



# FLORE

# Repository istituzionale dell'Università degli Studi di Firenze

# Tellurium-containing Thiol-peroxidase-like Antioxidants and their Catalytic

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

Original Citation:

Tellurium-containing Thiol-peroxidase-like Antioxidants and their Catalytic Mechanism / Capperucci, Antonella; Tanini, Damiano. - In: CURRENT CHEMICAL BIOLOGY. - ISSN 2212-7968. - ELETTRONICO. - 17:(2023), pp. 13-25. [10.2174/2212796817666221121155138]

Availability:

This version is available at: 2158/1353867 since: 2024-03-25T16:58:47Z

Published version: DOI: 10.2174/2212796817666221121155138

*Terms of use:* Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf)

Publisher copyright claim:

(Article begins on next page)

# Tellurium-containing thiol-peroxidase-like antioxidants and their catalytic mechanism

Antonella Capperucci, Damiano Tanini\*

<sup>a</sup>University of Florence, Department of Chemistry "Ugo Schiff", Via della Lastruccia 3-13, I-50019 Sesto Fiorentino (Florence), Italy.

\*Corresponding Author: damiano.tanini@unifi.it

# Abstract

The development of novel small molecules with effective catalytic antioxidant properties is highly sought after. A wide array of structurally diverse selenium- and tellurium-containing glutathione peroxidase mimics have been studied over the past two decades. Within this arena, organotellurium compounds generally exhibit higher catalytic properties with respect to selenium-containing analogues. Different mechanisms accounting for the thiol-peroxidase-like activity of various classes of organotellurium derivatives have been proposed. This review documents development of this area and provides an overview on the catalytic mechanisms proposed for the various classes of tellurium-containing thiolperoxidase-like-catalysts.

**Keywords**: Tellurium; Glutathione peroxidase; GPx-mimics; Thiol-peroxidase-like catalysts; Antioxidants; Organotellurium compounds.

# 1. Introduction

Trace elements such as copper, zinc, and selenium play an important role in the cellular defence against oxidative and nitrosative stress.[1] The biological role of sulfur and selenium is well documented. Selenium is an essential microelement required to accomplish several biological functions. At least 25 human selenoproteins – incorporating the amino acid selenocysteine – are known. Selenoproteins are involved in a number of essential biological functions, ranging from the biosynthesis of hormones to the maintenance of the redox homeostasis.[2]

The biosynthesis of selenocysteine has been described as "costly" and "inefficient".[3] However, its incorporation into proteins enables living systems to accomplish essential chemical functions that cysteine would not be very good at. Although selenium compounds and their sulfurated analogues share similar physical and chemical properties (*i.e.* oxidation states and functional group types), there are significant differences that explain the unique biochemistry of selenoproteins. A comprehensive comparative analysis on the chemical properties of selenium and sulfur has been recently provided by Reich and Hondal.[4]

On the other hand, while the biochemistry of selenium has been well studied, tellurium has not a known biological role and no trace of this heavy chalcogen is found in natural proteins. However, owing to their versatile redox properties, tellurium-containing compounds attracted considerable interests amongst organic and medicinal chemists. For example, a number of low-molecular-weight tellurium containing compounds catalyse the reduction of hydroperoxides and peroxynitrite using cellular reducing equivalents.[1] Additionally, the properties as modulators of inflammation of both selenium- and tellurium-containing antioxidants, as well as their effect of on osteoblastic activity has been studied by Engman, Ott, *et al.*[5]

A number of tellurium compounds have been reported to exhibit anticancer, [6-8] chemopreventive, [9-11] neuroprotective, [12] and hepatoprotective [13] properties. Examples of diaryl tellurides exhibiting protective effects on DNA damage in trout erythrocytes exposed to oxidative stress [14] have been described.

The activity of organotellurium compounds as inhibitors of several enzymes such as thioredoxin reductase (Trx),[6,15] cathepsin, caspase [16] and carbonic anhydrase (CA) [7,17] has also been documented.  $\beta$ -Aryltelluro-amines have also been demonstrated to behave as CA activators.[18]

Telluro-xylofuranosides showed *in vivo* antioxidant activity in *C. elegans* by modulating the expression of superoxide dismutase (SOD-3), and increasing the protection against Mn-induced toxicity.[19]

Tellurium-functionalized  $\beta$ -cyclodextrins, studied both for their glutathione peroxidase-like catalytic ability and thioredoxin reductase inhibitor activity, have been reported to sensitise resistant breast cancer cells to TRAIL-induced apoptosis both *in vitro* and *in vivo*.[15]

A comparative study on the bioactivation mechanisms and toxicity of chalcogen-containing unnatural amino acids highlighted that the *Te*-phenyl-L-tellurocysteine might represent a promising prodrug for the cancer treatment.[20] Tellurium-containing functional materials such as fluorescent CdTe quantum dots as probes in biological detection,[21,22] nanoparticles and nanotubes, with potential applications in medicinal chemistry [23,24] have also been reported.

In this *scenario*, the number of studies focusing on both the chemistry and the potential biological applications of organotellurium compounds steadily increased over the last decades. The synthesis and the investigation of the catalytic mechanisms of tellurium-containing derivatives with thiol-peroxidase-like properties have received particular attention. Indeed, the unique features of tellurium have been often exploited for the preparation of a broad variety of thiol-peroxidase-like systems. The introduction of tellurium-containing moieties onto natural products such as chrysin [25] and L-ascorbic acid [26] also represents a rewarding strategy to improve the antioxidant activity of such structures.

Tellurium-containing compounds generally exhibit higher catalytic properties with respect to seleniumcontaining analogues. Data on the toxicity of organotellurides, which in some cases seems to be comparable or lower to that of organoselenides, [27,28] contributed to further intensify the research in this field.

In this review, we highlight the catalytic mechanism of the main classes of tellurium-containing thiolperoxidase-like organic compounds. Selected applications based on the redox chemistry of organotellurium compounds are also presented.

# 2. Classes of tellurium-containing thiol-peroxidase-like compounds and their catalytic mechanisms

The thiol-peroxidase-like properties of a wide range of structurally diverse tellurium-containing compounds have been investigated over the past two decades. As aforementioned, the catalytic antioxidant properties of organotellurides are generally higher than those of related selenium-containing derivatives. Additionally, organotellurides bearing alkyltelluro moieties have been described as more effective thiol-peroxidase-like catalysts with respect to related aryltelluro-substituted derivatives.[29]

Tellurides, ditellurides, and tellurium-containing heterocycles have been reported to behave as effective mimics of glutathione peroxidase. The catalytic mechanisms of the main classes of organotellurium compounds with thiol-peroxidase-like properties will be discussed in the following sections.

# 2.1. Diorganyl ditellurides

Ditellurides have been reported to exhibit remarkable thiol-peroxidase-like activity. Both diaryl ditellurides [30] and dialkyl ditellurides [31] have been studied using different models. Selected examples of these compounds are reported in the Figure 1. Notably, functionalised dialkyl ditellurides **1c** and **1d** proved to behave as less effective thiol-peroxidase-like catalysts with respect to the structurally related tellurides.[31,32]





All the proposed catalytic mechanism of the thiol-peroxidase-like activity of 'ebselen-like' telluriumcontaining systems, including ditellurides and tellurinic esters, relies on the formation of tellurenyl sulfide intermediates. The reaction of the ditelluride **1** with a thiol (**2**) leads to a tellurol **3** and a tellurenyl sulfide **4**. The tellurol is reasonably oxidised to the corresponding tellurenic acid **5** upon reaction with hydrogen peroxide. The tellurenic acid **5** provides the tellurenyl sulfide **4** by reacting with the thiol. Finally, the further attack of the thiol **2** onto the sulfur atom of **4** affords the disulfide **6** and regenerate the tellurol **3** (Scheme 1, 'Ebselen-like' Path).[33]

Notably, the key tellurenyl sulfide **4** can undergo different pathways. As aforementioned, the thiophilic attack of excess thiol onto the tellurenyl sulfide directly affords a disulfide and a tellurol (or tellurolate), capable of restarting the catalytic cycle (Scheme 1, *Path A* and last step of *'Ebselen-like' Path*). On the other hand, a thiol-catalysed disproportionation – related to that originally postulated for selenenyl sulfides formed in the catalytic cycle of ebselen and ebselen-like systems – could convert tellurenyl sulfides **4** into the corresponding ditellurides and disulfides (Scheme 1, *Path B*). Tellurenyl sulfide intermediates **4** could also undergo oxidation providing the related tellurinic thiol esters **7**, which can be attacked by the thiol to generate the corresponding disulfide and tellurenic acids **5**. (Scheme 1, *Path C*).[33]



Scheme 1. Catalytic mechanism(s) accounting for the thiol-peroxidase-like properties of ditellurides.

Conformationally restricted dichalcogenides have demonstrated to behave as more effective thiolperoxidase-like catalysts compared with conformationally-unrestricted systems.[34,35] The GPx-like properties of conformationally restricted naphthalene *peri*- diselenide **8** and ditelluride **9**,[34] as well as those of *peri*-like 4,5-disubstituted fluorene diselenides **10** and ditellurides **11**,[35] have been evaluated and found higher compared with those displayed by acyclic diaryl dichalcogenides (Figure 2). Indeed, restricting the conformation around the diselenide bond to almost planar, as for the *peri*- and *peri*-like diselenides **8** and **10**, reduces the HOMO–LUMO energy gap and raises the energy of the HOMO with respect to conformationally-unrestricted diphenyl diselenide thus increasing the rate of oxidation of **8** and **10** in the rate-determining step. As expected, ditellurides **9** and **11** exhibited higher GPx-like antioxidant activity compared with related diselenides **8** and **10**. Additionally, the introduction of electron-donating substituents (*i.e.* methoxy groups) results in an enhancement of the catalytic activity by facilitating the ratedetermining oxidation step in the catalytic cycle.[34,35]



Figure 2. Structure of conformationally restricted diselenides 8,10 and ditellurides 9,11.

# 2.2. Diorganyl tellurides

A number of structurally diverse tellurides, including diaryl-, dialkyl-, and alkyl-aryl-substituted derivatives, have been reported to possess GPx-like activity. Telluroamino acid derivatives with remarkable thiol-peroxidase-like properties have also been prepared by Braga *et al.*[36]

The catalytic mechanism proposed for the thiol-peroxidase-like properties of tellurides is reported in the Scheme 2.[37-39] The first step involves the oxidation of **12**, leading to the telluroxide **13** which, in aqueous medium provides the dihydroxy tellurane **14**.[40] The reaction of **14** with a thiol (*i.e.* glutathione – GSH) affords the species **15** bearing the Te-S bond. Upon reaction with a second equivalent of thiol, **15** undergoes reductive elimination of the disulfide (*i.e.* GSSG) and regenerate the telluride **12**.



Scheme 2. Catalytic cycle for the thiol-peroxidase-like activity of organic tellurides.

Stopped-flow spectroscopy-based studies provided insights into the kinetic of steps involved in the catalytic mechanism. Detty *et al.* investigated the oxidation of benzenethiol to diphenyl disulfide with hydrogen peroxide in the presence of telluride-based catalysts **12a-c** (Figure 3) using the Tomoda's method. A dichloromethane:methanol mixture is used as the solvent in such a method. Notably, under these conditions the telluroxide-dihydroxy tellurane equilibrium established in aqueous medium also involves methanol, thus leading to the formation of further addition products (Scheme 3).[33]







Scheme 3. Aqueous and methanolic equilibria involving oxidised tellurides.

The oxidation of tellurides **12** into derivatives **14** was established to be the rate-limiting step in the mechanism of the thiol-peroxidase-like activity of compounds **12a-c**. The initial reaction of **14a** and **14b** with the thiol proceeds fast and its rate increased with increasing concentrations of the thiol. The reaction of PhSH with **14c** was found to be slower, reasonably because of the presence of the chelating 2-(1-*N*,*N*-dimethylaminoethyl)-phenyl ligand.

The formation of the disulfide (*i.e.* PhSSPh, **6a**) from **16** occurs *via* reductive elimination at the Te(IV) centre. Such a process can proceed through different paths, including i) the direct nucleophilic attack of the thiol on the sulfide ligand, engendering the reduced telluride **12**, PhSSPh, and MeOH, PhSH, or H<sub>2</sub>O (*Path* 

*A*); ii) the solvolysis of **16** to generate a thiotelluronium intermediate **17**, which undergoes nucleophilic attack by PhSH to provide **12** and PhSSPh (*Path B*). Alternatively, both intermediates **16** and **17** can react with the solvent providing the telluride **12** and PhSOMe, which can further react with PhSH to afford diphenyl disulfide (PhSSPh). Such pathways are summarised in the Scheme 4.[33]



**Scheme 4**. Possible pathways for the reductive elimination of PhSSPh from benzenethiol-containing complexes.

Organochalcogen derivatives having intramolecular E···X interactions (E = Se, Te; X = N, O) occupy a privileged position in organic and ligand chemistry. Such interactions also play a significant role in modulating the activity of chalcogen-containing enzyme mimics.[41,42] For example, the GPx-like activity of a range of Se-containing small molecules, including, amongst other, ebselen-like diselenides, *tert*-amide-based diaryl diselenides, and amine-based diaryl diselenides, has been demonstrated to be influenced by the presence of intramolecular chalcogen bonding interactions (IChBs) involving the selenium atom and a more electronegative heteroatom placed in its close proximity.[43-46] Intramolecular Se···X interactions influence the thiol-peroxidase-like properties of diselenides by i) activating the Se-Se bond towards oxidative cleavage; ii) stabilising the corresponding selenenic acid key intermediate from further oxidations; iii) favouring the selenophilic attack with respect to the thiophilic attack of the thiol.

While the effect of IChB interactions on the GPx-like activity of selenium-containing compounds has been widely investigated over the past years, related studies on functionalised organotellurium systems are still scarce in the literature. For example, Singh, Butcher, *et al.* reported a study on the intramolecular nonbonded chalcogen...OH interactions and the GPx-like activity of *o*-hydroxylmethylphenylchalcogens. However, whereas the catalytic performances of selenium-containing systems were easily evaluated through the coupled reductase assay, the formation of a precipitate after the addition of benzenethiol represented an hurdle for the investigation of the kinetic of thiol-disulfide interconversion catalysed by tellurium-containing analogues.[47]

In this context, we found that the thiol-peroxidase properties of aryl-alkyl tellurides bearing N- or Scontaining functionalities are influenced by the presence of intramolecular chalcogen bonding interactions. For example, the *N*-tosyl-protected  $\beta$ -aminotelluride **18a** and the phenyltelluro-substituted disulfide **19a** exhibited a significantly lower catalytic activity compared to structurally related compounds **18b** and **19b** (Figure 4).[32] A possible explanation of this behaviour can be envisaged in the presence of intramolecular chalcogen bonding interactions involving the tellurium atom and the tosyl or disulfide moiety of compounds **18a** and **19a**, respectively (Figure 5). On the other hand, such interactions cannot take place in the telluride **18b**, bearing a free amino group, and in the phenyltelluro-substituted *S*-allylsulfide **19b**.[32,48,49]

Chalcogen-bonding interactions, originated from the  $\sigma$  hole in the  $\sigma^*$  orbital of the covalent bonds of the tellurium atom,[50] could hamper the telluride oxidation or slow the rate of the thiol addition and that of the reductive elimination steps involved in the thiol-peroxidase catalytic pathway operating for tellurides.[33,51]



**Figure 4**. Structure and thiol-peroxidase-like activity of compounds **18a,b** and **19a,b**.  $T_{50}$  values, which are the time required to reduce the initial thiol concentration with 50% after the addition of  $H_2O_2$ , refers to the dithiothreitol (DTT) oxidation test. Similar results were achieved through the glutathione-glutathione reductase (GSH/GR) coupled assay.



Figure 5. Possible intramolecular chalcogen bonding in tellurides 18a and 19a.

The mechanism of some tellurium-containing GPx mimics and the role of intramolecular chalcogen bonding interactions on their catalytic cycle have also been computationally studied.[52]

# 2.3. Spirotelluranes and cyclic tellurinate esters

The thiol-peroxidase-like properties of spirotelluranes have also been studied. Mugesh *et al.* reported the synthesis and the investigation of the GPx-like antioxidant activity of the spirodiazatellurane **20**.[53] Although it exhibited remarkable stability in different solvents, **20** quickly undergoes reaction with thiols (*i.e.* benzenethiol or benzyl thiol) to afford the corresponding disulfides (*i.e.* BnSSBn) and the telluride **21**. In the presence of  $H_2O_2$  (or <sup>t</sup>BuOOH), the latter is oxidised to the telluroxide **22** which, upon intramolecular reaction, can provide the starting spirodiazatellurane **20** (Scheme 5, *path B*). On the other hand, the telluroxide **22** can be converted to **23** *via* addition of the thiol. The final reductive elimination step affords the disulfide and regenerates the telluride **21** (Scheme 5, *path A*).



Scheme 5. Catalytic mechanism accounting for the GPx-like activity of spirodiazatellurane 20.

The  $T_{50}$  value measured for the oxidation of BnSH with <sup>t</sup>BuOOH using the catalyst **20** was found to be 4.8 h, whereas the  $T_{50}$  value of the telluride **21** was determined to be 1.7 h. Interestingly,  $T_{50}$  values of the related spirodiazaselenurane and selenide were found to be 62 h and 88 h, respectively. Notably, the rate of the conversion of **20** to **21** ( $v_0 = 0.47 \ \mu$ M/min) is almost identical to that of the reaction of the related spirodiazaselenurane with benzyl thiol ( $v_0 = 0.53 \ \mu$ M/min). Conversely, the oxidation of the telluride **21** with H<sub>2</sub>O<sub>2</sub> proceeds much faster than the oxidation of the selenium-containing analogue. Thus, the catalytic activity of **20** mainly proceeds through the *path A* (Scheme 5), which foresees the formation of the key telluride intermediate **21**. However, the spirodiazatellurane **20** is the predominant species at high concentration of peroxide and low concentration of thiol, showcasing how the reversible spirocyclisation

(*path B*, Scheme 5) may protect the tellurium-containing group from further oxidation – *i.e.* formation of Te(VI) species – which would reduce its catalytic applications.[53]

Back *et al.* reported the synthesis and the study of the thiol-peroxidase-like catalytic activity of the spirodioxytellurane **24**.[54] Notably, such a compound is inert to *tert*-butyl hydroperoxyde but quickly reacts with benzyl thiol. Thus, the thiolysis of **24** reasonably provides entry into the catalytic cycle, depicted in the Scheme 6 (*Part A*), proceeding through compounds **25**, **26**, and **27**. Interestingly, the reaction of the spirodioxytellurane **24** with an excess of  $H_2O_2$  in absence of the thiol, afforded the 1,2,4-trioxa-3,5-ditellurolane peroxide derivative **28** (Scheme 6, *Part B*), which exhibited an excellent thiol peroxidase-like catalytic activity. However, the slow formation of **28** from **24** suggests that **28** does not play a central role in the catalytic cycle of **24**.



**Scheme 6**. Catalytic mechanism for the spirodioxytellurane **24** (*Part A*) and formation of 1,2,4-trioxa-3,5-ditellurolane derivative **28** (*Part B*).

The cyclic tellurinate ester **29** also exhibited remarkable catalytic antioxidant activity. Similarly to the catalytic mechanism of the spiro-derivative **24**, thiolysis rather than oxidation probably provides entry into the catalytic cycle depicted in the Scheme 7. The tellurenyl sulfide **32** proved to be unstable and – differently from the selenium-containing analogue – its catalytic performances could not be separately evaluated and its possible role in the catalytic mechanism could not be established.[54]



Scheme 7. Possible catalytic cycle for the cyclic tellurinate ester 29.

# 2.4. Alkyltelluro phenols

The introduction of an alkyltelluro moieties into the *ortho*-position of a phenolic derivatives has been described as a rewarding strategy to increase the rate constant for quenching of peroxyl radicals. For example, 2-(octyltelluro)phenol **33** quenches lipid peroxyl radicals 4 orders of magnitude more rapidly than phenol. This effect cannot be explained on the basis of the substituent effect on the BDE (binding dissociation enthalpy) of the O–H bond. The mechanism accounting for the observed data involves a first oxygen transfer step from the peroxyl radical to the tellurium; subsequently, a hydrogen atom transfer from the phenol to the alkoxyl radical occurs in a solvent cage. Notably, the alkyltelluro moiety is also involved in the regeneration of the phenolic antioxidant in the presence of thiol reducing agent (Scheme 8).[55,56]



**Scheme 8**. Proposed catalytic mechanism for quenching peroxyl radicals by *o*-(alkyltelluro)phenols in the presence of thiols.

The introduction of a tellurium-containing group onto the tocopheryl skeleton has been exploited to access new vitamin E-derived regenerable antioxidant systems. The synthesis and the antioxidant properties of novel tellurium-substituted derivatives of  $\beta$ - and  $\delta$ -tocopherol have been studied by Engman *et al.* (Figure 6).[57] The activity of such compounds, investigated using a membrane model system, was found higher than that of the parent tocopherols. Indeed, the presence of the tellurium atom enables the effective regeneration of the antioxidant by using *N*-acetylcysteine as the water-soluble reducing agent in a twophase system. Additionally, owing to the presence of the chalcogen these derivatives also exhibit GPx-like activity, catalysing the reduction of hydroperoxide in the presence of thiols.



Figure 6. Structure of tellurium-containing derivatives of vitamin E.

# 2.5. Tellurium-containing cyclodextrin derivatives

A number of studies focusing on the synthesis and the antioxidant activity of tellurium-containing cyclodextrin derivatives have also been reported.[58-60] Ren *et al.* synthesised and investigated the GPx-like properties of a cyclodextrinyl ditelluride, highlighting its catalytic efficiency and chemical stability.[58] Engman *et al.* reported the preparation and the study of the antioxidant properties of cyclodextrin-derived tellurides (Figure 7). The glutathione-peroxidase-like activity of compounds **34** and **35** was determined by investigating their ability to catalyse the oxidation of GSH in an aqueous buffer using different hydroperoxides (hydrogen peroxide, *tert*-butyl hydroperoxide, cumene hydroperoxide) through the coupled reductase assay. While the alkyltelluro-substituted derivative proved to be the most effective catalyst of the series, the catalytic activity of cyclodextrins bearing aryltelluro moieties was found to decrease with increasing electron density at the tellurium atom. Remarkably, cyclodextrin-derived tellurides **34** and **35** showed significant specificity for the reduction of cumene hydroperoxide. For example, compound **35** catalysed the reduction of cumene hydroperoxide almost 20 times faster than hydrogen peroxide. This specificity could be explained considering that the cyclodextrin part of derivatives **34** and **35** 

seems to provide a binding site for the lipophilic hydroperoxide, bringing the HOO group close to the tellurium atom.[59]

Lv *et al.* reported the synthesis of and the evaluation of the antioxidant catalytic activity of a series of chalcogen-containing cyclodextrin derivatives. The investigation of the GPx-like properties, determined using two enzyme assays, highlighted that i) tellurium-containing systems show higher catalytic activity with respect to selenium-containing analogues; ii) 2-chalcogen-functionalised cyclodextrin derivatives exhibit higher activity compared with related 6-functionalised-systems; iii) cyclodextrin-derived dichalcogenides (*i.e.* diselenides and ditellurides) are more effective catalysts than related chalcogenides (*i.e.* selenides and tellurides).[61]



$$\label{eq:R} \begin{split} &\mathsf{R} = \mathsf{Ph}, \, 4\text{-}\mathsf{MeO}\text{-}\mathsf{C}_{6}\mathsf{H}_{4}, \, 4\text{-}\mathsf{OH}\text{-}\mathsf{C}_{6}\mathsf{H}_{4}, \\ &\mathsf{4}\text{-}\mathsf{Me}_{2}\mathsf{N}\text{-}\mathsf{C}_{6}\mathsf{H}_{4}, \, {}^{n}\!\mathsf{Bu} \end{split}$$

Figure 7. Cyclodextrin-derived tellurides.

# 2.6. Telluroproteins

Tellurium-containing proteins and peptides have also been obtained. The preparation of telluriumcontaining peptides through the autolysis of total proteins obtained from *Saccharomyces cerevisiae* grown with inorganic tellurium was also reported. Such telluro peptides exhibited enhanced GPx-like activity and showed lower toxicity than inorganic tellurium.[62]

Tellurium-containing semisynthetic proteins have been prepared by incorporating tellurocysteine (Tec) into proteins such as subtilisin [63] and glutathione S-transferase.[64] Notably, the obtained telluroproteins exhibited remarkable GPx-like properties.

For example, the incorporation of a tellurocysteine residue into glutathione S-transferase (GST) enabled the synthesis of a telluroenzyme with remarkable GPx-like activity. The active site Ser9 residue of the glutathione-binding domain of GST from *Lucilia cuprina* (LuGST1-1) was indeed firstly replaced with a cysteine residue and finally substituted with a tellurocysteine residue through a cysteine-auxotrophic system. Combining an existing glutathione binding site with a bioincorporated catalytically active tellurocysteine residue, the synthesised telluroprotein exhibited interesting GPx-like properties.[64]

The mechanism of oxidation of the tellurium mutant of human GPx4 (Tec-GPx) has been *in silico* investigated and compared with that of Sec-GPx and Cys-GPx in order to establish the role of the chalcogen atom.[65] For Cys- and Sec-containing enzymes the study validates a mechanism proceeding through charge-separated intermediates with a thiolate or a selenolate center, respectively. Conversely, because of the fact that the tellurium hydrogen bond is not polarised, Tec-GPx the study suggests a catalytic path involving the direct oxidation of the tellurol moiety, leading to a telluroxide intermediate. The telluroxide can either undergo isomerisation to tellurenic acid or be attacked by GSH. The telluroxide moiety can also be further oxidised to provide the corresponding tellurinic form, which is the resting state of telluroenzymes. These mechanistic differences can explain the high GPx-like properties of semisynthetic telluroenzymes.[65]

# 3. Applications of the redox properties of tellurium-containing compounds

The reactivity of tellurium-containing GPx-like systems can also be exploited for the catalytic reduction of the peroxide functionalities of graphene oxide (GO).[66] Compound **36**, bearing the tertiary amine group, proved to be particularly effective. The GO reduction catalysed by **36** follows an enzyme-like mechanism. The tertiary amine group behaves as a base and readily deprotonates the tellurol intermediate, arising from the GSH-mediated reduction of the ditelluride **36**, to generate the tellurolate **37** The catalytic mechanism (Scheme 9) involves the reaction of glutathione (GSH) with the peroxide functionality of GO, leading to the corresponding ring opening-derived peroxide **38**, which rapidly reacts with **37** affording the tellurenic acid **39**. Reaction of GSH with **39** provides the tellurenyl sulfide **40**, which regenerates **37** by reacting with GSH. The attack of GSH at the sulfur center of the GO-derived compound **41** leads to the reduced graphene oxide (RGO), along with GSSG and H<sub>2</sub>O (Scheme 9). The NADPH-dependent glutathione reductase (GR) reduces GSSG to GSH, which acts as the thiol cofactor in the catalytic cycle.

Other tellurium- and selenium-containing GPx mimics have been demonstrated to catalysed GO reduction at different extent. On the other hand, although containing a highly reactive selenocysteine residue, glutathione peroxidase was unable to efficiently catalyse the reduction of GO.[66]

The chemistry and the properties of organotellurides have also been applied to the construction of a reversible near-infrared fluorescent probe for monitoring the changes of peroxynitrite (ONOO<sup>-</sup>) and glutathione (GSH) in cells and *in vivo*. Yu *et al.*[67] reported the synthesis and the study of the heptamethine cyanine-based probe **42**, bearing the 2-(phenyltellanyl)benzohydrazide moiety as the fluorescent modulator. Notably, this functionalised group could protect the tellurium atom of **43** from overoxidation through the reversible formation of a spirodiazatellurane derivative, as reported by Mugesh *et al.*[53] The detection mechanism reported in the Scheme 10 relies on a photoinduced electron transfer process (PET). Such a telluroenzyme mimic integrated system exhibited significant sensitivity and

selectivity, showing a selective turn on fluorescence response to ONOO<sup>-</sup> and being reduced by intracellular GSH. The probe could be efficiently applied to real-time imaging changes of ONOO<sup>-</sup>/GSH redox homeostasis in cells and living animals.



**Scheme 9**. Reduction of peroxide functions in graphene oxide catalysed by **36**. RGO = reduced graphene oxide; GSH = glutathione; *GR* = glutathione reductase.



**Scheme 10**. Tellurium-containing near-infrared fluorescent probe for monitoring the changes of ONOO<sup>-</sup> and GSH.

The features of tellurium-containing moieties can also be harnessed for the preparation of polymers with catalytic antioxidant properties. Smet *et al.* synthesised chalcogen containing hyperbranched polymers and evaluated their GPx-like activity. Polytellurides (Figure 8) showed higher catalytic performances compared to the corresponding polyselenides. For example, the GPx-like properties determined monitoring the oxidation of PhSH with H<sub>2</sub>O<sub>2</sub> highlighted the higher activity of polytellurides ( $v_0 = 56.64 \,\mu$ M/min; MW: 4750) with respect to related polyselenides ( $v_0 = 22.06 \,\mu$ M/min; MW: 4300). Polymers with higher molecular weight and degree of branching behaved as more effective catalysts, thus highlighting the importance of the incorporation of multiple catalytic sites in such macromolecules.[68]



Figure 8. Hyperbranched tellurium-containing polymer.

A soluble supramolecular tellurium-containing glutathione peroxidase mimic based on host-guest interaction was also reported.[69,70] Such a structure was demonstrated to form hollow vesicle-like aggregates in water. Interestingly, owing to the hydrophobic microenvironment of vesicle-like aggregates, the supramolecular self-assembled system exhibited typical catalytic behaviour and specific recognition ability for hydrophobic substrates.

The incorporation of tellurium moieties onto suitable substrates has also been exploited for the construction of a smart bifunctional artificial enzyme model with superoxide dismutase (SOD) and GPx activities by Liu *et al.* Such a star-shaped pseudo-block copolymer, prepared from a tellurium-containing temperature-sensitive block copolymer which can self-assemble with a suitable Mn(III) porphyrin through host–guest complexation, exhibited temperature-responsive SOD-like and GPx-like catalytic activities. Interestingly, stable SOD-like properties and the highest GPx-like activity were found under conditions close to body temperature.[71]

In this context, the synthesis of a microgel-based biomimetic GPx with temperature-responsive catalytic activity was reported by Yin *et al.* Such a microgel was efficiently constructed by combining one-pot method and atom transfer radical polymerisation (ATRP) approaches using a suitable telluride monomer, polyacrylamide, and PEG crosslinker.[72]

# 4. Concluding Remarks

A broad range of chalcogen-containing synthetic small molecules have been reported to possess promising biological and pharmaceutical activities. In this context, while selenium-containing compounds have been widely investigated, their tellurium-containing analogues have received far less attention. However, the properties of organotellurium compounds attracted the steadily increasing interest of chemists and biologists over the last two decades and led to the development of an array of structurally diverse systems with promising activities. The properties of chalcogen-containing compounds can be at least partially explained considering their interactions with biological targets, including those with thiols (*i.e.* GSH and cysteine), disulfides, and high-molecular-mass selenols. The properties of organochalcogen compounds – including their prooxidant activity, their capability to catalyse various reaction at the cellular level (*i.e.* modification of cysteine residues, thiol-disulfide interchange reactions), their direct or indirect modulation of the redox biology of cells, and their interaction with toxic electrophiles (*i.e.* metals) – need to be taken into account when considering their biological activity.[73]

Although the role of glutathione peroxidase-like properties of chalcogen-containing small molecules on their biological and pharmaceutical activity has been reconsidered, knowing the mechanism accounting for their thiol-peroxidase-like activity remains of paramount importance.

In this context, extrapolating the reactivity and the properties of organotellurium compounds from those of related selenium-containing molecules is often an oversimplification. Thus, detailed investigations on the chemical behaviour of various classes of tellurium-containing molecules with thiols in the presence of oxidants are highly desired. Indeed, knowing the diverse catalytic mechanisms that can operate for different GPx-like systems lays at the basis of the rational design and synthesis of new tellurium-containing catalytic antioxidants.

Furthermore, the identification of intermediates formed in the catalytic cycles operating for organotellurium compounds enables the comprehension of additional interactions involving tellurium-containing reactive intermediates and biological targets. Although the nature of reactive intermediates and metabolites formed in the physiological cell milieu is more complex and more difficult to be determined, the study of simplified models is crucial in order to elucidate possible mechanisms of action of chalcogen-containing small molecules under physiological conditions.

A number of classes of tellurium-containing derivatives have been investigated and different catalytic pathways have been proposed. The nature of substituents or functional groups present at selected position of tellurium-containing derivatives can significantly influence the catalytic mechanism, leading for example to the formation of spirotellurane intermediates. Additionally, intramolecular chalcogen bonding interactions involving the tellurium atom and an electronegative element (*i.e.* O, N) in its close proximity have been reported to play an important role on the catalytic antioxidant properties of tellurides and ditellurides. Thus, the introduction of suitable moieties represents a rewarding strategy that can be exploited to modulate the thiol-peroxidase like properties of tellurium-based systems.

As aforementioned, model-based studies represent a powerful tool to elucidate the mechanisms involved in the interactions of chalcogen-containing compounds with biological targets. Although several progresses have been made in this field, further studies are still required in order to decipher the nature and the fates of intermediates potentially formed from tellurium-containing compounds under physiological conditions.

# **Consent for publication**

Not applicable

# Funding

This research received no external funding.

#### **Conflict of interest**

The authors declare no conflict of interest

# Acknowledgements

We thank MIUR-Italy (Progetto Dipartimenti di Eccellenza 2018–2022 allocated to Department of Chemistry "Ugo Schiff").

# References

[1] Klotz, L.-O.; Kröncke, K.-D.; Buchczyk, D. P.; Sies, H. Role of Copper, Zinc, Selenium and Tellurium in the Cellular Defense against Oxidative and Nitrosative Stress, *J. Nutr.* **2003**, *133* (5 Suppl. 1), 1448S-1451S.

[2] Barchielli, G.; Capperucci, A.; Tanini, D. The Role of Selenium in Pathologies: An Updated Review. *Antioxidants* **2022**, *11*, 251.

[3] Gromer, S.; Johansson, L.; Bauer, H.; Arscott, L.D.; Rauch, S.; Ballou, D.P.; Williams, C.H., Jr.; Schirmer, R.H.; Arnér, E.S.J. Active sites of thioredoxin reductases: Why selenoproteins? *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 12618-12623.

[4] Reich, H.J.; Hondal, R.J. Why nature chose Selenium? ACS Chem. Biol. 2016, 11, 821-841.

[5] Lu, X.; Mestres, G.; Singh, V. P.; Effati, P.; Poon, J.-F.; Engman, L.; Ott, M. K. Selenium- and Tellurium-Based Antioxidants for Modulating Inflammation and Effects on Osteoblastic Activity, *Antioxidants*, **2017**, *6*, 13.

[6]. Engman, L.; Al-Maharik, N.; McNaughton, M.; Birmingham, A.; Powis, G. Thioredoxin reductase and cancer cell growth inhibition by organotellurium antioxidants. *Anti-Cancer Drugs*, **2003**, *14*, 153-161.

[7] Tanini, D.; Ricci, L.; Capperucci, A.; Di Cesare Mannelli, L.; Ghelardini, C.; Peat, T.S.; Carta, F.; Angeli, A.; Supuran, C.T. Synthesis of novel tellurides bearing benzensulfonamide moiety as carbonic anhydrase inhibitors with antitumor activity. *Eur. J. Med. Chem.* **2019**, *181*, 111586.

[8] Tanini, D.; Carradori, S.; Capperucci, A.; Lupori, L.; Zara, S.; Ferraroni, M.; Ghelardini, C.; Di Cesare Mannelli, L.; Micheli, L.; Lucarini, E.; Carta, F.; Angeli, A.; Supuran, C. T. Chalcogenides-incorporating carbonic anhydrase inhibitors concomitantly revertedoxaliplatin-induced neuropathy and enhanced antiproliferative action. *Eur. J. Med. Chem.* **2021**, *225*, 113793.

[9] Sredni, B.; Caspi, R. R.; Klein, A.; Kalechman, Y.; Danziger, Y.; Ben Ya'akov, M.; Tamari, T.; Shalit, F.; Albeck, M. A New Immunomodulating Compound (AS-101) With Potential Therapeutic Application. *Nature*, **1987**, *330*, 173-176.

[10] Kalechman, Y.; Albeck, M.; Sredni, B. In Vivo Synergistic Effect of the Immunomodulator AS101 and the PKC Inducer Bryostatin. *Cell. Immunol.* **1992**, *143*, 143-153.

[11] Vrana, J. A.; Rao, A. S.; Wang, Z.; Jarvis, W. D.; Grant, S. Effects of Bryostatin 1 and Calcium Ionophore (A23187) on Apoptosis and Differentiation in Human Myeloid Leukemia Cells (HL-60) Following 1-beta-D-arabinofuranosylcytosine Exposure. *Int. J. Oncol.* **1998**, *12*, 927-934.

[12] Ávila, D. S.; Colle, D.; Gubert, P.; Palma, A. S.; Puntel, G.; Manarin, F.; Noremberg, S.; Nascimento, P. C.; Aschner, M.; Rocha, J. B. T.; Soares, F. A. A. A Possible Neuroprotective Action of a Vinylic Telluride Against Mn-induced Neurotoxicity. *Toxicol. Sci.* **2010**, *115*, 194-201.

[13] Ávila, D. S.; Palma, A. S.; Colle, D.; Scolari, R.; Manarin, F.; da Silveira, A. F.; Nogueira, C. W.; Rocha, J. B.
T.; Soares, F. A. A. Hepatoprotective activity of a vinylic telluride against acute exposure to acetaminophen. *Eur. J. Pharmacol.* 2011, 661, 92-101.

[14] Tiano, L.; Fedeli, D.; Santroni, A. M.; Villarini, M.; Engman, L.; Falcioni, G. Effect of three diaryl tellurides, and an organoselenium compound in trout erythrocytes exposed to oxidative stress in vitro. *Mutat. Res.* **2000**, *464*, 269-277.

[15] Lin, T.; Ding, Z.; Li, N.; Xu, J.; Luo, G.; Liu, J.; Shen, J. 2-Tellurium-bridged β-cyclodextrin, a thioredoxin reductase inhibitor, sensitizes human breast cancer cells to TRAIL-induced apoptosis through DR5 induction and NF-κB suppression. *Carcinogenesis*, **2010**, *32*, 154–167.

[16] Cunha, R. L. O. R.; Gouvea, I. E.; Juliano, L. A glimpse on biological activities of tellurium compounds. *Acad. Bras. Cienc.* **2009**, *81*, 393-407.

[17] Angeli, A.; Tanini, D.; Capperucci, A.; Supuran, C. T. First evaluation of organotellurides as Carbonic Anhydrase I, II, IV, VII and IX inhibitors. *Bioorg. Chem.* **2018**, *76*, 268-272.

[18] Tanini, D.; Capperucci, A.; Supuran, C.T.; Angeli, A. Sulfur, selenium and tellurium containing amines act as effective carbonic anhydrase activators. *Bioorg. Chem.* **2019**, *87*, 516–522.

[19] Stefanello, S. T.; Gubert, P.; Puntel, B.; Mizdal, C. R.; de Campos, M. M. A.; Salman, S. M.; Dornelles, L.; Avila, D. S.; Aschner, M.; Soares, F. A. A. Protective effects of novel organic selenium compounds againstoxidative stress in the nematode Caenorhabditis elegans. *Toxicology Reports*, **2015**, *2*, 961–967.

[20] Rooseboom, M.; Vermeulen, N. P. E.; Durgut, F.; Commandeur, J. N. M. Comparative Study on the Bioactivation Mechanisms and Cytotoxicity of Te-Phenyl-L-tellurocysteine, Se-Phenyl-L-selenocysteine, and S-Phenyl-L-cysteine. *Chem. Res. Toxicol.* **2002**, *15*, 1610-1618.

[21] Deng, Z.T.; Zhang, Y.; Yue, J.C.; Tang, F.Q.; Wei, Q. Green and Orange CdTe Quantum Dots as Effective pH-sensitive Fluorescent Probes for Dual Simultaneous and Independent Detection of Viruses. *J. Phys. Chem. B*, **2007**, *111*, 12024-12031.

[22] Chen, H.; Lesnyak, V.; Bigall, N.C.; Gaponik, N.; Eychmüller, A. Self-Assembly of TGA-Capped CdTe Nanocrystals into Three-Dimensional Luminescent Nanostructures. *Chem. Mater.* **2010**, *22*, 2309-2314.

[23] Wachter, J. Metal Telluride Clusters — From Small Molecules to Polyhedral Structures. *Eur. J. Inorg. Chem.* **2004**, *1367*, 1367-1378.

[24] Zhang, B.; Hou, W.Y.; Ye, X.C.; Fu, S.Q.; Xie, Y. 1D Tellurium Nanostructures: Photothermally Assisted Morphology-Controlled Synthesis and Applications in Preparing Functional Nanoscale Materials. *Adv. Funct. Mater.* **2007**, *17*, 486-492.

[25] Fonseca, S. F.; Lima, D. B.; Alves, D.; Jacob, R. G.; Perin, G.; Lenardão, E. J.; Savegnago, L. Synthesis, characterization and antioxidant activity of organoselenium and organotellurium compound derivatives of chrysin. *New J. Chem.*, **2015**, *39*, 3043-3050.

[26] Tanini, D.; Lupori, B.; Malevolti, G.; Ambrosi, M.; Lo Nostro, P.; Capperucci, A. Direct biocatalysed synthesis of first sulfur-, selenium- and tellurium containing L-ascorbyl hybrid derivatives with radical trapping and GPx-like properties. *Chem. Commun.*, **2019**, *55*, 5705-5708.

[27] Ibrahim, M.; Hassan, W.; Meinerz, D. F.; Dos Santos, M.; Klimaczewski, C. V.; Deobald, A. M.; Costa, M.
S.; Nogueira, C. W.; Barbosa, N. B. V.; Rocha, J. B. T. Antioxidant properties of diorganoyl diselenides and ditellurides: modulation by organic aryl or naphthyl moiety. *Mol. Cell. Biochem.* 2012, 371, 97–104.

[28] Capperucci, A.; Coronnello, M.; Salvini, F.; Tanini, D.; Dei, S.; Teodori, E.; Giovannelli, L. Synthesis of functionalised organochalcogenides and *in vitro* evaluation of their antioxidant activity. *Bioorg. Chem.* **2021**, *110*, 104812.

[29] Kanda, T.; Engman, L.; Cotgreave, I. A.; Powis, G. Novel Water-Soluble Diorganyl Tellurides with Thiol Peroxidase and Antioxidant Activity, *J. Org. Chem.* **1999**, *64*, 8161-8169.

[30] Engman, L.; Stern, D.; Cotgreave, I. A.; Andersson, C. M. Thiol peroxidase activity of diaryl ditellurides as determined by a proton NMR method. *J. Am. Chem. Soc.* **1992**, *114*, 9737–9743.

[31] Tanini, D.; Ricci, L.; Capperucci, A. Rongalite-Promoted *on Water* Synthesis of Functionalised Tellurides and Ditellurides. *Adv. Synth. Catal.* **2020**, *362*, 1323-1332.

[32] Tanini, D.; Grechi, A.; Ricci, L.; Dei, S.; Teodori, E.; Capperucci, A. Novel functionalized organotellurides with enhanced thiol peroxidase catalytic activity. *New J. Chem.*, **2018**, *42*, 6077-6083.

[33] You, Y.; Ahsan, K.; Detty, M. R. Mechanistic Studies of the Tellurium(II)/Tellurium(IV) Redox Cycle in Thiol Peroxidase-like Reactions of Diorganotellurides in Methanol, *J. Am. Chem. Soc.* **2003**, *125*, 4918-4927.

[34] Press, D. J.; Back, T. G. Enhanced Glutathione Peroxidase Activity of Conformationally Restricted Naphthalene *peri*-Dichalcogenides, *Org. Lett.*, **2011**, *13*, 4104-4107.

[35] Jagdev, K.; Tanini, D.; Lownes, J. W.; Figliola, C.; Male, L.; Capperucci, A.; Grainger, R. S. Glutathione peroxidase mimics based on conformationally-restricted, *peri*-like, 4,5-disubstituted fluorene dichalcogenides, *Org. Biomol. Chem.*, **2021**, *19*, 10565-10569.

[36] Braga, A. L.; Alberto, E. E.; Soares, L. C.; Rocha, J. B. T.; Sudati, J. H.; Roos, D. H. Synthesis of telluroamino acid derivatives with remarkable GPx like activity. *Org. Biomol. Chem.* **2009**, *7*, 43-45.

[37] Detty, M. R.; Gibson, S. L. Tellurapyrylium dyes as catalysts for oxidations with hydrogen peroxide and as scavengers of singlet oxygen. Dihydroxytelluranes as mild oxidizing agents. *Organometallics*, **1992**, *11*, 2147-2156.

[38] Engman, L.; Stern, D.; Pelcman, M.; Andersson, C. M. Thiol Peroxidase Activity of Diorganyl Tellurides. *J. Org. Chem.* **1994**, *59*, 1973-1979.

[39] Vessman, K.; Ekstörm, M.; Berglund, M.; Andersson, C. M.; Engman, L. Catalytic Antioxidant Activity of Diaryl Tellurides in a Two-Phase Lipid Peroxidation Model. *J. Org. Chem.* **1995**, *60*, 4461-4467.

[40] Engman, L.; Lind, J.; Merényi, G. Redox Properties of Diaryl Chalcogenides and Their Oxides. *J. Phys. Chem.* **1994**, *98*, 3174-3182.

[41] Organoselenium Chemistry, Ed. Wirth, T. Wiley-WHC Verlag & Co, Weinheim, Germany, 2012.

[42] Lenardão, E.J.; Santi, C.; Sancineto, L. *New Frontiers in Organoselenium Compounds*; Springer: New York, NY, USA, **2018**.

[43] Bhabak, K. P.; Mugesh, G. Functional Mimics of Glutathione Peroxidase: Bioinspired Synthetic Antioxidants, *Acc. Chem. Res.* **2010**, *43*, 1408-1419.

[44] Bhabak, K. P.; Mugesh, G. Amide-based glutathione peroxidase mimics: effect of secondary and tertiary amide substituents on antioxidant activity. *Chem. Asian J.* **2009**, *4*, 974–983.

[45] Mugesh, G.; du Mont, W.-W. Structure-activity correlation between natural glutathione peroxidase(GPx) and mimics: A biomimetic concept for the design and synthesis of more efficient GPx mimics. *Chem. Eur. J.* **2001**, *7*, 1365–1370.

[46] Bhowmick, D.; Mugesh, G. Introduction of a catalytic triad increases the glutathione peroxidase-like activity of diaryl diselenides, *Org. Biomol. Chem.* **2015**, *13*, 9072-9082.

[47] Tripathi, S. K.; Patel, U.; Roy, D.; Sunoj, R. B.; Singh, H. B.; Wolmershäuser, G.; Butcher, R. J. *o*-Hydroxylmethylphenylchalcogens: Synthesis, Intramolecular Nonbonded Chalcogen…OH Interactions, and Glutathione Peroxidase-like Activity. *J. Org. Chem.* **2005**, *70*, 9237-9247.

[48] Tanini, D.; Grechi, A.; Dei, S.; Teodori, E.; Capperucci, A. An easy one-step procedure for the synthesis of novel β-functionalised tellurides. *Tetrahedron*, **2017**, *73*, 5646-5653.

[49] Tanini, D.; Borgogni, C.; Capperucci, A. Mild and selective silicon-mediated access to enantioenriched 1,2-mercaptoamines and β-amino arylchalcogenides. *New J. Chem.* **2019**, *43*, 6388-6393.

[50] Pascoe, D. J.; Ling, K. B.; Cockroft, S. L. The Origin of Chalcogen-Bonding Interactions. *J. Am. Chem. Soc.*, **2017**, *139*, 15160-15167.

[51] Nascimento, V.; Alberto, E. E.; Tondo, D. W.; Dambrowski, D.; Detty, M. R.; Nome, F.; Braga, A.L. GPx-Like Activity of Selenides and Selenoxides: Experimental Evidence for the Involvement of Hydroxy Perhydroxy Selenane as the Active Species. *J. Am. Chem. Soc.*, **2012**, *134*, 138-141.

[52] Kheirabadi, R.; Izadyar, M. Computational modeling of the kinetics and mechanism of tellurium-based glutathione peroxidase mimic. *Int. J. Quantum Chem.* **2020**, *120*, e26201.

[53] Sarma, B. K.; Manna, D.; Minoura, M.; Mugesh, G. Synthesis, Structure, Spirocyclization Mechanism, and Glutathione Peroxidase-like Antioxidant Activity of Stable Spirodiazaselenurane and Spirodiazatellurane, *J. Am. Chem. Soc.* **2020**, *132*, 5364-5374.

[54] Back, T. G.; Kuzma, D.; Parvez, M. Aromatic Derivatives and Tellurium Analogues of Cyclic Seleninate Esters and Spirodioxyselenuranes That Act as Glutathione Peroxidase Mimetics, *J. Org. Chem.* **2005**, *70*, 9230-9236.

[55] Poon, J.; Singh, V. P.; Engman, L. In Search of Catalytic Antioxidants–(Alkyltelluro)phenols, (Alkyltelluro)resorcinols, and Bis(alkyltelluro)phenols, *J. Org. Chem.* **2013**, *78*, 6008-6015.

[56] Amorati, R.; Valgimigli, L.; Dinér, P.; Bakhtiari, K.; Saeedi, M.; Engman, L. Multi-faceted Reactivity of Alkyltellurophenols Towards Peroxyl Radicals: Catalytic Antioxidant Versus Thiol-Depletion Effect, *Chem. Eur. J.* **2013**, *19*, 7510-7522.

[57] Singh, V. P.; Poon, J.-F.; Engman, L. Catalytic Antioxidants: Regenerable Tellurium Analogues of Vitamin E. Org. Lett. **2013**, *15*, 6274–6277.

[58] Ren, X.; Xue, Y.; Liu, J.; Zhang, K.; Zheng, J.; Luo, G.; Guo, C.; Mu, Y.; Shen, J. A Novel Cyclodextrin-Derived Tellurium Compound with Glutathione Peroxidase Activity, *ChemBioChem*, **2002**, *3*, 356-363.

[59] McNaughton, M.; Engman, L.; Birmingham, A.; Powis, G.; Cotgreave, I. A. Cyclodextrin-Derived Diorganyl Tellurides as Glutathione Peroxidase Mimics and Inhibitors of Thioredoxin Reductase and Cancer Cell Growth, *J. Med. Chem.* **2004**, *47*, 233-239.

[60] Jiao, A.; Yang, N.; Wang, J.; Xu, X.; Jin, Z. Cyclodextrin-derived chalcogenides as glutathione peroxidase mimics and their protection of mitochondria against oxidative damage. *J. Incl. Phenom. Macrocycl. Chem.* **2013**, *75*, 155-163.

[61] Wang, L.; Qu, X.; Xie, Y.; Lv, S. Study of 8 Types of Glutathione Peroxidase Mimics Based on  $\beta$ -Cyclodextrin, *Catalysts*, **2017**, *7*, 289.

[62] Morya, V. K.; Dong, S. J.; Kim, E.-k. Production and Characterization Te-Peptide by Induced Autolysis of Saccharomyces Cerevisiae. *Appl. Biochem. Biotechnol.* **2014**, *172*, 3390-3401.

[63] Mao, S.; Dong, Z.; Liu, J.; Li, X.; Liu, X.; Luo, G.; Shen, J. Semisynthetic Tellurosubtilisin with Glutathione Peroxidase Activity. *J. Am. Chem. Soc.* **2005**, *127*, 11588-11589.

[64] Liu, X.; Silks, L. A.; Liu, C.; Ollivault-Shiflett, M.; Huang, X.; Li, J.; Luo, G.; Hou, Y.-M.; Liu, J.; Shen, J. Incorporation of Tellurocysteine into Glutathione Transferase Generates High Glutathione Peroxidase Efficiency. *Angew. Chem. Int. Ed.* **2009**, *48*, 2020-2023.

[65] Bortoli, M.; Torsello, M Bickelhaupt; F. M.; Orian, L. Role of the Chalcogen (S, Se, Te) in the Oxidation Mechanism of the Glutathione Peroxidase Active Site. *ChemPhysChem*, **2017**, *18*, 2990-2998.

[66] Vernekar, A. A.; Mugesh, G. Catalytic Reduction of Graphene Oxide Nanosheets by Glutathione Peroxidase Mimetics Reveals a New Structural Motif in Graphene Oxide. *Chem. Eur. J.* **2013**, *19*, 16699-16706.

[67] Yu, F.; Li, P.; Wang, B.; Han, K. Reversible Near-Infrared Fluorescent Probe Introducing Tellurium to Mimetic Glutathione Peroxidase for Monitoring the Redox Cycles between Peroxynitrite and Glutathione in Vivo. *J. Am. Chem. Soc.* **2013**, *135*, 7674–7680.

[68] Thomas, J.; Dong, Z.; Dehaen, W.; Smet, M. Selenium/Tellurium-Containing Hyperbranched Polymers: Effect of Molecular Weight and Degree of Branching on Glutathione Peroxidase-Like Activity, *Macromol. Rapid Commun.* **2012**, *33*, 2127–2132.

[69] Yin, Y.; Jiao, S.; Zhang, R.; Wang, X.; Zhang, L.; Yang, L. Construction of a Soluble Supramolecular Glutathione Peroxidase Mimic based on Host-Guest Interaction. *Curr. Organocatalysis*, **2015**, *2*, 64-70.

[70] Yin, Y.; Jiao, S.; Lang, C.; Liu, J. A supramolecular microgel glutathione peroxidase mimic with temperature responsive activity. *Soft Matter*, **2014**, *10*, 3374-3385.

[71] Yu, S.; Yin, Y.; Zhu, J.; Huang, X.; Luo, Q.; Xu, J.; Shen, J.; Liu, J. A modulatory bifunctional artificial enzyme with both SOD and GPx activities based on a smart star-shaped pseudo-block copolymer, *Soft Matter*, **2010**, *6*, 5342-5350.

[72] Jiao, S.; Liang, X.; Zhang, R.; Zhong, S.; Zheng, Y.; Wang, S.; Liu, M.; Hu, X.; Yin, Y. Facile Construction of Microgel based Biomimetic Glutathione Peroxidase with Temperature Responsive Catalytic Activity, *ChemistrySelect* **2019**, *4*, 12143-12150.

[73] Nogara, P. A.; Bortoli, M.; Orian, L.; Rocha, J. B. T. Biological Activity of Synthetic Organoselenium Compounds: What do we Know about the Mechanism? *Curr. Chem. Biol.* **2022**, <u>10.2174/2212796816666220422135204</u>

