield 1987; Rayman 2012).

However, the selenium status should be analyzed considering its U-shaped effects, exhibiting advantages in selenium-deficient individuals but specific health risks in those with selenium excess (Duntas and Benvenga 2015; Misu et al. 2012; Rayman 2020; Rayman et al. 2012; Rayman and Stranges 2013; Rocourt and Cheng 2013; Zhou et al. 2013).

Particularly, in China, where COVID-19 emerged, the concentration of selenium in the soil, which generally reflects its presence in food and the selenium levels in human populations, varies from deficiency to excess (Dinh et al. 2018). Based on this premise and knowing the immunomodulatory property of selenium (Guillin et al. 2019; Steinbrenner et al. 2015), a very recent published study from Rayman group reported the better recovering of COVID-19 patients related to certain regions of China that had the most selenium in soil (Zhang et al. 2020c).

Selenium, as a cyclic selenyl amide ebselen, also emerges in the pandemic scenario as a potential repurposing approved pharmaceutical drug with anti-viral activity for the treatment of COVID-19 (Sies and Parnham 2020).

Considering what was mentioned before, in this chapter, the pharmacology of organoselenium compounds is discussed, emphasizing properties beyond their well-known antioxidant activity.

### Anti-viral activity

As previously described in Sect. 2.1 of this review, the pro-oxidant action of selenium compounds, including thiol oxidation, RS generation, DNA damage, and mitochondrial dysfunctions, can drive events that culminate in biological downstream effects by affecting kinases, phosphatases, and caspases, proteins involved in the DNA repair and transcription factors that regulate growth, proliferative, and death pathways in cancer cells and different pathogens. Furthermore, organoselenium compounds, particularly ebselen and diselenides, can oxidize critical thiol-containing proteins from viruses, bacteria, and fungi.

Ebselen has been shown to target critical proteins from different viruses due to its reaction with thiols. Toward human immunodeficiency virus type 1 (HIV-1), ebselen was found to be a potent integrase inhibitor, disrupting the interaction of the enzyme with the key growth-factor (lens-epithelium-derived growth-factor, LEDGF/p75), through the formation of a selenium–sulfur bond with a cysteinyl residue from the factor LEDGF/p75 (Zhang et al. 2020a). Similarly, the ebselen action as a potent HIV-1 capsid assembly disruptor was associated with its covalent binding to cysteine 198 and 218 residues in the HIV-1 capsid protein (Thenin-Houssier et al. 2016).

Regarding the hepatitis C virus, ebselen was recognized as a potent inhibitor of the NS3, a non-structural protein with helicase function. At concentrations higher than 10  $\mu\text{M}$ ,

ebesen caused an irreversible inhibition and formation of covalent adducts with all cysteines present in the viral helicase (Mukherjee et al. 2014).

Currently, extensive computational–experimental screenings on SARS-CoV-2 have identified several promising drugs that could serve as effective inhibitors of the virus proteins, mainly toward the protease Mpro protease (NSP5), a non-structural sulfhydryl protein involved in the processing of Orf polyproteins 1a and 1ab. The products of hydrolysis of polyproteins 1a and 1ab (NSP4 to NSP 16) are involved in the replication of SARS-CoV-2 as well as SARS-CoV and MERS-CoV (Pillaiyar et al. 2016).

Among various compounds investigated, ebesen appeared as one of the most potent inhibitors of the enzyme both in vitro and SARS-CoV-2 replication in Vero cells. The  $IC_{50}$  for MPro protease was near 0.7  $\mu\text{M}$  and for virus replication about 10  $\mu\text{M}$  (Jin et al. 2020; Sies and Parnham 2020).

Ebselen covalently attaches to the catalytic cysteine residue from Mpro site active (Cys 145), forming selenosulfide that leads to the enzyme inactivation. Atomistic molecular simulations also provided evidence that ebesen exhibits high-affinity binding for sites localized between the II and III domains of the protein, an important allosteric effect that regulates the enzyme catalytic site (Menendez et al. 2020).

Ebselen and its derivatives have been demonstrated as inhibitors of both Mpro and the papain-like protease (PL-Pro) from SARS-CoV-2 (Ma et al. 2020); however, they had higher inhibitory effects against Mpro than PLpro (Zmudzinski et al. 2020).

The anti-viral properties of diphenyl diselenide and its derivatives have been only rarely explored. Therefore, diphenyl diselenide has been reported to have virucidal and anti-viral actions against in vitro herpes simplex virus 2 (HSV-2), reducing the infectivity in 70.8% and 47%, respectively. Moreover, treatment with diphenyl diselenide was proven to be effective against oxidative stress and inflammation in HSV-2-infected mice (Sartori et al. 2016, 2017).

In this way, a recent high-throughput screening of a series of new anti-viral diphenyl diselenide derivatives against human herpes virus type 1 (HHV-1) and encephalomyocarditis virus (EMCV) in A549-infected cells revealed their effectiveness against the two viruses. The majority of compounds tested, especially *bis*[2-(hydroxyphenylcarbamoyl)] phenyl diselenide, exhibited high activity against HHV-1 and moderate activity against EMCV. The anti-HHV-1 activity of most effective diselenides ranged between 2 and 40  $\mu\text{g mL}^{-1}$  (Giurg et al. 2017). Recently, diphenyl diselenide was reported to be effective against bovine alphaherpesvirus 2 (BoHV-2), the agent of bovine herpetic mamillitis, both in vitro and in vivo in ewes transdermally infected with BoHV-2 (Amaral et al. 2020).

## Antimicrobial activity

In the last decades, several studies regarding the antimicrobial activity of organoselenium compounds, such as ebesen, diphenyl diselenide, and selenide-based compounds, toward pathogenic fungi and bacteria have appeared in the literature (Di Leo et al. 2019).

Data from different laboratories have indicated that ebesen and various ebessulfur derivatives exhibited high efficacy against several kinds of clinically relevant fungal strains, among them *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, and *Candida parapsilosis*. From these studies, the minimal inhibitory concentration (MIC) values found to ebesen ranged from  $\sim 0.5$  to 2  $\mu\text{g mL}^{-1}$ , whereas  $\sim 0.02$  to 12  $\mu\text{g mL}^{-1}$  was reported to its derivatives (Di Leo et al. 2019; May et al. 2018; Ngo et al. 2016; Thangamani et al. 2017). Moreover, ebesen and its structural derivatives, such as benzenoselenazol-3(2H)-one, and 2-methyl- and 2-n-propyl-benzenoselenazol derivatives, 2-phenylbenzothiazol-3(2H)-one, and 2-phenyl-7-azabenzoselenazol-3(2H)-one, exhibited similar inhibitory activity in assays with fluconazole-resistant strain of *C. albicans* (Orie et al. 2017).

Ebselen appeared as one of the most active compounds in studies that screened repurposing off-patented molecules with anti-fungal activity against *Candida auris* (De Oliveira et al. 2019; Wall et al. 2018).

The activity of ebesen nanoencapsulated was markedly increased against *C. parapsilosis*, *C. albicans*, and *C. tropicalis* when compared with the free form (Jaromin et al. 2018). In this way, Vartak and collaborators demonstrated the efficacy of a soluble vaginal film containing ebesen developed to treat vulvovaginal candidiasis, which exhibited an MIC value of 20  $\mu\text{M}$  against *Candida* species, a concentration significantly lower when compared to classical anti-fungal as fluconazole (MIC 500  $\mu\text{M}$ ) and miconazole (MIC 100  $\mu\text{M}$ ) (Vartak et al. 2020b). The same group also showed the superior efficacy of a novel topical nanoemulgel of ebesen against *C. albicans* and *C. tropicalis* when compared to the effect of a clinically used drug terbinafine that was ineffective even at 100  $\mu\text{M}$  (Vartak et al. 2020a).

Ebselen has also been suggested by several studies as a promising molecule to treat bacterial infections alone or in combination with other agents. The effectiveness of ebesen and its derivatives has already been demonstrated against diverse pathogens, including *Staphylococcus* ssp., *Streptococcus* ssp., and *Enterococcus* ssp. (Chen and Yang 2019; Thangamani et al. 2015a).

Ebselen exhibited a potent bactericidal activity against *Staphylococcus aureus* multidrug-resistant clinical isolates and reduced the bacteria load in a mouse model of staphylococcal skin infections, acting also synergistically with traditional antimicrobials (Thangamani et al. 2015b).

After an evaluation against a broad array of enterococcal isolates in vitro, ebselen was uncovered as a promising agent for decolonization of vancomycin-resistant *enterococci* from the gastrointestinal tract (AbdelKhalek et al. 2018).

By targeting cysteine residues in the active site from critical enzymes of *Mycobacterium tuberculosis* (antigen 85 complex; transpeptidase Ldt Mt2), ebselen and some derivatives were considered promising for treating tuberculosis (de Munnik et al. 2019; Favrot et al. 2013; Goins et al. 2017).

Similarly, from a high-throughput screening assay, ebselen was identified as a potent inhibitor of anthrax receptor (tumor marker endothelial 8, TEM8), via modification of a cysteine residue in the extracellular domain from the anthrax receptor (Cryan et al. 2013). In addition to the receptor modulation, Gustaffon and collaborators demonstrated that ebselen and its derivatives strongly inhibited *Bacillus anthracis* thioredoxin reductase (Gustafsson et al. 2016).

Screening ebselen and its derivatives for the treatment of ureolytic bacterial infections has revealed these organoselenium compounds as inhibitors of urease activity from *Sporosarcina pasteurii* and *Helicobacter pylori* through the interaction with a critical cysteine located at the entrance of the enzyme active site (Macegoniuk et al. 2016).

Very recent studies have demonstrated the synergistic therapeutic efficacy of ebselen and silver against the multi-drug-resistant bacteria, including *Acinetobacter baumannii*, *Escherichia coli*, and *S. aureus* (Chen et al. 2019; Dong et al. 2020; Wang et al. 2020).

Increasing evidence indicates the effectiveness of diphenyl diselenide, alone or as adjuvant with classical anti-fungal agents, against diverse strains of fungi. Diphenyl diselenide was effective against 32 *Aspergillus* isolates (MIC  $64 \mu\text{g mL}^{-1}$ ), which increased the fungicidal action of the drug caspofungin, but was ineffective against an aspergillosis mouse model (Melo et al. 2020).

In vitro, diphenyl diselenide was tested against nineteen *Pythium insidiosum* isolates and showed an MIC ranging from  $\sim 0.5$  to  $2.0 \mu\text{g mL}^{-1}$ , the fungistatic activity was reproduced in an animal model of pythiosis (Loreto et al. 2012). Moreover, diphenyl diselenide also increased the efficacy of flucytosine against 30 clinical isolates of *Cryptococcus* spp. (Rossato et al. 2019).

On clinical *C. glabrata* strains, the diphenyl diselenide MIC ranged from 0.25 to  $> 64$  ( $5.16 \mu\text{g mL}^{-1}$ ), values similar to that of found for fluconazole. Besides, a synergistic interaction was observed between diphenyl diselenide and the drug amphotericin B (Denardi et al. 2013).

Similar action profile was found against 40 clinical isolates of *Sporothrix brasiliensis*, in which diphenyl diselenide presented an MIC ranging from 4 to  $32 \mu\text{g mL}^{-1}$  and a synergistic interaction with itraconazole (73%) (Poester et al. 2019).

Along with diphenyl diselenide, various other diselenide derivatives have been pointed out as effective inhibitors of growth and biofilm formation in fungi and bacteria. Herein we highlighted the compounds camphor diselenide, 2,2'-dithienyl diselenide, *bis*[ethyl-*N*-(2'-selenobenzoyl)glycinate], *bis*[2'-seleno-*N*-(1-methyl-2-phenylethyl)benzamide], *bis*[2-(hydroxyphenylcarbonyl)]phenyl diselenide, and (*Z, Z*)-3,30-(4-(diseleno)phenylcarbonyl)acrylic acid, that in addition to *C. albicans* also showed antibiofilm activity against several bacteria strains, including *Enterococcus* spp., *Staphylococcus* spp., *Streptococcus* spp., and *Pseudomonas* spp. (Bueno Rosseti et al. 2014; Giurg et al. 2017; Pesarico et al. 2013; Rosseti et al. 2015; Sancineto et al. 2016; Shaaban et al. 2015).

There are also some studies comparing the anti-fungal potential of ebselen and diphenyl diselenide, alone or in combination with anti-fungal agents. One of them evaluated the effect of both compounds in combination with amphotericin B, caspofungin, itraconazole, and voriconazole against 25 clinical isolates of *Fusarium* spp. The MICs found for diphenyl diselenide and ebselen were  $4\text{--}32 \mu\text{g mL}^{-1}$  and  $2\text{--}8 \mu\text{g mL}^{-1}$ , respectively. The most effective synergic combinations were found to ebselen + amphotericin B (88%), ebselen + voriconazole (80%), diphenyl diselenide + amphotericin B (72%), and diphenyl diselenide + voriconazole (64%) (Venturini et al. 2016).

Likewise, a comparative study toward *C. parapsilosis* showed that ebselen presented higher anti-fungal activity than diphenyl diselenide against both echinocandin-susceptible and -resistant strains (Chassot et al. 2016). The efficacy of both compounds was also addressed against *Trichosporon asahii* strains, in which ebselen exhibited an MIC ranging from  $\sim 0.25$  to  $8 \mu\text{g mL}^{-1}$  and diphenyl diselenide from  $\sim 8$  to  $64 \mu\text{g mL}^{-1}$  (Felli Kubiça et al. 2019).

It is worth mentioning that the mechanisms of antimicrobial action proposed for these organoselenium compounds generally involve similar effects for both fungi and bacteria. Overall, the studies about the antimicrobial activity of different organoselenium compounds have revealed their effectiveness in increasing cell membrane permeability, inhibiting sulfhydryl enzymes, and inducing redox dyshomeostasis in the cells mainly through GSH depletion and RS overproduction, events that can culminate in death (Di Leo et al. 2019).

## Chemopreventive activity

A Janus-faced character of the element selenium, initially classified as carcinogenic (Nelson et al. 1943) and, subsequently, as anticarcinogenic (Shamberger and Frost 1969), has a long history. In that, some of the recent chapters based on clinical trials, cohort, and epidemiological studies have shown an inverse association between selenium

intake and risk of cancers in humans. Because an extensive discussion of the literature on this field is outside of the scope of this review, the readers are directed to some comprehensive reviews on this topic (Hatfield et al. 2014; Jablonska and Vinceti 2015; Rayman 2020; Stolwijk et al. 2020).

Since the pioneering studies on the anti-cancer activity of organoselenium compounds (El-Bayoumy 1985; Fiala et al. 1991; Nayini et al. 1989; Reddy et al. 1985, 1987; Tanaka et al. 1985), basic research on this topic has moved ahead at a rapid pace, bringing perspectives in cancer prevention and promotion, cancer drug resistance, and molecular mechanisms behind these effects (Chen et al. 2020; Gopalakrishna et al. 2018; Spengler et al. 2019). However, no attempt is made here to thoroughly discuss the beginning studies on chemopreventive effects of organoselenium, as these have been reviewed elsewhere (Nogueira and Rocha 2011; Nogueira et al. 2004).

With regard to ebselen, this organoselenium compound has been proposed to induce RS formation, calcium dys-homeostasis, Bax activation, and mitochondria-mediated apoptosis in different tumor cells, including multiple myeloma, pancreatic tumor, prostate, and leukocytes cancer lines (Gandin et al. 2018; Hanavan et al. 2015; Kaczor-Keller et al. 2020; Santofimia-Castaño et al. 2018). Besides, a very recent study reported that ebselen is an inhibitor of the 6-phosphogluconate dehydrogenase in leukemia cells, an enzyme essential for cell proliferation and tumor growth (Feng et al. 2020). Ebselen was proven to be a potent inhibitor of cell growth for the triple-negative model of breast cancer (Jupp and Giles 2012).

Ebselen and its derivatives have been also indicated as inhibitors of histone deacetylases in tumor cells (Wang et al. 2017b) and effective in reducing cancer cell migration and invasion by targeting multiple kinases with established roles in cancer progression (Bijian et al. 2012).

Thioredoxin reductase 1 (TrxR1)-based drugs have been proposed as promising anti-cancer therapies, because the overexpression of this selenoprotein has been detected in many human tumors. Herein, we highlight the compound ethaselen, an ebselen derivative, which has been pointed out in both in vitro and in vivo studies as a potent anti-proliferative drug, by inhibiting TrxR1 in various types of tumors (Wang et al. 2011a, 2012; Wu et al. 2020). This promising action motivated the use of ethaselen in phase I clinical trial in China, which includes patients diagnosed with advanced non-small-cell lung cancer. The phase 1a/1b finished in 2008, and currently, the compound will pass to phase 1c, where the patients will receive oral ethaselen tablets as treatment (600 mg/bid day) (Clinical Trials.gov Identifier: NCT02166242). Moreover, a number of methodological strategies have been carried out for synthesizing ethaselen derivatives with antitumoral activity (Ye et al. 2016).

In addition to TrR1, selenoprotein 15 (sep15) and GPx2 have been highlighted as important cellular redox regulators potentially involved in preventing and promoting cancer; however, the role of selenoproteins in cancer will be not addressed herein, but interested readers may refer to a comprehensive review published by Hatfield and collaborators (Hatfield et al. 2014).

In the search for novel organoselenium compounds with chemopreventive activity, a class of zidovudine (AZT)-based selenides, named chalcogenozidovudines, was screened as antitumoral candidates against human bladder carcinoma. This study uncovered 5'-(phenylseleno)zidovudine and its *p*-methyl and *p*-chloro derivatives as antitumor agents with potent apoptosis induction effects (de Souza et al. 2015). After a toxicological screening, the *p*-methyl derivative emerged as the most promising candidate for further antitumor studies by exhibiting lower toxicity than AZT on health immune cells and acute in vivo treatment (Ecker et al. 2017).

Increasing evidence indicates the chemopreventive activity of diselenides, especially diphenyl diselenide; as a result, one of the first related studies showed the effectiveness of diphenyl diselenide in inducing death in the human neuroblastoma cell line SH-SY5Y via ERK1/2-mediated apoptosis (Posser et al. 2011). The potential cytotoxic effects of diphenyl diselenide and diphenyl diselenide-loaded nanocapsules have also been reported against C6 glioma cells, in which both forms attenuated the tumor development. Similar results were observed against SK-Mel-103, a resistant melanoma cell line. In these studies, diphenyl diselenide at both forms caused a loss of viability, increased propidium iodide uptake, and nitrite levels in the malignant cells (Ferreira et al. 2019a, 2020).

A detailed discussion of the anti-proliferative activity of diselenide derivatives in malignant cells has been reviewed by others (Álvarez-Pérez et al. 2018; Gandin et al. 2018), and these reviews bring a list of compounds indicated as promising antitumor agents. Briefly, along with diphenyl diselenide on murine hepatoma cells (Hepa 1c1c7), the anti-proliferative potential of various diaryl, dialkyl, dipyridazinyl, dipyridinyl, and phenylcarbamate diselenides against other carcinoma cells have been addressed (Álvarez-Pérez et al. 2018; Gandin et al. 2018).

In terms of molecular mechanisms, cell-cycle arresting, caspase-independent and dependent apoptosis, p53 activation, and autophagy via c-Jun N-terminal kinase (JNK) activation are among the cytotoxic effects reported for diorganyl diselenides, including symmetric aromatic diarylseleno and acylselenourea derivatives as well as *m*-trifluoromethyl-diphenyl diselenide, *p*-methoxyl-diphenyl diselenide, and diphenyl methylselenocyanate (Chakraborty et al. 2016; Díaz et al. 2018; Garnica et al. 2018).

Furthermore, one way by which the majority of agents, such as ionizing radiation, chemotherapeutic agents, and

some targeted therapies, kill cancer cells consists of directly or indirectly generating reactive oxygen species (ROS) that block the key steps in the cell cycle (Watson 2013). Therefore, the use of antioxidant dietary supplements, and, consequently, the search for organoselenium compounds that could counteract the ROS generation and prevent tissue damage, allowing an increase in the maximum therapeutic dose of the anti-cancer drug, have been a matter of research interest (Panchuk et al. 2014, 2016).

In experimental models of cisplatin chemotherapy, ebselen has been proven to reduce ovarian damage and ototoxicity through modulation of oxidative injury and apoptosis (Orzáez et al. 2014; Soyman et al. 2018), whereas a naphthalimide-based organoselenium compound enhanced cisplatin antitumor efficacy and reduced its toxicity (Ghosh et al. 2015).

In an MCF-7-cultured cell model, diphenyl diselenide antigenotoxic activity has been associated with the prevention of cancer risk induced by tamoxifen hormone therapy (Melo et al. 2013). Besides, a synergistic antitumor action was identified when ebselen was associated with radiotherapy, which was attributed to the induction of apoptosis and inhibition of breast cancer cell progression (Thabet and Moustafa 2017).

Over the past decades, basic research in the anti-cancer potential of naturally occurring organoselenium compounds has made progress (Chen and Wong 2009; Ip and Ganther 1992; Jiang et al. 1999; Lu et al. 1995; Reddy et al. 2000; Sinha et al. 1999; Sinha and Medina 1997; Unni et al. 2005, 2001), and this knowledge has been translated with some success to clinical trials (Clark et al. 1996; Duffield-Lillico et al. 2003; Lippman et al. 2009; Mix et al. 2015a, b).

Aiming to use higher doses of chemotherapy and overcome drug resistance, the oral bioavailable methylselenocysteine has been investigated in combination with chemotherapeutic agents and proven to be effective against organ-specific toxicities induced by cyclophosphamide, cisplatin, and oxaliplatin, and to enhance antitumor activity in animal models of cancer (Cao et al. 2004, 2014). Very recently, a phase I randomized double-blinded study compared methylselenocysteine and selenomethionine pharmacodynamic effects in cancer patients to determine a safe and effective dose to be used in combination with anti-cancer therapy. However, the dose of 400 µg was considered too low to achieve the levels of selenium in plasma ( $\geq 5$  µM), which are expected to cause pharmacodynamic effects (Evans et al. 2020).

Previously published studies revealed that selenomethionine, the organic form of selenium used SELECT trial (Lippman et al. 2009), is ineffective against prostate cancer models (Li et al. 2008; Wang et al. 2009), whereas methylselenocysteine, classified in the second generation of organoselenium compounds, reduces tumor growth and

castration-resistant progression of prostate tumor (Christensen et al. 2013; Liu et al. 2015b; Zhan et al. 2013). Methylselenocysteine is considered the most effective among the other natural occurring selenium-containing molecules, because it is efficiently converted to the active intermediate methylselenol, requiring one-step activation by  $\beta$ -lyase, and does not get as easily serum protein interaction (Bhattacharya 2011; Ip 1998; Ip et al. 2000). Moreover, the anti-cancer effectiveness of methylselenocysteine and selenomethionine has been associated with the transamination reactions that generate  $\alpha$ -keto acid selenium metabolites, which are potent inhibitors of histone deacetylases (Kassam et al. 2011; Lee et al. 2009; Pinto et al. 2014).

In addition to methylselenocysteine, methylseleninic acid has been reported as a direct precursor of methylselenol, the key metabolite responsible for selenium's anti-cancer activity (El-Bayoumy and Sinha 2004), and effective against prostate cancer (Zhao et al. 2004). By inducing lipid peroxidation, methylseleninic acid sensitizes head–neck squamous cell carcinoma to radiation (Lafin et al. 2019).

Some of the molecular mechanisms underlying chemopreventive activity of naturally occurring organoselenium compounds described so far are the modulation of antioxidant defenses (selenoenzymes) and redox status of cells, programmed cell death, DNA repair, carcinogen detoxification, immune system, neo-angiogenesis, regulation of cell proliferation, and tumor cell invasion (Jung et al. 2013; Korbut et al. 2018; Pons et al. 2020; Wang et al. 2018a; Weekley et al. 2012; Whanger 2004; Zeng and Combs 2008; Zeng et al. 2011).

### Antidepressant- and anxiolytic-like activities

Ebselen, a safe and well-tolerated organoselenium (Lynch and Kil 2009; Parnham and Graf 1987), has attracted tremendous interest over the past decades. Although it never reached the market, the possibility to apply for novel applications or repurposing ebselen is at the core of basic academic research and clinical trials (Kil et al. 2017; Ogawa et al. 1999; Parnham and Sies 2013; Saito et al. 1998; Sharpley et al. 2020; Yamaguchi et al. 1998). In 2013, drug-repurposing studies indicated ebselen as a mood stabilizer; this is because it is an inhibitor of inositol monophosphatase (IMPase), induces lithium-like effects on mouse behavior, crosses the blood–brain barrier, down-regulates serotonin (5-HT) 2A receptor in the head-twitch and c-Fos models, inhibits glutamine synthase, and decreases myo-inositol concentration in the human brain (Masaki et al. 2016a, b; Singh et al. 2013, 2016).

More recently, ebselen has been suggested as an antidepressant (Antoniadou et al. 2018) and impulsivity lowering agent (Barkus et al. 2018) based on its neuropharmacological lithium-like effects in different animal models



of 5-HT<sub>2A</sub> function. Therefore, Fink and collaborators reported that elevated 5-HT<sub>2A</sub> receptor expression is associated with impulsive behavior in rodents (Fink et al. 2015).

The success of ebselen in experimental models of mood disorders (Posser et al. 2009) has encouraged the study of other organoselenium compounds that share with this compound some properties relevant to the antidepressant- and anxiolytic-like activities such as neuroprotective, anti-inflammatory, and the modulation of neurotransmitter systems (Nogueira et al. 2003; Nogueira and Rocha 2011).

The antidepressant-like property of diphenyl diselenide, a structurally simple compound, was first demonstrated by our research group in 2007 (Savegnago et al. 2007b) and, since that, substituted diorganoyl diselenides have been reported as effective agents in different animal models of depression (Acker et al. 2009; Brüning et al. 2015b; Da Rocha et al. 2012a; Dias et al. 2014; Quines et al. 2016b; Savegnago et al. 2008b).

Table 2 illustrates some protocols in which diaryl diselenides were effective at relatively low doses in rodents (Bortolatto et al. 2012; Brüning et al. 2011; Heck et al. 2019; Oliveira et al. 2017; Zborowski et al. 2020), excepting *m*-trifluoromethyl-diphenyl diselenide that was reported to be effective at minimal 50 mg kg<sup>-1</sup> dose in an acute protocol (Brüning et al. 2011). However, the *m*-trifluoromethyl-diphenyl diselenide effective antidepressant-like dose was reduced by tenfold when it was administered once daily for 8 days in mice (Rosa et al. 2017) and substantially decreased in a TNF- $\alpha$  model of depression (Brüning et al. 2015b). Moreover, this substituted diaryl diselenide has been reported to promote resilience to social avoidance induced by social defeat stress (Rosa et al. 2018c) and abolish the

depressant-like phenotype induced by repeated forced swim stress (Rosa et al. 2018b).

Evidence has been found to suggest that the simple substitution of hydrogen by the *m*-trifluoromethyl group on diphenyl diselenide generates an organoselenium compound that, different from the parent compound, modulates the opioid system in different animal models of mood disorders (Brüning et al. 2011; Martins et al. 2020; Rosa et al. 2017, 2018b). However, neither *m*-trifluoromethyl- nor *p*-methoxyl- diaryl diselenide was associated with anxiety phenotype after discontinuation (Oliveira et al. 2017) and withdrawal syndrome in mice (Rosa et al. 2017), which are experienced by users of antidepressant drugs.

We highlight herein the ambiguity of results obtained with the simplest diaryl diselenide, diphenyl diselenide, in different experimental models of anxiety that undoubtedly demonstrate its well-documented Janus-faced characteristic (Nogueira and Rocha 2010). Results from different groups of research indicate that diphenyl diselenide produced an anxiolytic-like effect in naive (Ghisleni et al. 2008a) and monosodium glutamate-exposed rats (Rosa et al. 2016), naive mice (Savegnago et al. 2008b), naive (Ibrahim et al. 2014b), and hyperglycemic zebrafish (dos Santos et al. 2018), and chick subjected to social separation-stress (Prigol et al. 2011). On the other hand, administration of diphenyl diselenide after repetitive mild traumatic brain injury exacerbated anxiety-like response in rats, increasing the telomeres and the levels of TNF $\alpha$  (Yamakawa et al. 2020). Moreover, in Carioca high- and low-conditioned freezing rats, an animal model of generalized anxiety, diphenyl diselenide induced both anxiogenic- and anxiolytic-like effects (Hassan et al. 2015).

**Table 2** Potential antidepressant-like activity of diaryl diselenides

	Experimental model	Minimal effective dose	Treatment	Predictive tests	Species	References
Diphenyl diselenide	Methimazole	5 <sup>a</sup>	90 days	FST	Rats	Dias et al. (2014)
	Monosodium glutamate	10	30 min	FST	Rats	Quines et al. (2016b)
<i>p</i> -Chloro-diphenyl diselenide	–	10	7 days	FST	Old rats <sup>b</sup>	Bortolatto et al. (2012)
	Streptozotocin	5	7 days	FST, TST	Mice	Zborowski et al. (2020)
	Dexamethasone	5	7 days	FST, TST	Mice	Heck et al. (2019)
<i>m</i> -Trifluoromethyl diphenyl diselenide	–	50	30 min	FST	Mice	Brüning et al. (2011)
	–	5	8 days	FST, mTST	Mice	Rosa et al. (2017)
	TNF- $\alpha$	0.1	30 min	FST, TST	Mice	Brüning et al. (2015b)
<i>p</i> -Methoxyl-diphenyl diselenide	–	5	30 min	mFST	Mice	Sartori et al. (2017)
	–	0.1	7 days	TST mFST	Mice	Sartori et al. (2017)

Diselenides (mg kg<sup>-1</sup>) were intragastrically administered, excepting <sup>a</sup>that was added in the diet (ppm/diet)

Depression predictive tests: *FST* forced swimming test, *TST* tail suspension test, *mFST* modified forced swimming test, *mTST* modified tail suspension test, *TNF* tumoral necrosis factor, <sup>b</sup>23 months, rats (Wistar), mice (Swiss)

The potential of selenides in tests predictive of depression and anxiety has received some attention over the past decade (Besckow et al. 2020; Donato et al. 2013; Gerzson et al. 2012; Jesse et al. 2011; Oliveira et al. 2012; Reis et al. 2017a; Sampaio et al. 2020; Victoria et al. 2014). According to Table 3, (octylseleno)-xylofuranoside challenged in the mouse TST produced an antidepressant-like activity at a very low dose. The minimal effective dose of (octylseleno)-xyloruranoside was, at least, 100-fold lower (Brod et al. 2016) than those of the other selenides shown in Table 3. Of note, ebselen (3–30 mg kg<sup>-1</sup>) did not produce an antidepressant-like activity in the TST (Posser et al. 2009).

A series of selenophene derivatives were evaluated as potential antidepressant molecules (Gai et al. 2012); among them, 3-(*p*-fluorophenylselenyl)-2,5-diphenylselenophene was reported to be effective in naive mice as well as in corticosterone and partial sciatic nerve ligation (PSNL) models of depression (Gai et al. 2014a, b, c; Gay et al. 2010). When it was subchronically administered, the anxiolytic-like property of 3-(*p*-fluorophenylselenyl)-2,5-diphenylselenophene was demonstrated in corticosterone (Gai et al. 2014b), sham-operated, and PSNL mice (Gai et al. 2014a) (Table 3).

Further investigations of organoselenium compounds, that similar to serotonin contain the indole nucleus, uncovered 1-methyl-3-(phenylselanyl)-1*H*-indole as an antidepressant- and anxiolytic-like molecule in the icv streptozotocin model (Bampi et al. 2019, 2020b) (Table 3).

Besides, 1-methyl-3-(phenylselanyl)-1*H*-indole was reported to be effective against depressive-like behavior and hyperglycemia in a model of type 1 diabetes induced by streptozotocin in mice (Bampi et al. 2020a). The

introduction of the *p*-chloro substituent at the-phenylselanyl group affords 3-[(*p*-chlorophenyl)selanyl]-1-methyl-1*H*-indole, an antidepressant-like compound effective against lipopolysaccharide-induced depression- and anxiogenic-like phenotype, without promoting locomotor impairment in mice (Casaril et al. 2017, 2019b). It was demonstrated that this substituted selenium indole derivative was also effective in the acute restrain stress-induced depressive-like behavior in mice (Casaril et al. 2019a).

In the search for new potential antidepressant-like compounds, the same group synthesized and demonstrated the antidepressant activity of another *N*-heterocycle derivative, 3-[(*p*-methoxyphenyl)selanyl]-2-phenylimidazo[1,2-*a*]pyridine (Domingues et al. 2018, 2019). Very recently, an isoquinoline derivative has been reported as an antidepressant-like compound that selectively and reversibly inhibited cerebral monoamine oxidase (MAO) B activity in C57Bl/6 mice (Sampaio et al. 2016, 2020).

It may be mentioned that the drug interaction with multiple targets, instead of a single one, has raised considerable interest in the treatment of complex diseases as mood disorders (Koeberle and Werz 2014). On the other hand, the lack of target specificity, possibly because organoselenium compounds react with a multitude of protein thiols, could result in drugs potentially good for everything but effective for nothing. Therefore, the proposed mechanisms to explain the antidepressant- and anxiolytic-like properties of the above-reported organoselenium compounds indicate multiple molecular sites of action; most of them demonstrated using empirical and non-robust methodologies.

**Table 3** Potential antidepressant-like activity of selenides

	Experimental model	Minimal effective dose	Predictive tests		References
			Depression	Anxiety	
(Octylseleno) xilofuranoside	–	0.001	TST	–	Brod et al. (2016)
(Fluorophenylselenyl)-2,5-diphenyl selenophene	–	50	FST	–	Gay et al. (2010)
	Corticosterone	0.1 <sup>a</sup>	FST, TST	LD, NSF	Gai et al. (2014b)
	Partial sciatic nerve ligation	1	FST, TST	LD	Gai et al. (2014a)
1-Methyl-3-(phenylselanyl)-1 <i>H</i> -indole	Streptozotocin (intracerebro ventricular)	10	FST, Splash	–	Bampi et al. (2020b)
		10 <sup>a</sup>	Social interact, TST Splash	EPM	Bampi et al. (2019)
(Chlorophenyl)selanyl]-1-methyl-1 <i>H</i> -indole	Lipopolysaccharide	1	TST Splash	EPM MB	Casaril et al. (2019b)
	Acute restrain stress	1	TST Splash	–	Casaril et al. (2019a)

Selenides (mg kg<sup>-1</sup>) were intragastrically administered to Swiss mice 30 min before tests, excepting <sup>a</sup>that means repeated treatment (7 days), *FST* forced swimming test, *TST* tail suspension test, *LD* light dark test, *NSF* novelty suppressed-feeding, *EPM* elevated plus maze, *MB* marble burying

## Anti-inflammatory and anti-nociceptive activities

Over the last decades, the anti-inflammatory properties of ebselen have been well recognized in cellular systems and studies with laboratory animals (Aruoma 1997; Baek et al. 2016; Brüne et al. 1991; Cotgreave et al. 1988, 1989; Dimmeler et al. 1991; Gao and Issekutz 1993; ICHIKAWA et al. 1987; Kuhl et al. 1986; Leurs et al. 1989; Safayhi et al. 1985; Schewe et al. 1994; Zembowicz et al. 1993; Zhang et al. 2002), and the pioneer studies were previously summarized elsewhere (Nogueira and Rocha 2011; Nogueira et al. 2004; Schewe 1995) and need not to be repeated here.

Although a vast body of literature supports the potential use of ebselen as a drug that in addition to its antioxidant property acts in multiple cellular mechanisms involved in the inflammatory process (Parnham et al. 1991; Schewe 1995; Smith et al. 2012; Xu et al. 2018), its medical application in inflammatory human diseases is until expected. One plausible explanation for the lack of ebselen effectiveness in chronic inflammatory diseases is that ROS cause endothelial dysfunction and tissue damage (Halliwell 2012), but can also help to resolve it (Halliwell 2006; Sareila et al. 2011), which illustrates the paradoxical action of antioxidants in certain diseases (Halliwell 2013).

As described earlier, simple diaryl diselenides showed potent anti-inflammatory activity in vitro and in vivo acute inflammatory models (Galet et al. 1994; Nogueira et al. 2003; Shen et al. 2004; Shin et al. 2009). From these studies, structure–activity relationship can be distinguished and indicated *m*-hydroxyphenyl diselenide as a potent anti-inflammatory agent in lipopolysaccharide-activated macrophage cells (Shin et al. 2009).

Shortly after, inspired by the Shin study, the anti-inflammatory properties of diphenyl diselenide were identified in classically activated macrophages. In this study, diphenyl diselenide reduced the expression of NO synthase and, consequently, the NO production, diminished the levels of ROS and arginase activity, and down-regulated classical and alternative activation phenotype of macrophages (Rupil et al. 2012). By modulating pro-inflammatory markers and oxidative stress, diphenyl diselenide has been reported to be effective in a mouse model of carrageenan-induced pleurisy (Luchese et al. 2012b), ischemia and reperfusion-induced cerebral injury (Brüning et al. 2012a), and experimental toxoplasmosis (Barbosa et al. 2014; Doleski et al. 2017a, b).

In an experimental model of ulcerative colitis, repeated treatment with diphenyl diselenide (50 mg kg<sup>-1</sup>, i.g.) was found to be more effective than ebselen (50 mg kg<sup>-1</sup>) to reverse colon damage, neutrophil infiltrate, and oxidative stress markers in rats (Petronilho et al. 2016). When supplemented in the diet, diphenyl diselenide reduced the levels of serum pro-inflammatory cytokines (IL-1, TNF- $\alpha$ ) and increased the IL-10 concentration in middle-aged rats and

dairy sheep (Biazus et al. 2019; Leite et al. 2015). The modulation of purinergic signaling and nucleotide-binding oligomerization domain-like receptor (NLRP3) inflammasome gene expression was reported as the underlying mechanisms by which diphenyl diselenide induced an anti-inflammatory response in methyl-mercury chloride-induced immunotoxicity in grass carp (Souza et al. 2019). Moreover, by modulating splenic purinergic signaling, diphenyl diselenide reduced inflammatory and hemorrhagic processes induced by fumonisin B1 in silver catfish (Baldissera et al. 2020b).

Recent evidence associates the anti-inflammatory properties of selenomethionine and its hydroxyl analogue with suppression of the NF- $\kappa$ B pathway and the increase in the expression of selenoproteins encoding genes in trachea and liver of lipopolysaccharide-exposed chicken (Qu et al. 2020; Shi et al. 2020) and spleens of Kunming mice exposed to lipopolysaccharide (Tang et al. 2019).

## Antinociceptive activity

Increasing evidence indicated that redox modulation is important in the sensitization of peripheral nociceptors (Bhave and Gereau 2004; Choi and Lipton 2000; Meotti et al. 2009), supporting the potential of drugs aimed at restoring the redox homeostasis and relieving pain. Therefore, organoselenium compounds have been screened for antinociceptive activity, and some of these findings showed that both diphenyl diselenide and ebselen, systemically or locally administered, were effective in mouse models of nociception (Nogueira et al. 2003; Rosa et al. 2015; Savegnago et al. 2007a, 2008a; Zasso et al. 2005). It is important to note that ebselen, different from diphenyl diselenide (Savegnago et al. 2007c), produced a synergistic pronociceptive effect when administered with glutamate, which was blocked by a reduced glutathione depleting agent (Meotti et al. 2009).

*p*-Methoxyl-, *m*-trifluoromethyl-, and *p*-methyl-substituted diaryl diselenides were reported to be as effective as a non-substituted diphenyl diselenide in experimental models of nociception (Brüning et al. 2014, 2010; Donato et al. 2015; Jesse et al. 2009; Oliveira et al. 2016; Pinto et al. 2008), suggesting that the characteristics of substituents at the aryl moiety do not alter the antinociceptive property of diselenides (Araujo et al. 2020; Brüning et al. 2015a; Savegnago et al. 2007a).

Over the last decade, considerable efforts have been made to synthesize organoselenium compounds with greater antinociceptive activity and fewer side effects, resulting in a multitude of molecules with relative success, namely imidazole diselenide derivative (Chagas et al. 2013b, 2017a, b), dipyrindil diselenide and its *m*-amino-substituted derivative (Reis et al. 2019; Rosa et al. 2018a), salicylic acid–selenium derivative (Chagas et al. 2014), *bis*-vinylselenide derivatives

(Jesse et al. 2007, 2008; Savegnago et al. 2006a), selenosulfide derivative (Sari et al. 2014), and quinoline (Pinz et al. 2016), indole (Birmann et al. 2018), and pyrazole (Oliveira et al. 2020) selenide derivatives. However, the organoselenium compounds synthesized so far have low aqueous solubility and pharmacokinetic and toxicokinetic practically unknown (Fischer et al. 1988; Müller et al. 1988; Prigol et al. 2013; Sies 1994), limiting the possibility of their therapeutic applications.

Therefore, the rationale to incorporate *p*-methoxydiphenyl diselenide in polymeric nanocapsules was based on the enhancing of its pharmacokinetic properties (Sari et al. 2017), and resulted in a more prolonged anti-hypernociceptive action and greater restorative effects than the free compound in a mouse model of neuropathic pain (Sari et al. 2018a, b).

### Hepato and gastroprotective activities

In the earlier 50s, Schwarz and Foltz demonstrated the effectiveness of element selenium against dietary necrotic liver degeneration in rats (Schwarz and Foltz 1957) and, since that, naturally occurring and synthetic organoselenium compounds have been widely investigated as possible hepatoprotective molecules (Brzački et al. 2019; Ibrahim et al. 2010; Jiang et al. 2016; Kono et al. 2001; Ozaki et al. 1997; Reis et al. 2017b; Schwarz and Fredga 1969; Shimohashi et al. 2000; Tiegs et al. 1998; Wang et al. 1992; Wendel and Tiegs 1986; Wilhelm et al. 2010, 2011).

Three decade-long studies on the protective action of ebselen in a diversity of experimental models of hepatotoxicity, such as galactosamine (Wendel and Tiegs 1986), paracetamol (Qiu-Ju et al. 1994; Rocha et al. 2005), CCl<sub>4</sub> (Wasser et al. 2001), lipopolysaccharide and *Propionibacterium acnes* (Koyanagi et al. 2001), alcohol (Oshita et al. 1994; Pivetta et al. 2006), ischemia–reperfusion (Ozaki et al. 1997), manganese (Ismail 2019), and radiocontrast media (Basarslan et al. 2013), have indicated the modulation of NF-κB-dependent pathway and activation of the immune system as the mechanisms accounted for this action (Shimohashi et al. 2000; Tiegs et al. 1998; Wang et al. 1992).

Diphenyl diselenide and its substituted derivatives have been also screened for hepatoprotective activity in 2-nitropropane (Borges et al. 2005, 2006; Ibrahim et al. 2010), metal (Borges et al. 2008; Dalla Corte et al. 2016), acetaminophen (Carvalho et al. 2013, 2017; da Rosa et al. 2012; Wilhelm et al. 2009b, c), bisphenol A (Müller et al. 2018), thioacetamide (Stefanello et al. 2015b), lipopolysaccharide/galactosamine (Wilhelm et al. 2009a), and organophosphate (Acker et al. 2012; Costa et al. 2013) models of damage in rodents.

Regarding the hepatic injury induced by CCl<sub>4</sub>, repeated administration of *p*-methylbenzoyl diselenide derivative

(Filho et al. 2013) and selenocystine (Uzma et al. 2011) has proven to be effective, whereas treatment with diphenyl diselenide potentiated CCl<sub>4</sub> damage, suggesting that biotransformation of this toxicant by cytochromes P450 was activated by diphenyl diselenide (Nogueira et al. 2009).

Despite the significance to avoid gastric mucosal irritation in the design of potential anti-inflammatory drugs and the importance of prescribing antisecretory drugs for long-term use of anti-inflammatory therapy (Graham and Chan 2008), the gastroprotective activity of organoselenium compounds has been few explored (Ibrahim et al. 2018) over the last decade. Therefore, the knowledge on this subject is supported by previously published studies, which demonstrated that ebselen and diphenyl diselenide not only reduce HCl secretion, but also inhibit gastric lesions in a great number of experimental models (Beil et al. 1990; Ineu et al. 2008; Kurebayashi et al. 1989; Leyck and Parnham 1990; Ohta et al. 2002; Savegnago et al. 2006b; Tabuchi and Kurebayashi 1993; Tabuchi et al. 1994, 1995).

### Renoprotective activity

Studies on the renoprotective activity of organoselenium compounds remained to be explored; as a result, most of the literature of the last 2 decades focuses on ebselen and diphenyl diselenide effects on models of renal damage.

With regard to ebselen activity, it protected against ischemic renal injury (Noiri et al. 2001) as well as gentamicin- (Dhanarajan et al. 2006), sodium arsenite- (Al-Brakati et al. 2019), sporadic Alzheimer's disease (AD) model- (Klann et al. 2020), and radiocontrast- (Ozgun et al. 2012) induced renal damage in rodents. In a model of renal ischemia/reperfusion damage, ebselen associated with *N*-acetylcysteine was proven to be effective (Kizilgun et al. 2011).

Using experimental models of diabetes, beneficial effects of ebselen and its *m*-hydroxyl derivative were demonstrated in Zucker diabetic fat rats (Gealekman et al. 2004) and the ApoE/GPx1 double knockout mouse (Tan et al. 2013). Although the authors suggest synthetic mimetics as a useful therapeutic strategy in reducing diabetic complications, late chronic intervention with ebselen reduced oxidative stress, but failed to attenuate functional or structural kidney damage in the Akita mouse model of nephropathy (Tan et al. 2015).

Since its approval by the Food and Drug Administration in 1978, cisplatin has been one of the most used drugs for solid cancer treatments. However, nephrotoxicity is the most well-known and clinically important toxicity of this chemotherapeutic (Ghosh 2019). In an attempt to counteract the main drawback of the cisplatin use, which limits its application, organoselenium compounds have been investigated in models of renal damage induced by this chemotherapy. Ebselen (Lynch et al. 2005; Yoshida et al. 2000),

*p*-methoxyl-diphenyl diselenide (Wilhelm et al. 2012), naphthalamide (Ghosh et al. 2015), selenocyanate isoquinoline derivative (Ghosh et al. 2013), and diselenole (Bortolatto et al. 2014) have appeared in the literature as effective organoselenium compounds against cisplatin-associated nephrotoxicity. In a juvenile rat model of cisplatin-induced nephrotoxicity, diphenyl diselenide (12 mg kg<sup>-1</sup>, i.g.) was reported to be as effective as ebselen (11 mg kg<sup>-1</sup>, i.g.) in rats (Fulco et al. 2020).

Searching for naturally occurring organoselenium compounds that reduce renal toxicity and enhance the antitumor activity of cisplatin, selenomethionine, and methylselenocysteine was highlighted as promising molecules (Cao et al. 2014; García Sar et al. 2011).

Based on the well-reported effectiveness of diphenyl diselenide against toxicity induced by metals (Brandão et al. 2008; Santos et al. 2005a, b), the potential renoprotective activity of this diselenide was investigated in a mercuric chloride model of renal injury (5 mg kg<sup>-1</sup>, s.c.). From these studies, the Janus-faced duality of diphenyl diselenide was recognized; an acute dose of 31 mg kg<sup>-1</sup> (s.c.) potentiated mercuric chloride-induced nephrotoxicity (Brandão et al. 2011), whereas a 5-day repeated dose (5 mg kg<sup>-1</sup>, i.g.) protected against toxic effects of this metal in the kidney of mice (da Luz Fiuza et al. 2015). It is acknowledged that diphenyl diselenide effects on renal injury induced by mercuric chloride depend on the dose of this organoselenium and the protocol of administration of both compounds.

Moreover, diphenyl diselenide (7.14 mg kg<sup>-1</sup>, i.g.) repeated administration for 7 days protected against glycerol induced nephrotoxicity in rats (Brandao et al. 2009), whereas its binaphthyl derivative (50 mg kg<sup>-1</sup>, i.g.) was effective at a higher acute dose in mice (Ibrahim et al. 2011).

## Cardioprotective activity

Regarding selenium status, both excess and deficiency are associated with some adverse health conditions (Rayman 2020), and a well-known example relates to cardiovascular disorders and increased mortality in individuals who have selenium-deficient levels (Bleys et al. 2008; Lubos et al. 2010). Further of note, Keshan disease, endemic cardiomyopathy, and Kashin–Beck disease, deforming arthritis, are both associated with selenium deficiency in China (Navarro-Alarcon and López-Martínez 2000; Xiong et al. 2010).

Hypercholesterolemia, a very important risk factor to cardiovascular disease, has been related to selenium deficiency, which would lead to the decrease in low-density lipoprotein removal from blood and in apolipoprotein B catabolism, through down-regulation of low-density lipoprotein receptor activity mRNA expression (Dhingra and Bansal 2005, 2006; Lee et al. 2003).

In addition to the significance of selenium to cardiac health maintenance (Gunes et al. 2017; Rocca et al. 2018; Yang et al. 2017), organoselenium compounds have been investigated in models of cardiotoxicity and ischemia/reperfusion injury, in which redox imbalance triggers a number of signaling pathways mediated by reactive oxygen and nitrogen species, and, that antioxidants play a role.

Based on the fact that cardiotoxicity is one of the recognized drawbacks of anti-cancer treatments (Dong and Chen 2018), ebselen was tested and proven to be effective against chemotherapeutic daunorubicin-induced cardiomyopathy in rats (Saad et al. 2006). From experiments with reconstituted human heart, cytosolic fractions emerge the molecular mechanism of ebselen cardioprotective activity, the inhibition of reductive anthracycline alcohol metabolite formation (Mordente et al. 2015).

The suppression of cardiomyocyte apoptosis, anti-inflammatory, and antioxidant activities have been implicated in the cardioprotective action of ebselen against ischemia/reperfusion injury in rats (Cheng et al. 2019; Steinbrenner et al. 2016).

Used as an adjuvant in heart preservation, ebselen was added to a cardioplegic histidine–tryptophan–ketoglutarate (HTK) solution and proven to enhance myocardial protection in a piglet model of cardiopulmonary bypass (Liu et al. 2015a).

Considering that oxidized low-density lipoprotein (LDL) is recognized as a key stage in the development of atherosclerosis, diphenyl diselenide and its substituted diaryl diselenides were investigated in a model of LDL oxidation in vitro, in which the antioxidant and antiatherogenic effects were reported (de Bem et al. 2008; Stralioetto et al. 2013a). Shortly after, the same authors demonstrated that diphenyl diselenide reduced oxidized LDL-induced cytotoxicity and down-regulated NF-κB pathway in murine macrophage cells (Stralioetto et al. 2013b). In animal models, diphenyl diselenide reduced hypercholesterolemia in cholesterol-fed rabbits (De Bem et al. 2009) and tyloxapol-exposed mice (Da Rocha et al. 2009; Sartori Oliveira et al. 2016). The reduction of atherosclerotic plaque formation and endothelial dysfunction, and antiatherogenic properties of diphenyl diselenide were attributed to the increase of the antioxidant defenses in the cardiovascular system of low-density lipoprotein receptor knockout (LDLr <sup>-/-</sup>) mice (Hort et al. 2011; Mancini et al. 2014).

Moreover, the cardioprotective activity of diphenyl diselenide was demonstrated in a toxoplasmosis model of cardiac toxicity (Machado et al. 2016).

The naturally occurring organoselenium compound selenomethionine has recently been exploited in HOCl-induced dysfunction in myoblastic cells. In this study, cardiac myoblast protection was attributed to the antioxidant activity of selenomethionine. However, selenomethionine

supplemented ( $2 \text{ mg kg}^{-1}$ ) in the diet had limited efficacy in a rat cardiac ischemia/reperfusion injury (Reyes et al. 2019). In an apolipoprotein E-deficient (ApoE $^{-/-}$ ) mouse model of atherosclerosis, selenomethionine ( $2 \text{ mg kg}^{-1}$ ) added within a high-fat diet-fed decreased the formation of atherosclerotic plaque and M1 inflammatory-type macrophages. The translational applicability of this study was highlighted by the decrease in the extent of extracellular trap release from phorbol myristate acetate (PMA)-stimulated mouse bone marrow-derived cells, which was replicated on cultured neutrophils isolated from acute coronary syndrome patients (Zhang et al. 2020e). Although at a lower concentration in the diet ( $0.5 \text{ mg kg}^{-1}$ ), selenomethionine was effective against myocardial oxidative stress and inflammation induced by LPS through the miR-128-3p-p38MAPK-NF- $\kappa$ B pathway in chicken (Liu et al. 2020a).

Cardiovascular injury has been associated with radiation in cancer therapy (Eldabaje et al. 2015), in which the redox modulation plays an important role. Therefore, selenomethionine ( $4 \text{ mg kg}^{-1}$ ) was able to protect the rat heart tissue against radiation-induced injury by down-regulating the expression of dual oxidase (Duox1 and Duox2); two important pro-oxidant enzymes (Kolivand et al. 2019).

### Insulin-mimetic activity

The beneficial or harmful effects of selenium on type 2 diabetes are a matter of controversy, resembling the U-shaped behavior of this nutritionally essential trace element in animals and humans. A detailed discussion of the literature on this field is outside of the scope of this review, and has been reviewed by others (Duntas and Benvenega 2015; Kohler et al. 2018; Rayman 2020; Rayman and Stranges 2013; Schomburg 2020).

Despite some controversy, high dietary selenium intake has been associated with protection against obesity and type 2 diabetes (Wang et al. 2016a, 2017a), but the mechanisms to explain this action are unknown or unclear. The demonstration that activation of redox-sensitive thermogenic cascade and the uncoupling protein 1 (UCP1) initiates thermogenesis in brown adipose tissue, a tissue metabolically reprogrammed that requires bioenergetic substrates to increase mitochondrial respiration and produce heat via the UCP1, further support the evidence that selenium could be beneficial in type 2 diabetes and obesity (Lettieri-Barbato 2019).

Very recently, an elegant study, which applied a mass spectrometric tool to identify selenium insertions in proteins, demonstrated the existence of facultative protein selenation, which correlates with impacts on thermogenic adipocyte function. In this study, selenium as selenocysteine (Sec) was selectively incorporated into regulatory sites on key metabolic proteins as an alternative to cysteine

at position 253 in the UCP1. It is important to highlight that UCP1-Sec253 is highly sensitive to redox modulation and that increasing the pool of this type of facultative selenoprotein coincides with brown adipose tissue-dependent energy expenditure (Jedrychowski et al. 2020).

In addition to the selenium role as an integral component of several enzymes, such as formate dehydrogenase, glutathione peroxidase, selenoprotein P and W, and the deiodinases (Beckett and Arthur 2005), the possibility to mimic the insulin action has been reported to help in explaining the antidiabetogenic properties of inorganic forms of this element. For a more in-depth discussion of issues that support selenate as an effective insulin-mimetic, readers are directed to a comprehensive review (Stapleton 2000).

Regarding organoselenium compounds, the effectiveness of ebselen and diphenyl diselenide has been reported in a number of experimental models of diabetes, and its complications (Barbosa et al. 2008, 2006; Bubolz et al. 2007; Chander et al. 2004; De-Mello et al. 1996; Gealekman et al. 2004; Kade et al. 2009; Soares et al. 2014; Zhou et al. 2016).

Over the last 10 years, most of the research has focused on the underlying mechanisms of ebselen antidiabetogenic properties. Experimental models in which ebselen, besides reducing hyperglycemia, stimulates insulin secretion (Wang et al. 2014) and hepatic glycogen synthesis (Costa et al. 2012), modulates expression of glucose transporter (GLUT2) and glucokinase, suppresses gluconeogenesis by decreasing phosphoenolpyruvate carboxykinase (PEPCK) expression (Park et al. 2014), and prevents islet apoptosis as well as preserves mass and function of  $\beta$ -cells, by reducing oxidative stress markers and enhancing intranuclear location of critical insulin transcription factors (Mahadevan et al. 2013; Sasaki et al. 2013), are listed in Table 4.

However, when evaluated against oxidative stress-induced endothelium-dependent vasodilation in diabetic patients, ebselen was proven to be ineffective, at least at the dose tested in this trial ( $150 \text{ mg}$  per oral, twice daily) (Beckman et al. 2016).

Diphenyl diselenide insulin-like properties have been associated with the increase in low-density lipoprotein receptor (LDLr) expression and the translocation of glucose transporter (GLUT4) through the adenosine monophosphate kinase (AMPK) activation (da Rocha et al. 2013a, b), the decrease of cholesterol levels and reduction of visceral fat (da Rocha et al. 2011; Ribeiro et al. 2013), and the modulation of gluconeogenesis enzymes, in addition to regulating hyperglycemia (Acker and Nogueira 2014). Recently, a study from our research group demonstrated that the anti-hyperglycemic effect of diphenyl diselenide is associated with an up-regulation of insulin receptor and glucose transporter driven by the product of FoxO genes that were also up-regulated at the transcriptional level (dos Santos et al. 2020).

**Table 4** Insulin-mimetic activity of ebselen, diphenyl diselenide, and *p*-chloro diphenyl diselenide in different experimental models

	Experimental model	References
Ebselen	Glucose-stimulated insulin secretion in murine islets	Wang et al. (2014)
	Post stroke-induced hyperglycemia	Park et al. (2014)
	Diazinon-induced hyperglycemia	Costa et al. (2012)
	$\beta$ -cell mass and function of Zucker diabetic fatty rats	Mahadevan et al. (2013)
	Metabolism and secretion of $\beta$ -cells of Goto-Kakizaki non-obese diabetic rats	Sasaki et al. (2013)
Diphenyl diselenide	Acephate-induced hyperglycemia	Acker et al. (2014)
	HepG2 and L6 myoblasts cells	da Rocha et al. (2013b)
	Ovariectomy-induced metabolic disorders	da Rocha et al. (2011)
	Fructose and hydrochlorothiazide-induced metabolic Disorders	Ribeiro et al. (2013)
	Glucose-induced hyperglycemia in Zebrafish	dos Santos et al. (2020)
<i>p</i> -Chloro Diphenyl diselenide	Feeding behavior	Bortolatto et al. (2015)
	Monosodium glutamate-induced neuroendocrine obesity	Quines et al. (2016a, 2017a, 2018)
	High-fructose load-induced hyperglycemia	Quines et al. (2017b)

Moreover, both diphenyl diselenide and its *p*-chloro derivative, by inhibiting the hypothalamic 5-hydroxytryptamine (5HT) uptake, increase satiety suggesting their potential use as weight-reducing agents (Bortolatto et al. 2015). The *p*-chloro derivative satiating action was also reported to be most related to the lower orexin levels in the hypothalamus than the activation of thermogenesis in brown adipose tissue in rats (Bortolatto et al. 2017). From different experimental models (Quines et al. 2016a, 2017a, 2018; b) emerged evidence that *p*-chloro derivative modulates glucose metabolism as well as reverses metabolic and mitochondrial dysfunction. Table 4 lists some experimental models in which ebselen, diphenyl diselenide, and its *p*-chloro derivative exert insulin-mimetic activity.

With regard to the effects of supplementary organoselenium compounds on glucose tolerance, selenomethionine was found to be effective in increasing pancreatic and hepatic RNA levels of GPx1 and glucose tolerance, even though it was unsuccessful in restoring insulin storage and secretion in nicotinamide/streptozotocin-induced mild diabetic mice (Ueno et al. 2014, 2018).

### Neuroprotective activity

The history of ebselen borderline efficacy on brain ischemia and stroke clinical trials (Saito et al. 1998; Yamaguchi et al. 1998) was described by Parnham and Sies (2013), their commentaries, and personal perspectives reordered how the early research on this compound unwound.

With regard to the knowledge of the last 30 years, most derived from basic research that provided the full picture of ebselen neuroprotective effects in a great number of in vitro and in vivo models of brain toxicity. However, no attempt

is made here to thoroughly discuss these reports; these have been adequately reviewed elsewhere (Hassan et al. 2016; Nogueira and Rocha 2011; Nogueira et al. 2004).

Since the pioneering study of Ünlü et al. (2002), the neuroprotective effects of ebselen on a spinal cord injury (SCI) model have been investigated. Applying the same dose (Aras et al. 2014; Jia et al. 2018; Kalayci et al. 2005) but an SCI model quite different from other studies, ebselen was proven to have a limited beneficial effect on the regeneration of the injury in the spinal cord white matter of rats (Ślusarczyk et al. 2019). Conversely, the improvement of motor function 14 days after the injury and the raise of anti-apoptotic and antioxidant markers had been previously reported (Jia et al. 2018; Kalayci et al. 2005). The authors suggest that these conflicting outcomes are explained by the fact that the neuroprotective effects of ebselen are not persistent long time after the administration (Ślusarczyk et al. 2019).

Glutamate, the main excitatory neurotransmitter in the mammalian central nervous system (CNS), in addition to have a large array of physiological functions, behaves as a potent neurotoxin in pathological conditions in which its metabolism is altered; therefore, neuronal death induced by glutamate is named excitotoxicity (Magi et al. 2019; Watkins and Jane 2006). Moreover, excitotoxicity has been implicated in different conditions, such as hypoxic/ischemic, traumatic brain injury, epilepsy, hypoglycemia, neuropsychiatric, and neurodegenerative disorders, among others (Olloquequi et al. 2018; Sharma et al. 2019; Zhang et al. 2020d), and organoselenium compounds have been investigated as potential therapeutic alternatives on this pathological phenomenon.

Diphenyl diselenide neuroprotective activity had been previously reported in the literature (Ghisleni et al. 2003,

2008b; Machado et al. 2006; Nogueira et al. 2001; Posser et al. 2008) and, since that, propagated in experimental models of ischemia/reperfusion (Brüning et al. 2012a), stroke (Dobrachinski et al. 2014), auto-immune encephalomyelitis (Chanaday et al. 2011), mania (Brüning et al. 2012b), acetaminophen- (da Silva et al. 2012), chlorpyrifos- (Adedara et al. 2018), mycotoxin- (Baldissera et al. 2020c), manganese- (Adedara et al. 2016), and methyl-mercury- (Baldissera et al. 2020a; de Freitas et al. 2009; Glaser et al. 2013, 2014; Meinerz et al. 2011) induced neurotoxicity.

The modulation of the glutamatergic system, the anti-inflammatory property, and antioxidant activity have been reported to play a role in diphenyl diselenide neuroprotective activity (Dalla Corte et al. 2012; Nogueira and Rocha 2010). In an attempt to explore the contribution of TrxR in neuroprotective effects of diselenides, diphenyl diselenide and its derivatives were investigated in the NADPH oxidation assay. The results revealed that diselenides were reduced to their selenol intermediates, indicating their role as substrates for cerebral TrxR (de Freitas and Rocha 2011). Consequently, any or all of these mechanisms of action could contribute to the neuroprotective action of diphenyl diselenide.

Glutaminase, an enzyme that catalyzes the hydrolysis of glutamine to glutamate, has been accounted for the generation of excitotoxic glutamate in the CNS and associated with ischemia, HIV-associated dementia, neurodegenerative diseases, and multiple sclerosis. Therefore, drug-like glutaminase inhibitors have been screened as potential neuroprotective agents. Ebselen was found as a potent inhibitor of glutaminase; however, due to the multiplicity of biological effects and lack of selectivity, Thomas and collaborators argue that it may be not a good prototype inhibitor for glutaminase inhibition *in vivo* (Thomas et al. 2013), which was confirmed by the Kosten study (Kosten et al. 2019).

In traumatic brain injury models, organoselenium compounds have opposite effects, whereas ebselen (3 to 30 mg kg<sup>-1</sup>, i.g) was neuroprotective, reducing nitric oxide levels and modulating the TLR4-mediated P38 MAPK signaling pathway (Wei et al. 2014), and diphenyl diselenide (10 and 25 mg kg<sup>-1</sup>, i.p) exacerbated post-concussive angiogenic behavior and increased TNF $\alpha$  levels and longer telomeres (Yamakawa et al. 2020).

Given the fact that organoselenium compounds are effective in experimental models associated with the overproduction of ROS in the brain (Burger et al. 2006; Fachinnetto et al. 2007; Souza et al. 2010) and antioxidant defenses are overwhelmed in sepsis (Cassol et al. 2010), diphenyl diselenide and ebselen have been investigated in a cecal ligation and perforation model of sepsis in rats (Silvestre et al. 2014). This study revealed that diphenyl diselenide (50 mg kg<sup>-1</sup>) reduced oxidative stress, mitochondrial dysfunction, and creatine kinase activity in cerebral structures of sepsis-survivor rats, whereas ebselen (50 mg kg<sup>-1</sup>) was reported to be less

effective. The lower effectiveness of ebselen in this model was attributed to the reduced viability of rat hippocampal astrocytes via its action on the mitochondrial activity (Santofimia-Castano et al. 2013), whereas diphenyl diselenide positively modulated mitochondrial dysfunction (Dobrachinski et al. 2014) and reduced hepatic lipid peroxidation in a rat model of sepsis (Prauchner et al. 2011).

Although using different experimental models of Parkinson's disease, ebselen was reported to be ineffective against dopaminergic toxicity induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the nigrostriatal tract of mice (Dhanasekaran et al. 2006), whereas diphenyl diselenide restored motor impairment, the decrease in ipsilateral striatal tyrosine hydroxylase levels, and mechanical and thermal nociception induced by 6-hydroxydopamine in rats (Da Rocha et al. 2013a, b; Sampaio et al. 2017b).

Regarding naturally occurring selenide-containing amino acids, we are only aware of very few published reports to date. In a culture of the hippocampal neurons, selenomethionine was effective against neuronal death induced by  $\beta$ -amyloid peptide (25–35) and Fe<sup>2+</sup>/H<sub>2</sub>O<sub>2</sub> (Xiong et al. 2007), whereas selenocysteine antagonized oxygen–glucose deprivation-induced neurotoxicity (Wang et al. 2018b). The antioxidant potential of these amino acids was associated with their neuroprotective effects.

As shown by the massive indexed literature in the last decade, the effects of organoselenium compounds on memory have attracted the interest of the scientific community; therefore, the neuroprotective effects of these compounds on memory will be addressed separately in the next section.

## Memory-enhancing activity

Cognitive decline and Alzheimer's dementia are conditions associated with lower levels of nonmetal element selenium (Loef et al. 2011; Cardoso et al. 2017; Rayman 2020; Reddy et al. 2017). An argument in favor of selenium supplementation in this condition (Rayman 2012) is that oxidative damage is a key component in the course of Alzheimer's disease (AD) (Butterfield and Halliwell 2019), even though the etiology and pathophysiology of this disease are still unknown.

In this way, experimental models are essential to understand the disease pathogenesis and to perform pre-clinical screening of novel therapies; however, often, they replicate only specific memory-associated cognitive impairments, which fail to resemble brain features of AD patients (Drummond and Wisniewski 2017). Research efforts in this field have uncovered ebselen (Table 5) as an inhibitor of acetylcholinesterase (AChE) activity (Luo et al. 2014; Martini et al. 2015; Mazzanti et al. 2009) and divalent metal transport (DMT1), which has been associated with the reduction of iron-induced tau hyperphosphorylation in human neuroblastoma SH-SY5Y cells (Xie et al. 2018a,



**Table 5** Effects of ebselen on end points of Alzheimer's disease experimental models

End points	Effects	Experimental model	References
Acetylcholinesterase	Inhibits	In vitro	Luo et al. (2014); Martini et al. (2015)
		In vivo	Mazzanti et al. (2009)
Divalent Metal Transport 1	Inhibits	In vitro	Xie et al. (2018a, 2012)
Amyloid precursor protein (APP)	Reduces	In vitro	Xie et al. (2018a)
Ferrous iron-induced tau hyperphosphorylation	Reduces	In vitro	Xie et al. (2012)
$\beta$ -amyloid (A $\beta$ ) generation	Represses	In vitro	Xie et al. (2018a)
BACE1 and presenilin	Inhibits		
Spatial and recognition memory	Improves	Sporadic AD	Martini et al. (2019)
Apoptose, oxidative stress (hippocampus)	Reduces		
Apoptose, oxidative stress (cortex)	Reduces	Sporadic AD	Unsal et al. (2016)
$\beta$ -Amyloid and tau	Reduces	Triple-transgenic AD	Xie et al. (2017)
Spatial memory	Improves		
Acetylcholinesterase	Inhibits	Scopolamine-induced Amnesia	Martini et al. (2018)
Spatial recognition memory	Improves		

AD Alzheimer's disease

2012). Ebselen has been shown to improve memory and hallmarks of the disease in triple-transgenic (Xie et al. 2017) and sporadic AD models (Martini et al. 2019; Unsal et al. 2016), and scopolamine-induced amnesia, as well (Martini et al. 2018).

Several strategies have been employed to synthesize a series of ebselen derivatives aiming at achieving potential anti AD compounds; among them, we highlight the fusion of ebselen with donepezil and tacrine, potent AChE inhibitors used in clinical practice (Luo et al. 2013, 2014; Mao et al. 2013; Wang et al. 2016b). However, such structural changes have not been reported to provide significant therapeutic advantages.

Since the 2000s and the pioneering work of Rosa et al. (2003), diphenyl diselenide and its derivatives have been proven to be effective against memory impairment in rodent and non-rodent models (Jardim et al. 2017; Pinton et al. 2010; Souza et al. 2010; Stangherlin et al. 2008; Zamberlan et al. 2014; Zborowski et al. 2016). Some examples of experimental models are listed in Table 6, in which diphenyl diselenide-supplemented diet alone or in association with exercise or caffeine improved memory impairment in aged rats (Cechella et al. 2014a, b, 2018; Leite et al. 2014) and hypothyroidism condition (Dias et al. 2012); when administered by gavage, it was also effective in an ovariectomy model of menopause (da Rocha et al. 2012b).

**Table 6** Effects of diphenyl diselenide and its derivatives in experimental models of memory impairment

	Associated with	Experimental model	Effects	References
Diphenyl diselenide	–	Middle-aged	↑ STM, LTM	Cechella et al. (2014a)
	+ Exercise			
	–	Middle-aged	↑ STM	Leite et al. (2014)
	+ Caffeine		↑ LTM	
	–	Old	↑ STM, LTM, pCREB	Cechella et al. (2014b)
	+ Exercise			
	–	Hypothyroidism	↑ MWM	Dias et al. (2012)
	–	Menopause	↑ MWM, AChE	da Rocha et al. (2012b)
<i>p</i> -Chloro-diphenyl diselenide	–	Old	↑ LTM	Bortolatto et al. (2012)
<i>p</i> -Methoxyl-diphenyl diselenide	–	Sporadic AD	↑ MWM, SDPA, YM	Pinton et al. (2011, 2013a, b)
	–	A $\beta$ -fragment 25–35	↓ cell death, apoptosis, ↑ MWM	Pinton et al. (2013c)

old 24 months old, middle-aged 18 months old, LTM long-term memory, STM short-term memory, MWM Morris water maze, SDPA step-down passive avoidance, YM Y maze, AChE acetylcholinesterase activity

In primary cultures of murine hippocampal neurons, diphenyl diselenide was reported to be tenfold more potent than ebselen against neurotoxicity induced by amyloid A $\beta$  (1–42), a factor associated with pathophysiological events of AD (Godoi et al. 2013).

Moreover, *p*-chloro diselenide derivative repeated administration enhanced memory and induced an antidepressant-like effect in old rats (Bortolatto et al. 2012). Regarding *p*-methoxyl derivative, this organoselenium compound supplemented in the diet or intragastrically administered was proven to be effective against sporadic AD models (Table 6) (Pinton et al. 2011, 2013a, b, c).

In particular, selenomethionine is the naturally occurring organoselenium most studied in models of AD (Attaran et al. 2020; Zhang et al. 2016a, 2018; Zheng et al. 2017a); its effects include increase of neurogenesis, reduction of A $\beta$ , tau hyperphosphorylation, and neurofibrillary tangles formation, tau autophagic clearance, activation of glial cells, and regulation of metal dyshomeostasis, thereby improving learning and memory (Song et al. 2014; Xie et al. 2018b; Zhang et al. 2016b, 2017a, b; Zheng et al. 2019a).

A very recent study published by Zhang and collaborators proposed a novel mechanism by which selenomethionine improves cognitive impairment in AD. Using a selenoprotein K (SELENOK) knockout mice and AD model, the authors demonstrated that the decrease in SELENOK levels is associated with disequilibrium between synaptic and extrasynaptic NMDARs, suggesting that SELENOK is involved in the regulation of NMDARs and synaptic plasticity. The same study evaluated brain samples from AD patients and found reduced levels of SELENOK, but not of TrxR1, indicating a correlation between the decreased SELENOK level and AD. Selenomethionine restored synaptic deficits by modulating NMDARs and SELENOK in the brain of the AD mouse model (Zhang et al. 2020f). Table 7 summarizes the animal models of AD in which selenomethionine, diphenyl diselenide, and *p*-methoxyl-diphenyl diselenide were successfully investigated.

**Table 7** Natural and synthetic organoselenium compounds tested in animal models of AD

	A $\beta$ -fragment 25–35	Sporadic AD <sup>a</sup>	Triple- transgenic AD <sup>b</sup>
Selenomethionine			++
Ebselen		++	++
<i>p</i> -Methoxyl- diphenyl diselenide	++	++	

<sup>a</sup>Icv streptozotocin-induced Sporadic AD, <sup>b</sup>APP<sup>swe</sup>, PS1M146V, and tauP301L

++ means effective

In terms of selenide effects on memory, we are only aware of a few published reports to date (Bortolatto et al. 2013b; Duarte et al. 2017; Peglow et al. 2017; Ramalho et al. 2018; Yan et al. 2019).

### Antioxidant activity

The pioneering article of Muller and collaborators, demonstrating the GPx-like activity of ebselen (Müller et al. 1984), opened new avenues in the field of organoselenium applications and, since that, a multitude of synthetic entities with different chemical characteristics has been synthesized and their antioxidant properties investigated. As a result, major databases have been flooded with research articles related to antioxidant, GPx-like, radical-, and peroxynitrite-scavenging activities of newly developed molecules (Bortolatto et al. 2013a; Chagas et al. 2015; Fonseca et al. 2015; Ibrahim et al. 2012a, b, 2014a, 2019; Junior et al. 2017; Luchese et al. 2012a; Peglow et al. 2017; Phadnis et al. 2014; Sauer et al. 2017; Singh et al. 2019; Stefanello et al. 2015a; Talas et al. 2015).

The GPx-like activity, the molecules' ability to emulate the reaction catalyzed by the native enzyme, has been viewed, although with some controversy (Barbosa et al. 2017; Wirth 2015), as the critical mechanism to design potential therapeutic agents, and it is undoubtedly the most studied property in the last decade (Ninomiya et al. 2011; Sarma and Mugesh 2008). In fact, several excellent reviews dealing with GPx-like activity have been published in the literature during recent years (Bhowmick and Mugesh 2015; Elsherbini et al. 2016; Orian and Toppo 2014; Sands et al. 2018).

The performance of cyclic and acyclic diorganyl selenides, and aryl and heteroaryl diselenides (Bhabak and Mugesh 2010; Sands et al. 2018) on the GPx-like assays has been investigated trying to overcome their low solubility in water, instability, and poor availability, which limit their therapeutic applications, and specially challenging to replicate in vivo conditions that require aqueous media and glutathione as the stoichiometric thiol (Sands et al. 2018). The studies have addressed synthetic approaches (Saeed et al. 2016), the merits of assays for measuring GPx-like activity, the nature of peroxides and thiols, the use of different solvents, the solubility of the reactants; their catalytic activities, redox mechanisms, and structure–activity relationships (Bhowmick and Mugesh 2018; Elsherbini et al. 2014; Hodage et al. 2012; Ibrahim et al. 2015; Jiang et al. 2015; Prabhu et al. 2012; Selvakumar et al. 2011; Singh et al. 2014, 2015; Thomas et al. 2012; Yu et al. 2018). The GPx-like activity of natural selenium-containing amino acids, selenocystine, methylselenocystine, and selenomethionine has been also investigated and revealed selenocystine as the most efficient mimetic (Kumar et al. 2011).

On the basis of selenium nutritional essentially for humans and other mammalian species (Rayman 2000, 2020), organic and inorganic sources have been used to the selenium supplementation in the animal industry and the organoselenium forms have been recognized to be more efficient in absorption, antioxidant activity, and tissue accumulation than inorganic selenium ones (Calvo et al. 2017; Shini et al. 2015).

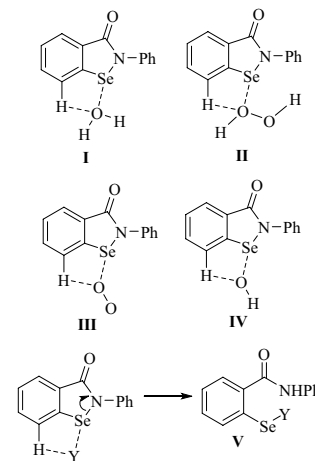
Therefore, diphenyl diselenide was effective in enhancing serum basal antioxidant status (Table 8) and anti-inflammatory response in dairy sheep (Biazus et al. 2019), suggesting its nutraceutical application.

The selenium supplementation in the diet has been related with beneficial effects that increase the aquaculture potential of fish species (Zheng et al. 2018); therefore, diphenyl diselenide was effective to increase basal antioxidant tonus in tissues of silver catfish (Menezes et al. 2016). When nanocapsules were applied as carriers of diphenyl diselenide in the diet, an improvement in the muscle antioxidant capacity and growth performance of silver catfish were reported (Baldissera et al. 2020a, b, c, d) (Table 8).

The use of selenomethionine or its hydroxyl derivative supplemented in the diet has been also related with the enhancing in the antioxidant status in tissues of piglets and broilers (Chao et al. 2019; Falk et al. 2020; Wang et al. 2011b) (Table 8). A mechanistic proteomic study demonstrated that selenomethionine increases GPxs activities and down-regulates Rap1/MAPK/ERK signaling in chicken skeletal muscles (Liu et al. 2020b), highlighting the role of these pathways in inhibiting oxidative stress.

The antioxidant property of diphenyl diselenide ( $3 \text{ mg kg}^{-1}$ , 60 days) has been evaluated in models of oxidative stress induced by environmental concentrations of pesticides, atrazine (Marins et al. 2018), quinclorac (de Menezes et al. 2012), and clomazone (Menezes et al. 2013), in fishes.

As mentioned above, the GPx-like activity of organoselenium compounds has been not believed to be enough to justify their antioxidant properties in biological systems (Bartolini et al. 2015b; Wirth 2015). As a result, over the past few years, the mechanisms underlying organoselenium antioxidant effects have attracted interest. In 2015, Thomas and collaborators published an elegant study analyzing the charge density around Se–N and Se–C covalent bonds and the Se...O chalcogen-bonding modes in ebselen, which provides insights into the mechanism of drug action in this class of organoselenium antioxidants. This study revealed the optimized structures of ebselen with water and ROS, which would lead to the Se–N-bond cleavage (Thomas et al. 2015) (Scheme 3). The Se–N-bond cleavage is favored by the interaction between the nucleophile and the selenium atom, which weak the Se–N bond.



**Scheme 3** Structures of ebselen intermediates with  $\text{H}_2\text{O}$  (I),  $\text{H}_2\text{O}_2$  (II),  $\text{O}_2^{2-}$  (III), and  $\text{HO}^\cdot$  (IV), and the general representation of ebselen Se–N-bond cleavage (V). Y represents the nucleophiles ( $\text{H}_2\text{O}$ ,  $\text{H}_2\text{O}_2$ ,  $\text{O}_2^{2-}$ , and  $\text{HO}^\cdot$ )

**Table 8** Effects of organoselenium compounds in basal antioxidant status

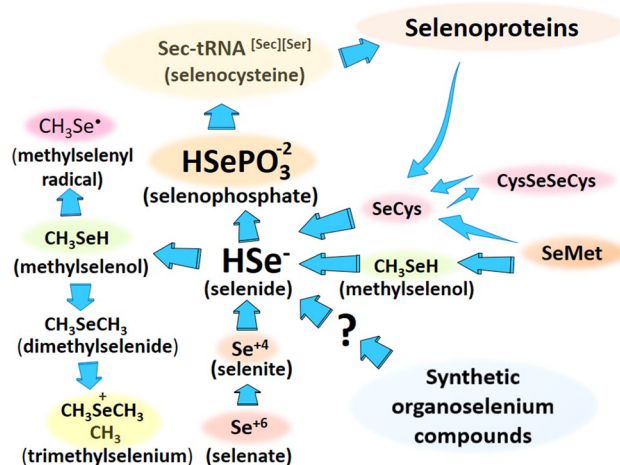
	Supplementation	Species	Antioxidant markers	Other effects	References
Diphenyl diselenide	$3 \mu\text{mol kg}^{-1}$ (s.c) 5 doses	Sheep	$\uparrow$ CAT, $\uparrow$ SOD, $\uparrow$ GST, $\uparrow$ GPx $\downarrow$ ROS, $\downarrow$ LP	$\uparrow$ IL-10 $\uparrow$ milk fat	Biazus et al. (2019)
	$3 \text{ mg kg}^{-1}$ 60 days	Silver catfish	$\uparrow$ AA, $\uparrow$ NPSH $\downarrow$ ROS, $\downarrow$ PC		Menezes et al. (2016)
Diphenyl diselenide nanocapsules	$3 \text{ mg kg}^{-1}$ feed 30 days	Silver catfish	$\uparrow$ CAT, $\uparrow$ SOD, $\uparrow$ ACAP, $\downarrow$ ROS, $\downarrow$ LP	$\uparrow$ [Se]	Baldissera et al. (2020d, a, b, c)
Selenomethionine	$0.15 \text{ mg kg}^{-1}$ 40 days	Broilers	$\uparrow$ GSH, $\uparrow$ SOD, $\uparrow$ GPx, $\uparrow$ T-AOC $\downarrow$ MDA	$\uparrow$ [Se] $\uparrow$ meat quality	Wang et al. (2011b)
OH-selenomethionine	$0.5 \text{ mg kg}^{-1}$ 28 days	Piglets	$\uparrow$ GPx $\downarrow$ MDA	$\uparrow$ [Se]	Chao et al. (2019)

CAT catalase, SOD superoxide dismutase, GST glutathione S-transferase, GPx glutathione peroxidase, ROS reactive oxygen species, LP lipid peroxidation, IL interleukin, ACAP antioxidant capacity against peroxy radicals, PC protein carbonyl, AA ascorbic acid, T-AOC total antioxidant capability, MDA malondialdehyde, GSH glutathione

A molecular mechanism accounted for the organoselenium compounds antioxidant activity is the effect as “thiol modifier” by the activation of the Keap1/Nrf2 signaling pathway. In fact, increasing evidence has indicated that ebselen and diphenyl diselenide, by behaving as soft electrophiles, can oxidize critical cysteinyl residues in Keap1 that activates the Nrf2 signaling pathway and the subsequent transcription of antioxidant enzymes in cells (de Bem et al. 2013; dos Santos et al. 2020). This molecular mechanism of “adaptive stress response” activating the Nrf2 pathway, thereby leading to increased cellular protection, has also been demonstrated for other diselenide derivatives (Bartolini et al. 2015a).

## Conclusion

Regarding its effects on mammalian cells, selenium is an element with two faces. Its deficiency is associated with an increased risk of diseases, including cancer, viral infection, and cardiovascular pathologies. In contrast, chronic exposure to dietary levels of selenium just above the ideal levels can increase the risk of cancer, neurodegenerative diseases, and type 2 diabetes. A great quantity of literature data has indicated a role for selenium in immunological and inflammatory responses; however, the exact molecular role played by selenium in these pathophysiological processes is still elusive. From the point of view of nutrition, the ideal selenium body burden is still unknown, but it seems evident that the ideal blood and body levels of selenium are narrow. Supplementation with either organic or inorganic forms of selenium should be implemented only after laboratory determination of deficient blood selenium levels. The supplementation should be discontinued or diminished as soon as the ideal level is attained. The narrow ideal levels of selenium ingestion are related to its unique reactivity in the physiological milieu. Metabolically, inorganic selenium (e.g., selenite or  $\text{Se}^{+4}$  and selenate or  $\text{Se}^{+6}$ ) is metabolized to selenide ( $\text{HSe}^-$ ), which can be incorporated in selenoproteins as selenocysteinyl residues. An excess of selenide can generate reactive and toxic metabolites that can deregulate cell physiology via disruption of thiol-containing proteins (for instance, methylselenyl radical). Our knowledge on how an excess of selenium ingestion interferes with the normal physiology of the 25 human selenoproteins is still very limited. In contrast to inorganic selenium forms, the metabolism of organic forms of selenium will depend greatly on their chemical structure. For instance, selenomethionine can be metabolized to methylselenol, selenocysteine, and selenide (Fig. 4), but an excess of selenomethionine can also generate reactive intermediates (Fig. 4) and even cause death in animals and humans. Other naturally occurring selenium compounds (methylselenocysteine, selenocystine, etc.)



**Fig. 4** Main metabolites of common dietary inorganic selenium forms (selenite or  $\text{Se}^{+4}$  and selenate or  $\text{Se}^{+6}$ ) and from selenomethionine (SeMet) to selenide ( $\text{HSe}^-$ ). Selenide is the key intermediate in the incorporation of selenium into the organic moiety of serine forming the selenocysteinyl residue at the level of the specific t-RNA (Sec-t-RNA[Ser][Ser]) that will be incorporated in the structure of selenoproteins. Selenomethionine (a naturally occurring organic form of selenium) can be metabolized directly to methylselenol or via the transsulfuration pathway to a minor amount of selenocysteine (SeCys) (Burk and Hill 2015), which due to its reactivity is expected to be oxidized to selenocystine (CysSeSeCys). The methylselenol can be demethylated to selenide, and SeCys and CysSeSeCys can also be metabolized to selenide. The methylselenol intermediate can be further methylated to dimethylselenide (which can be excreted via inhalation) and trimethylselenium cation (which is excreted in the urine). The methylselenol can also be oxidized to dimethyldiselenide or can form the extreme reactive selenyl radical. The elusive metabolism of synthetic organoselenium compounds into the inorganic selenide pool is indicated by a quotation mark

can also be metabolized to inorganic selenium, but some synthetic organoselenium compounds (for instance, ebselen) do not release the selenium from its organic moiety. Differences in the metabolism of synthetic organoselenium compounds can have nutritional and pharmacological consequences and we have little knowledge about the metabolism of the majority of synthetic selenium-containing organocompounds. Another point that has not been studied is the potential metabolism of organoselenium compounds by intestinal microorganisms (Takahashi et al. 2020). This is of particular importance, because the oral route has been shown to be a potential route to administer pharmacological active selenium compounds (Nogueira and Rocha 2011). Indeed, we do not know which of them can contribute to the inorganic pool of selenium in vivo (either directly or after metabolic changes in the gastrointestinal tract) (Fig. 4). It is important to emphasize that organic forms of selenium will contribute to selenoprotein synthesis only when they can be metabolized to selenide (Fig. 4).

The remarkable interest in organic molecule-containing selenium was reinvigorated in the late 1970s when ebselen (a molecule originally synthesized in 1924) was shown to be a mimetic of GPx and an antioxidant. Contrary to the expectations of the researchers, ebselen was not a source of selenium for GPx biosynthesis, but it was an interesting compound with pharmacological potential both as an anti-inflammatory and antioxidant agent in a variety of in vitro and in vivo models of diseases (Parnham and Sies 2013). In the late 1990s, ebselen was tested in 3 human clinical trials to treat brain ischemia and stroke with a borderline efficacy. However, its efficacy was not considered sufficient to justify its clinical use in brain ischemia and related pathologies. Despite the clinical failures of ebselen, it was proven to be a safe drug for human use. To date, there are approved and ongoing clinical trials with ebselen to treat bipolar disorder and moderate and severe COVID-19. Here, in this review, we have discussed some organoselenium compounds with potential pharmacological applications, including some ebselen derivatives and several diselenides. Although ebselen and diselenides can have some overlapping pharmacological properties, their molecular targets are not identical. However, they have similar anti-inflammatory and antioxidant activities, possibly, via activation of transcription factors regulating the expression of antioxidant genes. In short, our knowledge about the pharmacological properties of simple organoselenium compounds is still elusive. However, contrary to our early expectations that they could imitate selenoproteins, organoselenium compounds seem to have non-specific modulatory activation of antioxidant pathways and specific inhibitory effects in some thiol-containing proteins. For instance, the inhibition of 5'-IMPase (an enzyme that is a target of lithium) via oxidation of a critical cysteinyl residue in the protein is thought to be involved in the antidepressive effects of ebselen (Singh et al. 2013). Of potential significance for the treatment of SARS-CoV-2 infection, ebselen has been shown to inhibit the two thiol-containing virus proteases (the main protease and the papain-like protease) and to decrease the virus replication in vitro (Jin et al. 2020; Sies and Parnham 2020). The thiol-oxidizing properties of organoselenium compounds have been considered the molecular basis of their chronic toxicity; however, the acute use of organoselenium compounds as inhibitors of specific thiol-containing enzymes can be of therapeutic significance. In summary, the outcomes of the clinical trials of ebselen as a mimetic of lithium or as an inhibitor of SARS-CoV-2 proteases will be important to the field of organoselenium compounds synthesis. In addition, the development of computational techniques that could predict rational modifications in the structure of ebselen and other organoselenium compounds to increase their specificity is also required to construct a library of thiol-modifying agents with selectivity toward specific target proteins.

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