Organoselenium compounds as antioxidants

Magdalena Obieziurska-Fabisiak, Agata J. Pacuła-Miszewska, Anna Laskowska and Jacek Ścianowski*

Department of Organic Chemistry, Faculty of Chemistry, Nicolaus Copernicus University, 7 Gagarin Street, 87-100 Torun, Poland
Email: jsch@umk.pl

Dedicated to Prof. Józef Drabowicz on the occasion of his 76th anniversary

Received 10-14-2022  Accepted 11-17-2022  Published on line 12-01-2022

Abstract

Reactive oxygen species (ROS) are responsible for many of civilization’s diseases, including cancer, diabetes, and Alzheimer's disease, decomposition of products in the food industry, and deterioration of physicochemical properties of polymers and nanomaterials. In recent years, several organoselenium compounds have been synthesized and used as peroxide scavengers, which are the source of many antioxidant substances. This review aims to collect and divide the organoselenium compounds obtained in the last twelve years with antioxidant activity, which can prove helpful in a) medicine as supplements preventing diseases caused by oxidative stress, b) as food additives preventing oxidation, or c) in the materials industry as Se-containing nanoparticles and polymers. In addition, the most common methods for determining GPx-like antioxidant activity are presented.

Keywords: GPx mimics, organoselenium compounds, antioxidants
Table of Contents

1. Introduction
2. Methods of Measuring GPx-like Antioxidant Activity
3. Antioxidants in Medicine
   3.1. Ebselen and its derivatives
      3.1.1. Modification of ebselen rings A and B
      3.1.2. Modification of ebselen ring B
   3.2. Diselenides and their derivatives
      3.2.1. Diselenides obtained by Braga et al. and Rocha et al.
      3.2.2. Diselenides designed by Singh et al.
      3.2.3. Diselenides synthesized by Mugesh et al.
      3.2.4. Diselenides designed by Ścianowski et al.
   3.3. Other organoselenium compounds as antioxidants
4. Antioxidants in Other Applications
5. Conclusion
References

1. Introduction

The formation of reactive oxygen species (ROS) in living organisms is related to many basic biological processes, such as the respiratory chain, metabolism of purine nucleotides, microsomal hydroxylation cycle, and reactions involving oxidoreductases. The products of these reactions, which include the superoxide anion radical (O$_2^-$) and hydrogen peroxide (H$_2$O$_2$), should be reduced in subsequent biochemical reactions and safely removed from the body. However, may not be the case for various reasons, for example, stress, improper diet, and strenuous exercise.

The imbalance between the rate of ROS formation and the efficiency of the antioxidant system is known as oxidative stress. Excessive production of ROS with the simultaneous depletion of antioxidant reserves causes the oxidation of fatty acids, proteins, and DNA. Efforts to reduce oxidative stress can be manifested in the clinical improvement of patients, while excessive production of ROS is the primary cause or secondary complication of the disease. Toxic oxidation products are the initiators of several diseases, such as atherosclerosis, hypertension, diabetes, inflammation, Alzheimer’s disease, and cancer.

Antioxidants are compounds that possess the ability to prevent or inhibit the oxidation of other chemicals, and among them, we find molecules of both natural and synthetic origin. The biological systems include endogenous compounds produced by the organism, which in turn can be divided into derivatives of enzymatic (e.g., glutathione peroxidase (GPx), thioreredoxin reductase (TrxR), superoxide dismutase (SOD), and catalase) and non-enzymatic (e.g., lipoic acid, glutathione, ferritin, albumin) origin. When endogenous antioxidants are unable to protect the body against the effects of ROS, there is a need for exogenous antioxidants derived from natural sources, such as plants (e.g., flavonoids, phenolic acids, carotenoids, organosulfur compounds, vitamins) or minerals (selenium, zinc, manganese) provided via appropriate diet. The second group of antioxidants is compounds of synthetic origin, delivered to organisms in the form of dietary supplements and bioequivalent to their natural forms (e.g., vitamin C compared to chemically synthesized $\alpha$-ascorbic acid). Synthetic antioxidants are also utilized as additives to prevent the oxidation of unstable ingredients in the food, pharmaceutical,
cosmetic, and materials industries. The classifications of antioxidants, along with the most representative examples, are shown in Figure 1.°

**Figure 1.** Antioxidants, classification with examples.

In the biological context, selenium was considered for many years only as a poison and carcinogen.°,° A breakthrough moment that changed the perception of selenium and revealed its positive face came in the second half of the 20th century. At that time, two researchers, Schwarz and Foltz, confirmed that trace amounts...
of selenium are necessary for the proper functioning of animals and human organisms. Selenium biology has developed rapidly in recent decades and is now known in various forms as an essential trace element in living organisms. Nutritional functions of selenium in the human body are provided by the action of 25 selenoproteins. A key role in effectively reducing harmful peroxides is played by one, so far the best known in mammals, selenoenzyme - glutathione peroxidase (GPx). The biological activity of this protein is related to the presence of selenocysteine (Sec) in its active site. Since these discoveries, the incorporation of a selenium atom in the structure of various small molecules enabled the design of many potential Se-therapeutics. Numerous publications in the field of medicinal chemistry present the significant biological potential of organoselenium compounds in diversified activity assays.

Glutathione peroxidase (GPx) catalyzes the reduction of H$_2$O$_2$ and other organic peroxides using glutathione (GSH) as a cofactor. Under physiological conditions, in the first step, active selenol (E-SeH) is oxidized to selenenic acid (E-SeOH). Acid reacts with glutathione (GSH) to form the selenenyl sulfide. Regeneration of selenol takes place as a result of the reaction of sulfide with another molecule of glutathione (GSH) and the release of its oxidized form - disulfide (GSSG). In oxidative stress conditions, when the level of hydrogen peroxide (H$_2$O$_2$) is high and glutathione (GSH) is low, over-oxidation of selenol takes place, and the formation of seleninic acid (E-SeOOH) occurs (Figure 2).

Figure 2. GPx catalytic cycle. GSH: reduced form of glutathione; GSSG: the oxidized dimeric form of glutathione; GR: glutathione reductase.

Looking at the GPx catalytic cycle, it should be noted that catalysis will be possible only if the chalcogen atom is easily reduced to the appropriate nucleophilic form and only if non-reversible overoxidation is prevented. The unique property of selenenic and seleninic species compared to sulfur analogs results from their easy oxidation-reduction reactions with the participation of thiols. The formation of sulfonic acid is irreversible and sulfinic acid can be reduced only in a few cases by sulfiredoxin. Therefore, an additional evolutionary benefit of using selenocysteine in the redox protein instead of cysteine is evident. An in-depth analysis of the structure and understanding of the mechanism of GPx activity placed the mentioned selenoenzyme in the center of chemists' attention. Scientists are trying to synthesize organoselenium compounds that are specific mimetics of GPx and...
thus possess potent antioxidant activity. In this review, we have collected information from the last twelve years on topics covering the roles of organoselenium compounds as antioxidants in a) medicine and b) in materials chemistry and the food industry.

2. Methods of Measuring GPx-like Antioxidant Activity

This section presents the most common methods of measuring antioxidant activity that has been used in the studies listed below.

**Method A: GSH/GR coupled assay**

The glutathione reductase (GR) coupled assay was the first indirect method to evaluate GPx-mimic activity, developed by Wilson et al. The GR enzyme, at the expense of the cofactor NADPH (β-nicotinamide adenine dinucleotide 2′-phosphate), catalyzes the reduction of the oxidized form of glutathione (GSSG), formed during the catalytic action, back to GSH. The initial reduction rates ($v_0$) of NADPH are recorded by using UV spectroscopy at 340 nm. The GPx-like catalytic activity is studied using various peroxides for this reaction, e.g., hydrogen peroxide ($H_2O_2$), tert-butyl hydroperoxide ($t$-BuOOH), or cumene hydroperoxide (Cum-OOH). The half and summary equations of the involved reaction are shown below (Eqn 1,2,3).

\[
\begin{align*}
2GSH + H_2O &\xrightarrow{\text{GSH peroxidase}} GSSG + 2H_2O \\
gssg + \text{NADPH} + H^+ &\xrightarrow{\text{GSH reductase}} 2GSH + \text{NADP}^+ \\
H^+ + \text{NADPH} + H_2O_2 &\xrightarrow{\text{Se-cat.}} \text{NADP}^+ + 2H_2O
\end{align*}
\]

**Method B: PhSH assay**

In this direct method developed by Tomoda et al., benzenethiol (PhSH) is used as an alternative to glutathione. The reduction of hydrogen peroxide in the presence of PhSH with simultaneous formation of diphenyl disulfide (PhSSPh) is assessed using different techniques: a) spectrophotometrically through the UV absorption increase at 305 nm due to PhSSPh formation; b) using the HPLC analysis because the amount of PhSSPh formed is determined by the time required for 50% conversion of PhSH to PhSSPh ($t_{1/2}$ values) and calculated as the peak areas at different time intervals. The equation of the described reaction is shown below (Eqn 4).

\[
2\text{PhSH} + H_2O_2 \xrightarrow{\text{Se-cat.}} 2H_2O + \text{PhSSPh}
\]

**Method C: DTT$^{\text{red}}$ / DTT$^{\text{ox}}$ NMR assay**

The GPx-like antioxidant activity of compounds can be assessed using the test presented by Iwaoka et al. The organoselenium catalyst reduces hydrogen peroxide ($H_2O_2$) and is regenerated in the presence of dithiothreitol (DTT$^{\text{red}}$). The rate of the reaction is measured using $^1$H NMR spectroscopy in CD$_3$OD$^{21}$ or D$_2$O. The appearance of signals representing the formed disulfide (DTT$^{\text{ox}}$) in specific time intervals is recorded. The equation of the reaction is shown below (Eqn 5).
Method D: DPPH assay
Shaaban et al. described another easy method to assess the radical scavenging activities of organoselenium compounds and nutritional products. The antioxidant activity of a compound is estimated by its ability to reduce stable DPPH• radical (purple color in methanol) to DPPHH (colorless) by the decrease in the absorbance at 517 nm.

Method E: ABTS assay
In this method presented by Shaaban et al., the antioxidant activity of organoselenium compounds is assessed by their ability to decolorize the ABTS• (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) radicals and the corresponding radical-scavenging activity is estimated by the decrease in the absorbance at 734 nm.

3. Antioxidants in Medicine

3.1. Ebselen and its derivatives
Ebselen (N-phenylbenzisoselenazol-3(2H)-one) 5 is one of the first synthetic glutathione peroxidase (GPx) mimetics to catalyze essential reactions involved in protecting cells from oxidative damage and free radicals. Currently, it is in the second and third phases of clinical trials as a therapeutic in treating diseases caused mainly by oxidative stress (Figure 3). This section presents recent advances in synthesis of new ebselen analogs with enhanced GPx-like activity. Modifications of the ebselen 5 structure mainly include the replacement or substitution of the phenyl group on the nitrogen atom (ring B) or the connection of various substituents on the benzamide ring A.

Figure 3. Structure of ebselen.

3.1.1. Modification of ebselen rings A and B. A series of benzisoselenazolones with additional substituents on the benzamide ring was examined in terms of antioxidant activity by Kumar et al. (2014) utilizing Method B. The high GPx-like activity of benzisoselenazolone 6 (Figure 4), which forms selenol intermediate 8, suggests the presence of the bulky N-quininamine substituent and the ortho-CH₃ benzamide substituent stabilizes compound...
8, which regenerates benzisoselenazolone 6 through its reaction with H₂O₂ (Figure 4). Compound 6 showed a much higher antioxidant activity than other benzisoselenazolones presented in this article and is 10³-fold more active than ebselen 5.\textsuperscript{29}

![Figure 4](image-url) The high GPx-like activity of benzisoselenazolone 6 and generation of selenol 8.

The GPx-like activity of the ebselenol series was also described by Kumar \textit{et al.} in 2016 and compared with ebselen 5 using GSH/H₂O₂ and GSH/t-BuOOH assays (Method A).\textsuperscript{19} All obtained compounds possessed antioxidant activity higher than ebselen 5. Moreover, all derivatives were more active when the oxidant was H₂O₂. The compounds were also assessed as GPx-mimics using Method B.\textsuperscript{20} Ebselenol 10 (Figure 5) was a 15-fold more active catalyst than ebselen 5. The authors suggest that such high activity of compound 10 was most likely a result of the hydroxyl group and the selenium center proximity.\textsuperscript{30} In 2021, Kumar \textit{et al.} synthesized N-methyl ebselenamine compounds and then assessed their antioxidant activity (Method A),\textsuperscript{19} noting that the excellent GPx-like activity of the obtained derivatives may be related to the close proximity of the -NHMe group and the selenium atom. Of all the compounds, derivative 11 showed the highest antioxidant activity (2.5-fold more active than ebselen 5 and 5-fold more active than α-tocopherol).\textsuperscript{31}

In 2014, in Wirth's research group, a series of new N-chiral benzisoselenazolones was synthesized. The GPx-like activity of all derivatives was determined by Method B\textsuperscript{20} (using a high-performance liquid chromatography (HPLC) assay) and by Method A\textsuperscript{19} (by the UV–Vis assay), each with two different peroxides, H₂O₂ and CumOOH as the substrates. Most of the obtained derivatives showed GPx-like activity similar to that of ebselen 5. In contrast, the highest antioxidant activity was observed for the derivative 14 (Figure 5) with the hydroxyl group (about two-fold higher than that of ebselen 5 in Method A\textsuperscript{19}).\textsuperscript{34}

In the last seven years, several N-alkyl,\textsuperscript{35} N-aryl,\textsuperscript{36} and chiral benzisoselenazolones\textsuperscript{37,38,39} were obtained by Ścianowski \textit{et al.} The evaluation of the antioxidant activity was based on Method C\textsuperscript{21} The compounds 15-23 that exhibited the highest antioxidant activity in each of the mentioned groups are presented in Figure 5. In the
same research group, the oxygen atom of the carbonyl group was replaced with a sulphur atom by synthesizing the benzoselenazothiones, and the obtained derivatives were assessed in terms of their GPx-like antioxidant activity (Method C). The best peroxide scavenger was \( N \)-propyl benzoselenazole-3(2H)-thione (2-fold more active than ebselen 5).\(^{40}\)

**Figure 5.** Ebselen analogs 6-23 with potential GPx-like activity.

### 3.2. Diselenides and their derivatives

In addition to benzoselenazolones, diselenides constitute the second significant group of compounds with potential antioxidant activity similar to GPx. Diphenyl diselenide \((\text{PhSe})_2\) is the simplest compound among diselenides exhibiting antioxidant potential higher than ebselen, probably because of intramolecular interactions that stabilize its selenylsulfide intermediate, preventing the reduction of \( \text{H}_2\text{O}_2 \). In the recent years, a number of diselenides have been synthesized and evaluated \textit{in vitro} for GPx-like antioxidant activity by several leading research groups.
3.2.1. Diselenides obtained by Braga et al. and Rocha et al. Chiral diselenides and their derivatives from (-)-ephedrine were prepared and monitored as GPx mimetics by Braga et al. (2012). Diselenide 24 and derivative 25 showed catalytic performance 11.5- and 4-fold higher, respectively, compared to the standard (PhSe)\(_2\).\(^{41}\) By combining the structures of ebselen 5 and derivative 24 (the highest antioxidant activity in the previous work), Braga and co-workers obtained amido-based diselenide 26, which was 9- and 3-times more active than the standard benzoselenazolone 5 and (PhSe)\(_2\).\(^{42}\) The same research group confirmed that alkyl diselenide 27 containing a cholesterol unit in its structure possessed an antioxidant effect 3-fold higher than ebselen 5.\(^{43}\) Aniline-based diselenide 28 substituted with the p-CF\(_3\) group was 5- and 2-times more active than ebselen 5 and (PhSe)\(_2\), respectively. The obtained results showed that the catalytic efficiency increased with the electron-withdrawing capacity of the substituent in the para position. The amino group participates in stabilizing the selenolate intermediate through a hydrogen bond with the selenium atom, creating a zwitterionic form.\(^{44}\)

In 2012, Braga, in cooperation Hassan and Rocha, obtained β-amino-based diselenides and disulfides. Diselenide 29 showed a very significant antioxidant potential (5-times higher than (PhSe)\(_2\)) and non-toxic effect.\(^{45}\) The same scientists continued the idea of synthesizing organoselenium compounds with a heteroatom close to the selenium atom, noting the interesting GPx-like activity of this type of derivative. In 2015, they presented the synthesis of aliphatic and aromatic 2-picolylamide-based diselenides with proximal non-bonding Se--O interactions. The aromatic compound 30 possessed about 5-times higher antioxidant potential than (PhSe)\(_2\).\(^{46}\) Three years later (2018), Braga and Rocha conducted the synthesis of a new class of chiral diselenoamino acid derivatives from phenylalanine and valine. Diselenide 31 showed antioxidant activity similar to (PhSe)\(_2\). The obtained results suggested that the catalytic activity of the GPx mimetics presented in this paper depends on the steric effects that can be influenced by the number of carbon atoms between the selenium atom and the amino acid residue and/or by the amino acid lateral residue.\(^{47}\)

In 2014, Ibrahim, Rocha et al. revealed that an amino group in amino diselenides drastically enhances their GPx-like catalytic activities by synthesizing 1-(2-(2-(1-aminoethyl)phenyl)diselanyl)phenyl)ethanamine 32 and comparing the results obtained with activity observed for (PhSe)\(_2\) (two times higher activity than (PhSe)\(_2\)).\(^{48}\) In 2019, the same compound 32 was tested in vitro and in vivo in mice, showing no acute toxicity.\(^{49}\)

The GPx-like activity for all the diselenides and their derivatives 24-32 was evaluated according to Method B.\(^{20}\) The relative activity observed for the individual derivatives 24-32 and their structures are summarized in Figure 6.
Figure 6. Diselenides and their derivatives 24-32 with potential GPx-like activity assessed by Braga, Rocha et al.

3.2.2. Diselenides designed by Singh et al. Another research group specialized in synthesizing organoselenium compounds with potential antioxidant activity is that of Singh et al. In 2014, they assessed the antioxidant potential of nicotinoyl-based organoselenium compound 33 (2,2’-diselenobis[3-amidopyridine]), and it was twice as more active than ebselen. The results obtained in this work inspired the authors to synthesize new pyridine-based GPx mimics by substituting suitable functional groups. In the same year, an article appeared about the synthesis of pyridoxine-derived diselenides and other organoselenium derivatives (selenides, seleones, seleninic acids, selenosulfides) was performed. Among all derivatives, the lower potential was observed for selenide 34, seleone 35, selenosulfide 38 and the highest for diselenide 36 (1.5-fold more active than ebselen) and seleninic acid 37 (2-fold active than ebselen). In the next paper (2015), Singh et al. proposed to modify diselenide 36 by introducing a bromine atom in the 6-position of the pyridine ring. This substitution increased the antioxidant activity of derivative 39 (2-fold more active than ebselen). In 2021, Singh, Kumar et al. received a series of diselenides 40a-d, selenazolonamines 41a-d, selenoxides 42a-d. They noticed that electron-donating substituents dramatically increased the antioxidant potential. Moreover, the selenoxides 42a-d showed a GPx-like activity higher than the corresponding selenazolonamines 41a-d. The highest antioxidant activity was observed for diselenide 40d (2-fold more active than ebselen). The GPx-like activities of all
compounds 33-42 were assessed by utilizing Method A.\textsuperscript{19} The relative activities for the individual derivatives 33-42 and their structures are summarized in Figure 7.

Figure 7. Diselenides and their derivatives 33-42 with potential GPx-like activity assessed by Singh et al.

3.2.3. Diselenides synthesized by Mugesh et al. As mentioned above, the high activity of amine-based diselenides is related to the presence of basic amino groups which can deprotonate the selenol to generate a more reactive selenolate in the catalytic cycle of GPx (See Figure 2). Mugesh et al., in various studies, assessed the antioxidant activity of tert- and sec-amino-based diselenides. Modification of the aromatic tert-amino diselenide 43 ring\textsuperscript{54} by introducing a 4- or 6-methoxy group increased the antioxidant activity of the new derivatives 44 and 45.\textsuperscript{55} The sec-amino diselenides 46a-d containing alkyl substituents turned out to be unstable and rapidly cyclized to the corresponding isoselenazolones 47a-d. These, in turn, showed GPx-mimetic activity 2- and 3-fold higher than ebselen 5. Stable diselenides 48a-d presented lower antioxidant activity than isoselenazolones 47a-d and marginally better than ebselen 5.\textsuperscript{56} The antioxidant activity was also assessed for diselenide 49 and compared with the derivative 44.\textsuperscript{57} The GPx-mimic activity for derivatives 43-48 was evaluated...
using Method A\textsuperscript{19} and for compound 49 using Method B.\textsuperscript{20} The relative activities for the individual derivatives 43-49 and their structures are summarized in Figure 8.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{Diselenides and their derivatives 43-49 with potential GPx-like activity assessed by Mugesh \textit{et al.}}
\end{figure}

3.2.4. Diselenides designed by Ścianowski \textit{et al.} N-alkyl,\textsuperscript{35} N-aryl,\textsuperscript{36} and N-chiral\textsuperscript{37,39} amido-based diselenides were synthesized in the Ścianowski research group. A significant increase in the antioxidant potential was observed for appropriate diselenide derivatives: N-alkyl selenenic acids 52a-f and water-soluble potassium salts of these acids 53a-f.\textsuperscript{58} The salts 53a-f showed the highest GPx-mimetic activity among all compounds presented by the Ścianowski group. Additionally, the solubility of these salts 53a-f in water gives them great potential in pharmacology. The GPx-mimic activity for all derivatives 50-57 was assessed using Method C.\textsuperscript{21,22} The relative activities for the individual derivatives 50-57 and their structures are summarized in Figure 9.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9.png}
\caption{Diselenides and their derivatives 43-49 with potential GPx-like activity assessed by Mugesh \textit{et al.}}
\end{figure}
3.3. Other organoselenium compounds as antioxidants

Braga et al. (2012) assessed the GPx-like catalytic activity of selenides and selenoxides using Method B.\textsuperscript{20} The selenoxide 58 with an amino chelating group showed 3-fold higher activity than ebselen 5. Selenide 59 was a poorer catalyst than selenoxide 58, but showed catalytic activity comparable to ebselen 5.\textsuperscript{59} In 2016, Manichetti and Braga synthesized different benzo[\textit{b}][1,4]selenazines. The best antioxidant potential tested using Method C\textsuperscript{21} was observed for benzoselenazine 60 which was lower than that of diphenyldiselenide.\textsuperscript{60}

The antioxidant activity of dithiaselenepanes was assessed using Method C\textsuperscript{21} by Capperucci et al. (2016). According to this assay 3,7-dimethyl-1,2,5-dithiaselenepane 61 was more active than (PhSe)\textsubscript{2}. Intriguingly, the more hindered dithiaselenepane 62 showed lower catalytic efficiency than 61.\textsuperscript{61} In 2019, a series of cyclic and open-chain selenides was obtained within the same research group. They suggested that the nature of the functional groups close to the selenium atom strongly influenced the catalytic antioxidant properties of organoselenides. β-Seleno nitriles 63 and 64 and 2-oxo-1,4-oxaselenane 65 were the best catalysts according to Methods A\textsuperscript{19} and C.\textsuperscript{21} As in the previous report,\textsuperscript{61} also, in this case, a higher GPx-like activity of cyclic selenides compared to acyclic analogs was observed.\textsuperscript{62} In the same research group (2015), resveratrol-based benzoselenophenes 66-68 were obtained, for which the antioxidant activity was assessed using Method D.\textsuperscript{23} All the selenophene derivatives 66-68 were more efficient than resveratrol (about 1.5-fold more active) when tested under the same conditions.\textsuperscript{63}

Singh et al. (2017) prepared phenolic 2,3-dihydrobenzo[\textit{b}]-selenophene antioxidants bearing an HO-group in ortho, meta and para positions with respect to the Se atom. Compound 70, carrying the phenolic group in ortho position, was found to be the best catalyst, three-fold more active than (PhSe)\textsubscript{2}. Compound 69 (HO-group
in para position) was slightly more active than the reference compound. The antioxidant activity was determined using Method B.

Quinoline derivatives containing selenium were synthesized by Alves et al. in 2021. For these compounds, the antioxidant activity was assessed using Method D and Method E. The obtained results indicated that compounds 71 and 72 were effective DPPH and ABTS radical scavengers, respectively.

Shaaban et al., in their recent papers (2018, 2022), obtained a series of selenides and determined their GPx-like antioxidant activity using Methods D and E. In the first article, the quinoid-based N-substituted maleanilic acid 73 and its corresponding methyl ester 74 were more active (approximately 1.5-fold) than ebselen 5. Compounds 75 and 76 showed GPx-like activity similar using Method D like vitamin C.

Iwaoka et al., in their reports (2010, 2015, 2017), assessed the antioxidant activity of water-soluble cyclic 77, 81, 83-86 and linear selenides 78-80, 82 using Methods A and C in water and methanol. As a result, they managed to formulate some general characteristics of the compounds that contribute to the increased GPx-mimic activity: 1) the most preferred cyclic ring size is five, 2) generally, the reactivity of the substituents increases in the series NH2 < HO < CO2H in aqueous medium and vice versa in methanol, 3) in most cases a greater number of substituents increases the activity of the compound, 4) the stereo configuration of the substituents does not affect the activity of the compounds in water, unlike in methanol.

Mugesh et al. (2012, 2015) tested GPx-like antioxidant activity for diaryl selenides bearing amide moieties and spirodiazaselenuranes using Method A. The reactivity of the selenides 87, 89 and the spirodiazaselenuranes 88, 90 indicated that the substituents attached to the nitrogen atom have a significant effect on the antioxidant activity. It has been observed that the introduction of electron-withdrawing groups generally decreased, while the introduction of electron-donating groups significantly increased the GPx activity of both diaryl selenides and spirodiazaselenuranes.

The effect of introducing the methoxy group (in proximity to the selenium atom) on GPx-like antioxidant activity was investigated in cyclic selenium esters (2014) and a series of o-(hydroxymethyl)phenyl selenides (2016) by Press and Back. In both cases, it was observed that a single electron-donating methoxy group in para position to selenium increased the catalytic activity. In contrast, m-methoxy groups have little effect, and o-methoxy substituents inhibit the activity. Moreover, the effects of multiple methoxy groups were not cumulative. The best peroxide scavengers (Method B) were cyclic selenium ester 91 and selenide 92.

McNeil and Back (2016) found that the dimeric form 94 acted roughly twice as fast in Method A than the monomer 93 due to two redox centers in 94 instead of one in 93. Therefore, dimeric form 94 better mimicked the multivalent selenoenzyme GPx, which possessed four redox-active selenocysteine moieties.

In 2020, Ścianowski et al. presented a new method for the synthesis of N-substituted unsymmetrical phenylselenides with an o-amido function. The highest H2O2-scavenging potential (Method C) was observed for the derivative 95 with N-(3-methylbutyl) substituent. The phenylselenide 95 showed 2-fold higher activity than ebselen 5.

The structures of all the derivatives mentioned above 58-95, with high antioxidant activity, are summarized in Figure 10.
Figure 10. Other organoselenium compounds 58-95 with potential GPx-like activity.
4. Antioxidants in Other Areas

In the food industry, antioxidants are considered food additives. They protect food against fatty acid oxidation (rancidity), extend the time of shelf life consumption, and prevent the loss of food value. They react with primary oxidation products (mainly fats), creating less reactive radicals. For the general population, the main source of Se in the diet are organic forms (generally greater than 80%).

Ebselenols substituted with a hydroxyl group in the benzisoselenazolone ring were evaluated for their capacity to inhibit peroxidation of linoleic acid in a two-phase chlorobenzene/water system open to the atmosphere using HPLC with UV detection assay. While ebselenols 97 inhibited peroxidation at the same time as the standard α-tocopherol, ebselenols 96 stopped this process for much longer. In the absence of a reducing agent (ascorbic acid), ebselenol 96 scavenged peroxide radicals with a stoichiometric number as high as n = 3 (for comparison, α-tocopherol is known to trap two peroxyl radicals per molecule, so the stoichiometric number is n = 2). The presented properties of ebselenols 96, 97 (Figure 11) indicate that these compounds can be used in food technology (as antioxidants protecting food against autooxidation of fatty acids and thus prolonging the shelf time), in polymer producers, or the oil industry (as antioxidants protecting against autoxidation, which corresponds to the oxidative deterioration of organic materials).

![Figure 11. The structures of ebselenols 96 and 97 with high antioxidant activity.](image)

Unique physical, chemical, and antioxidant properties have made selenium nanoparticles (SeNPs), particularly popular. Additionally, SeNPs, due to their higher bioavailability and lower toxicity compared to other chemical forms of selenium, may be a promising source of selenium in the diet.

In 2018, Huang et al. designed the first Se@pDA self-assembly nanocomposite that exhibited remarkable ROS scavenging property due to excellent GPx-mimic ability of selenium and polydopamine (pDA) reducibility (Figure 12). Compared to a single composite, the Se@pDA nanocomposite possessed exceptional multi-antioxidative capacity mimicking intracellular enzymatic and non-enzymatic antioxidants that constitute the antioxidant machinery system. Experimental data have shown that Se@pDA nanozymes can be effective in ameliorating the oxidative damage caused by ROS in lipids as well as in DNA, compared to individual Se or pDA nanoparticles.
Selenium-containing polymers, due to the unique properties of selenium, are susceptible to various stimuli, such as light, radiation, or redox reaction. The most interesting factor, in the context of this review, is the redox (oxidative- and reductive-reactivity) stimulus.

P(EG\textsubscript{x}-SeHC) \textsuperscript{99}, water-soluble selenium-containing polymers, were prepared by ring-opening polymerization (ROP) of EG\textsubscript{x}-SeHC \textsuperscript{98} (derived from selenohomocysteine (SeHC)) and oligoethylene glycol by Lu \textit{et al.} in 2019 (Figure 13).\textsuperscript{83} The obtained polymer, is a promising protein mimic because of its peptide skeletons and helical conformations on the one hand, and on the other hand, due to the presence of selenocysteine, it shows redox responsivity. Compared to the oxidation of homocysteine-derived polypeptides,\textsuperscript{84} which normally requires six hour treatment with 1\% acetic acid and 300 mM of 1\% H\textsubscript{2}O\textsubscript{2} at 38 °C, P(EG\textsubscript{x}-SeHC), \textsuperscript{99} could be oxidized with 20 mM H\textsubscript{2}O\textsubscript{2} in one hour in water at room temperature to obtain \textsuperscript{100}. The presented features indicate that selenopolypeptides could find potential applications as chiral materials, stimuli-responsive carriers, autoxidation, and anti-inflammatory agents.

Redox reactions play a significant role in drug delivery and the release of selenium-containing polymers. This is because selenoxide and selenone possess better hydrophilicity than selenium. Xu \textit{et al.}, in their papers (2010, 2013),\textsuperscript{85,86} presented amphiphilic block polymers with selenide moieties in the main chain or in the side chain. The polymers self-assembled to form micelles, and then they were structurally disrupted under the mild conditions of 0.1\% H\textsubscript{2}O\textsubscript{2}, releasing the desired compound. X-ray photoelectron spectroscopy (XPS) and \textsuperscript{77}Se NMR measurements in both cases showed that transformation from selenide to selenone is associated with the change of hydrophobic to hydrophilic character.\textsuperscript{85,86}
5. Conclusions

Antioxidants play a significant role in protecting the body against the negative effects of ROS, excess of which is the initiator of many diseases. The development of antioxidants containing selenium in their structure is strongly related to the progress in synthesizing compounds capable of mimicking the catalytic cycle of the essential antioxidant selenoenzyme - glutathione peroxidase. Benzoselenazolones, diselenides, selenides, selenoxides, or selenoesters are compounds that, in connection with their GPx-like activity, can be considered as potential antioxidant drugs in medicine. Ebselenols can additionally be used as diet additives in the food industry. On the other hand, the antioxidant properties of Se-containing nanoparticles and polymers provide a wide spectrum of possibilities for their use in the materials industry. This article reviews the literature from the past 12 years to 2022.

References

https://doi.org/10.1016/0014-5793(73)80755-0
https://doi.org/10.1016/0006-2952(84)90083-2
https://doi.org/10.1074/jbc.M206626200
https://doi.org/10.1126/science.1080273
https://doi.org/10.1021/ja00197a065
https://doi.org/10.1021/ja00085a040
https://doi.org/10.1002/ejoc.200901114
https://doi.org/10.1016/j.tetlet.2011.11.025
https://doi.org/10.1016/j.ejmech.2016.06.005
https://doi.org/10.1016/j.ejmech.2019.06.075
https://doi.org/10.1016/j.tox.2016.06.002
https://doi.org/10.1007/s11033-014-3417-x
https://doi.org/10.1093/mmy/myaa115
https://doi.org/10.1016/j.bcp.2013.08.028
https://doi.org/10.1039/C4OB00027G
https://doi.org/10.1002/ange.201510947
https://doi.org/10.1039/D0OB02368J
https://doi.org/10.1002/chem.201003417


https://doi.org/10.1039/C3OB42336K

https://doi.org/10.1002/chem.201403229

https://doi.org/10.1021/acs.joc.5b00797

https://doi.org/10.1002/ajoc.202100169

https://doi.org/10.1002/chem.200800963

https://doi.org/10.1016/j.tet.2012.09.020

https://doi.org/10.1002/anie.201502430

https://doi.org/10.1039/C5OB01294E

https://doi.org/10.3390/ma13030661

https://doi.org/10.1021/ja209570y

https://doi.org/10.1002/ejoc.201600351

https://doi.org/10.1080/10426507.2016.1252365

https://doi.org/10.1002/adsc.201900168

https://doi.org/10.1039/C5OB00193E

https://doi.org/10.1002/chem.201702350

https://doi.org/10.2174/1573406416666200403081831


https://doi.org/10.3390/antioxid11071231

5633. 
https://doi.org/10.1021/acs.joc.5b00544

https://doi.org/10.3390/molecules22030354

https://doi.org/10.1039/c2ob26156a

https://doi.org/10.3390/molecules200712959

https://doi.org/10.1021/jo501689h

https://doi.org/10.1139/cjc-2015-0329

https://doi.org/10.1021/jo200283b

https://doi.org/10.3390/molecules25153354

https://doi.org/10.1016/j.scitotenv.2008.06.024

https://doi.org/10.1021/jo00119a024

https://doi.org/10.1021/jo052133e

https://doi.org/10.1002/anie.201510947

80. Huang, Y.; Su, E.; Ren, J.; Qu, X. Nano Today 2021, 38, 101205. 
https://doi.org/10.1016/j.nantod.2021.101205

https://doi.org/10.1016/j.lwt.2020.109475

https://doi.org/10.1002/che.201801725

https://doi.org/10.1039/C9CC03767E

https://doi.org/10.1021/ja500372u

https://doi.org/10.1039/c0py00144a

https://doi.org/10.1039/C1SM06673K
Magdalena Obieziurska-Fabisiak was born in Inowroclaw, Poland in 1992. At the Nicolaus Copernicus University in Toruń, she obtained her Master’s degree in 2016, and in 2021 she received her Ph.D. degree in Organic Chemistry. Currently, she is working there as a research assistant. During her Ph.D. studies, she completed practice at the group of Prof. Claudio Santi (University of Perugia). Her research interest is focused on the synthesis and biological activity of new organoselenium catalysts.

Agata Pacuła-Miszewska obtained her Master’s degree in Pharmacy at the Medical University of Gdańsk in 2012. In 2018, she received her PhD degree in Organic Chemistry at the Nicolaus Copernicus University in Toruń and is currently working there as an assistant professor. During her PhD studies she has completed a practice at the group of Prof. Claudio Santi (University of Perugia), Prof. Thomas Wirth (Cardiff University) and a post-doctoral internship at Prof. Stefano Menichetti Group (University of Florence). Her research interest is focused on the synthesis and activity evaluation of biologically potent organoselenium compounds.
Anna Laskowska received her Engineering degree in Chemistry and Food Technology in 2018 and her Master’s degree in Chemistry in 2019 at the Nicolaus Copernicus University in Torun. Currently, she is pursuing her Ph.D. in the AST Doctoral School from the same university under the supervision of Professor Jacek Ścianowski in the Faculty of Chemistry and Department of Organic Chemistry.

Jacek Ścianowski graduated from the University of Lodz in 1989. He prepared his Ph.D. thesis at the Nicolaus Copernicus University in Toruń in 1998. Currently, he works at NCU as a Full Professor and Head of the Department of Organic Chemistry. His research interests have encompassed natural product chemistry, the application of terpenes in asymmetric synthesis, chalcogen chemistry, particularly the use of selenium and tellurium derivatives in organic transformations, and medicinal chemistry.

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)