Drug Resistance Updates 63 (2022) 100844

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Selenium and tellurium in the development of novel small molecules and nanoparticles as cancer multidrug resistance reversal agents

Enrique Domínguez-Álvarez [a], Bálint Rácz [b], Małgorzata Anna Marć [b], Muhammad Jawad Nasim [c], Nikoletta Szemerédi [b], Jitka Viktorová [d], Claus Jacob [c], Gabriella Spengler [b,*]

[a] Instituto de Química Orgánica General (IQOG), CSIC, Juan de la Cierva 3, 28006 Madrid, Spain
[b] Department of Medical Microbiology, Albert Szent-Györgyi Health Center, Albert Szent-Györgyi Medical School, University of Szeged, Semmelweis utca 6, 6725 Szeged, Hungary
[c] Division of Bioorganic Chemistry, School of Pharmacy, Saarland University, D-66123 Saarbruecken, Germany
[d] Department of Biochemistry and Microbiology, Faculty of Food and Biochemical Technology, University of Chemistry and Technology Prague, Technická 3, 166 28 Prague 6, Czech Republic

ARTICLE INFO

Keywords:
Selenium
Tellurium
Cancer
Multidrug resistance (MDR)
Free radicals
Efflux pumps
Apoptosis
Inflammation
Autophagy
Drug combination
Drug development

ABSTRACT

Selenium is an essential trace element that is crucial for cellular antioxidant defense against reactive oxygen species (ROS). Recently, many selenium-containing compounds have exhibited a wide spectrum of biological activities that make them promising scaffolds in Medicinal Chemistry, and, in particular, in the search for novel compounds with anticancer activity. Similarly, certain tellurium-containing compounds have also exhibited substantial biological activities. Here we provide an overview of the biological activities of seleno- and tellurocompounds including chemopreventive activity, antioxidant or pro-oxidant activity, modulation of the inflammatory processes, induction of apoptosis, modulation of autophagy, inhibition of multidrug efflux pumps such as P-gp, inhibition of cancer metastasis, selective targeting of tumors and enhancement of the cytotoxic activity of chemotherapeutic drugs, as well as overcoming tumor drug resistance. A review of the chemistry of the most relevant seleno- or tellurocompounds with activity against resistant cancers is also presented, paying attention to the synthesis of these compounds and to the preparation of bioactive selenium or tellurium nanoparticles. Based on these data, the use of these seleno- and tellurocompounds is a promising approach in the development of strategies that can drive forward the search for novel therapies or adjuvants of current therapies against drug-resistant cancers.

1. Introduction

Selenium was discovered in the year 1817 by the Swedish chemist Jons Jacob Berzelius. It was named after the ancient Greek word 'Selene', which refers to the Moon (Berzelius, 1818). Selenium (Se) is a micronutrient with exceptional physiological and pharmacological features and essential biological functions, and can be considered as one of the most deeply studied elements in cancer chemoprevention (Sanmartín et al., 2012, Manzanares et al., 2015).

Selenium participates in the prevention of cancer, cardiovascular diseases, viral infections, infertility, and neurological disorders. The anticancer and chemopreventive activities of Se and of selenocompounds have been extensively reviewed by many authors, as well as its implications in nutrition and in human health (Ali et al., 2018; Avery and Hoffmann, 2018; Bartolini et al., 2017; Fairweather-Tait et al., 2011; Misra et al., 2015; Navarro-Alarcon and Cabrera-Vique, 2008; Radomska et al., 2021; Rayman, 2000, 2012; Sanmartín et al., 2012; Valente et al., 2021). Proper levels of bioavailable Se are critically important for numerous aspects of human health. Among them, the central nervous system, the male reproductive system, the endocrine system, cardiovascular system, immune system, and muscle function can be highlighted.

Se is a trace element with a narrow safety range. At low concentrations, it acts as an antioxidant, whereas at high concentrations it can behave as a prooxidant. Nevertheless, the toxicity and effectiveness of Se compounds markedly depends on the administered form of Se, besides

* Corresponding author.
E-mail address: spengler.gabriella@med.u-szeged.hu (G. Spengler).

https://doi.org/10.1016/j.drup.2022.100844

Available online 2 May 2022

the actual dose. Consequently, the administered selenocompounds should be considered as prodrugs whose effects depend on several metabolic pathways and on the redox status (Alcolea and Pérez-Silanes, 2020). The functional properties of Se compounds are related to their ambivalent nature, as they can act as antioxidants (selenocysteine balancing redox homeostasis and protecting phagocytic cells from oxidative stress generated by ROS) or prooxidants: Se-compounds can trigger a strong generation of ROS through the redox cycle, provoking oxidative stress in cancer cells (Menon and Shanmugam, 2020).

However, it is important to highlight that not all selenocompounds are 'marvelous': the chemical form in which they are present is crucial, as certain forms can be toxic, whereas others can exhibit the desired biological action with a good selectivity towards cancer. Moreover, not only the activity/untoward toxicity of the respective selenocompounds needs to be taken into account. Their metabolites are also of utmost importance, to the extent that most of the selenocompounds commonly found in the diet (selenite, selenomethionine, methylselenocysteine, and selenocystine) can be considered as prodrugs that enable the cellular release of their metabolites, which are responsible for their relevant observed chemopreventive and anticancer activities (Weekley and Harris, 2013).

Tellurium is considered to be a toxic, non-essential and infrequent element, and was discovered in 1782 by Franz Joseph Müller von Reichenstein, from ores mined in the gold regions of Transylvania. Its name is derived from the Roman earth goddess Tellus, meaning "Earth" in Latin. Tellurium derivatives are effective antioxidants and chemoprotective agents, even more potent than their selenium and sulfur isosteres. Various reports describe antileishmaniasis, anti-inflammatory, antiatherosclerotic, and immuno-modulating activities of tellurium. Furthermore, tellurium nanoparticles exert lipid-lowering, antioxidant, and free radical scavenging activities (Zare et al., 2017). Additionally, they might be interesting candidates as potential chemopreventive and antitumor agents.

2. Biochemistry of seleno- and telluro-compounds

Numerous selenium and tellurium derivatives have appeared to possess an antiproliferative effect in various biological assays and synergistically interact with chemotherapeutic agents. Selenium and tellurium compounds achieve their antiproliferative effect through various mechanisms of action: generating ROS, acting as pro-oxidants, boosting the antioxidant defenses of the cell, influencing cell signaling and autophagy, inducing apoptosis, interfering with protein-kinase signaling, inducing cell cycle arrest and sensitizing cells to known apoptosis inducers, such as doxorubicin. They are also involved in inflammation processes, can stimulate the immune response, and can act as synergistic enhancers of the activity of known chemotherapeutic drugs used in clinical practice, overcoming the resistance of tumors to the action of these known chemotherapeutics. Other important effects are that they can inhibit cancer metastasis and the angiogenic processes. Finally, the activity of multidrug resistance efflux pumps such as P-gp can be blocked by these compounds (Avery and Hoffmann, 2018; Fairweather-Tait et al., 2011; Misra et al., 2015; Radomska et al., 2021; Rayman, 2000, 2012; Sanmartín et al., 2012; Valente et al., 2021). Fig. 1 illustrates these different mechanisms through which the seleno- and tellurocompounds can affect cancer and multidrug-resistant cancer cells.

In the following subsections, the different effects mentioned above will be reviewed individually, to provide a comprehensive overview of the activities of seleno- and tellurocompounds against cancer and drug-resistant cancers.

2.1. Chemopreventive effects

The trace element Se is involved in many cellular processes, and as a component of selenoproteins, it has a preventive effect against specific forms of cancer. Moreover, a relationship was found between the administration of low doses of Se and the reduction of inflammatory

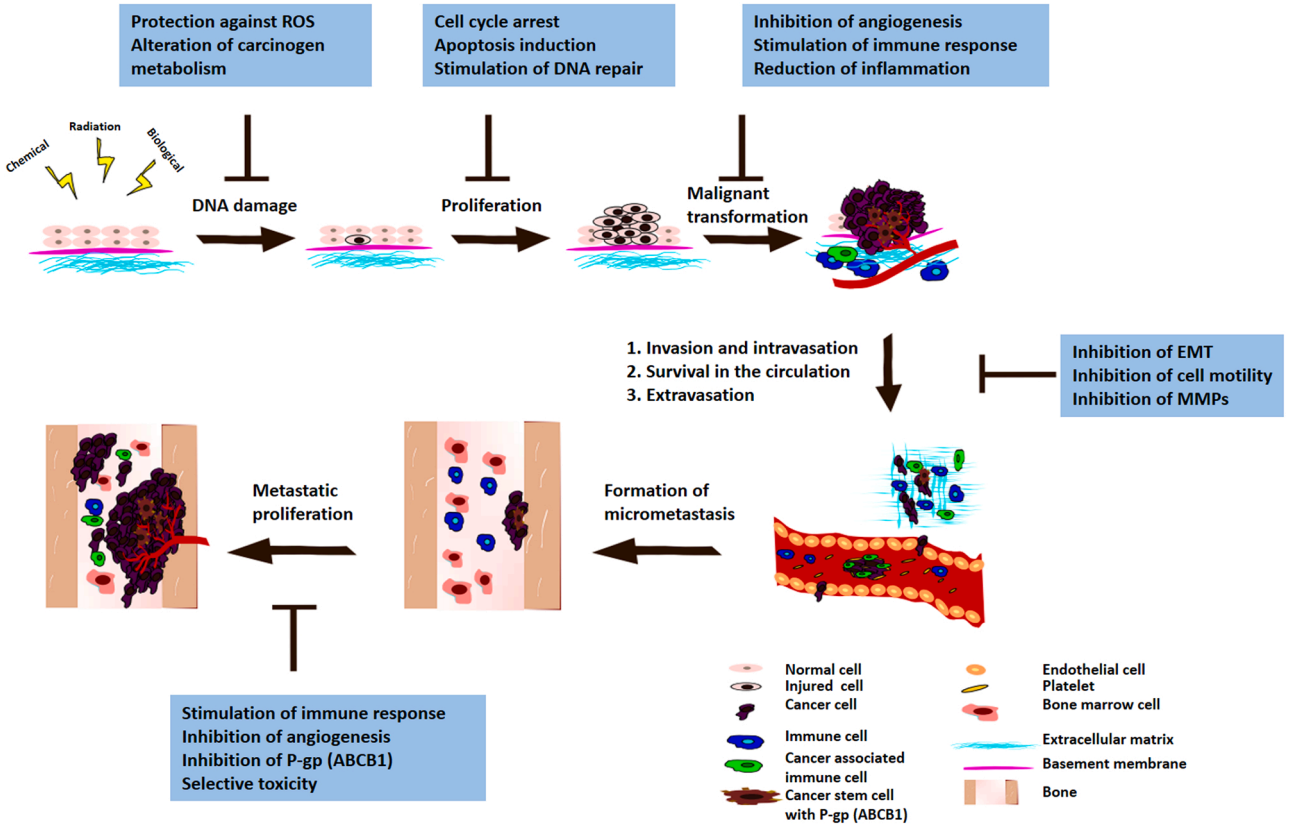


Fig. 1. Modes of action of seleno- and tellurocompounds against cancer cells.

processes, blood pressure regulation, and the prevention of heart disease. The chemopreventive activity of Se compounds *in vivo* is linked with their influence on the regulation of the cell cycle, apoptosis stimulation and inhibition of tumor cell migration and invasion (Sanmartín et al., 2012). Moreover, a preceding report evaluated the antiproliferative activity of broccoli biofortified with Se towards lung (NCI-H460), kidney (786−0), breast (MCF-7), human glioma (U251), and colon adenocarcinoma cell lines (HT-29). The proapoptotic effect of organic Se derivatives has been demonstrated against various tumor cell lines, such as colon, prostate, lymphoma and leukemia or liver cancer. Furthermore, the chemopreventive and anticancer activity of selenocompounds is not only correlated with their complex molecular mechanism of action, but highly dependent on the chemical form and dosage (Sanmartín et al., 2012). Some research correlates low Se status with an elevated risk of developing cancer. However, other studies contradict this claim. Se plays a key role in the chemoprevention of certain cancers. Besides this, the underlying molecular and genetic mechanisms of Se's action have not been entirely determined. One of the main mechanisms related to the chemopreventive effect of selenocompounds is the cytoprotection due to the reduction of ROS generation (decrease in DNA and cell membrane damage caused by ROS) (Radomska et al., 2021). Se can be metabolized into various Se compounds, many of which can exert significant biological activity through redox reactions, affecting cellular metabolism, DNA repair and epigenetics (Avery and Hoffmann, 2018). Bioactive metabolites of Se include hydrogen selenide and methylated Se compounds such as methylseleninic acid, which exhibits chemopreventive activities (Avery and Hoffmann, 2018). The chemopreventive effect of Se was related to its antioxidant potential, specific biotransformation, p53 protein kinase suppression, upregulation of p53 protein expression, modulation of cell divisions and protection against toxic effects of heavy metals. Moreover, Se is associated with the suppression of angiogenesis, disruption of cell cycle progression, inhibition of inflammation, histone modifications, influence on cell metabolism, stimulation of the immune response (cellular and humoral), estrogen and androgen receptor modulation - and influence on their expression (Radomska et al., 2021). Additionally, Se can sensitize neoplastic cells to other apoptotic inducers, such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and doxorubicin. Moreover, it has been observed that Se induces a specific senescence response in non-cancerous cells (Sanmartín et al., 2012).

As for Te-containing compounds, Wieslander and Engman confirmed that bis(4-aminophenyl)telluride and diphenyltelluride were more efficient at the amelioration of butylated hydroxytoluene-induced cytotoxicity in human lung fibroblasts than its Se and S analog. Moreover, bis (4-aminophenyl)telluride was highly reactive in the antioxidant activity evaluation by DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) assay (Wieslander et al., 1998; Engman et al., 1995).

In recent years, new formulations such as quantum dots (QDs) and nanoparticles have become increasingly popular. QDs are defined as tiny light-emitting, nearly spherical semiconductor nanocrystal particles on the nanometer scale with a diameter of 10 nm or less, containing approximately 200–10,000 atoms. Clinical trials were conducted with photothermal therapy with CdTe QDs for the diagnosis and treatment of some types of tumors (Chu et al., 2012, Smith et al., 2008). Moreover, another research project applied the non-toxic and potent immunomodulator ammonium trichloro(dioxoethylene)tellurate(IV) as an antitumor drug candidate. Consequently, Te compounds exhibited activity against neurological disorders such as Parkinson's and some autoimmune diseases. Interestingly, topical formulations demonstrate promising activity in the treatment of dermatitis or exhibited anti-viral activity with the inhibition of cysteine proteases (Tiekink, 2012). The synthetic and non-toxic organotellurium derivative – ammonium trichloro (dioxoethylene-*O,O*') tellurate (AS101) exhibited noteworthy immunomodulatory and neuroprotective activities, via integrin αvβ3 inhibition and a presynaptic cell-surface-adhesion receptor. AS101 also diminished serum corticosterone levels in mice, and increased their hippocampal BDNF expression (Gross et al., 2017).

2.2. Influencing the redox state of cells

In malignant cells, elevated ROS levels play a crucial role in tumor progression and recurrence, as the elevated levels of ROS are balanced by high levels of detoxification and of antioxidant enzymes in cancer stem cells, leading to resistance towards antineoplastic therapies. However this redox balance is fragile, and breaking this delicate balance may be an effective therapeutic approach (Liou and Storz, 2010). Because of the dual role of ROS, both pro-oxidant and antioxidant strategies have emerged, although modulating ROS signaling alone may not be an effective approach, due to the high levels of antioxidant enzymes, but in combination with other pharmaceuticals it may enhance cytotoxicity in cancer cells (Goler-Baron and Assaraf, 2012; Gupta et al., 2012; Cui et al., 2018; Soll et al., 2020; Mosca et al., 2021).

Se and Te derivatives have exhibited a potent impact on cellular redox homeostasis in many studies: in a MCF-7 human breast cancer cell line Seleno-Cys, a Se amino acid, decreased the levels of UCP2 and MnSOD antioxidant proteins (Pons et al., 2020); Se-containing flavonoid derivatives were able to modulate thioredoxin reductase activity, a commonly upregulated redox system in malignant cells, leading to apoptosis (Martins et al., 2015). A selenohydantoin and its palladium complex possessed pro-oxidant activity in cancerous cells, thus besides having antiproliferative properties, they also exerted an anti-migratory effect on a human metastatic MDA-MB-231 breast cancer cell line. (Živanović et al., 2017). Sodium selenite cytotoxicity depends on its intracellular accumulation. Interestingly, the uptake of selenite by cells depended on the concentration of thiols in the extracellular milieu: it was favored by a higher thiols concentration, which can reduce selenite (as well as other redox-active Se compounds), easing its cellular uptake. These thiols, in drug resistant tumors, were mainly excreted as cysteine conjugates by the action of multidrug resistant pumps overexpressed in drug-resistant cells. Therefore, this mechanism may be the underlying basis for the high sensitivity of resistant tumors to selenite and, by extension, to Se compounds (Olm et al., 2009). Selenite has been used as a sensitizer of MDR cancer cells towards anticancer drugs such as doxorubicin (Björkhem-Bergman et al., 2002). This study confirmed this observation that drug-resistant cell lines (in this case U-1285dox and GLC_4/ADR, both resistant to doxorubicin) were more sensitive to sodium selenite than the doxorubicin-sensitive parental cell lines U-1285 and GLC_4. Interestingly, the doxorubicin-sensitive cells (less affected by selenite) increased the expression of antioxidant enzymes 4-fold (thioredoxin reductase and glutathione reductase), an effect which was not observed in drug-resistant cells, and which may explain the significantly higher cytotoxicity of selenite towards them. The upregulation of these enzymes is a cellular defense mechanism against the high reactivity of selenite towards cellular thiols, which results in a fatal alteration of the cellular thiolstat in which the antioxidant enzymes do not increase their expression, as happens in these two evaluated dox-resistant cell lines (Björkhem-Bergman et al., 2002). Selenocystine exhibited a similar pattern of action to selenite (more effective towards dox-resistant cells than to dox-sensitive cells), albeit with a less pronounced difference between sensitive and drug-resistant cell lines than the one observed for selenite (Björkhem-Bergman et al., 2002). Interestingly, H157 buccal mucosa squamous carcinoma cells exposed to sodium selenite at micromolar and submicromolar concentrations formed endogenous Se nanoparticles (SeNPs) in both the cytoplasm and organelles, by cellular reduction of the Se anion to elemental Se; these SeNPs are detectable by transmission electron microscopy (TEM) after an adequate fixing treatment (Bao et al., 2015). This endogenous formation of SeNPs may be the mechanism underlying the anticancer effects of selenite: the latter was associated with alterations in the expression of 504 genes, a decrease in cyclooxygenase and annexin levels, and cytotoxicity (Bao et al., 2015). Sodium selenate is less active than sodium selenite, but sensitizes a highly resistant oral cancer cell line (KBV20C) (Choi et al., 2015).

Interestingly, specific organotellurium derivatives have demonstrated promising GPx-like catalytic activities, in certain cases even more accentuated than the ones determined for their Se isosteres (Wieslander et al., 1998; Engman et al., 1995). Among ROS-involved Te compounds, the novel Te-containing amphiphilic compound DP41 induced superoxide radical production, caused ER stress and oxidative stress response in HCT-116 colon cancer cells, as well as inducing apoptosis in these cancer cells, but not in normal ARPE-19 cells (Du et al., 2014). Besides this, micromolar concentrations of tellurides were capable of hindering both thioredoxin reductase activity and the cellular growth of specific cancer cells. Te compounds demonstrated higher activity than their corresponding Se and S isosteres. Their strong antioxidant activity is related to scavenging hydrogen peroxide, hydroxyl radicals, and peroxynitrite (Rooseboom et al., 2002). Another organotellurium compound, diphenyl ditelluride (DPDT), and an inorganic Te compound, tellurium tetrachloride ($TeCl_4$), were associated with a decreased GSH/GSSG ratio in HT-29 human colon cancer cell line that ultimately resulted in apoptosis with DPDT and necrosis with $TeCl_4$ (Vij and Hardej, 2012).

Furthermore, some *in vitro* studies on cell lines discovered the ability of organotellurium compounds (e.g., 4,4'-dihydroxydiphenyl-telluride) to sequester free radicals, to reduce peroxynitrite (ONOO-) in the presence of organic thiols (RSH) and protect metallothionein proteins against ROS. Although the behavior of Te compounds is very similar to their Se relatives, their properties are slightly different and they exhibit stronger reactivity, which increases their toxicity, but this is evidently dependent on the form of the element. Unfortunately, some studies reported that the toxicity of Na_2TeO_3 is related to a Te-induced oxidative stress, and to a widespread damage to DNA and proteins (Castellucci Estevam et al., 2015).

Se is a known essential trace element, but Te is considered to be a toxic element. A possible explanation of the toxicity of tellurium is its affinity to Se. Te compounds, thanks to this affinity, tend to bind to the Se compounds present in the cells. When these Se atoms form part of the selenoproteins, this may result in the deactivation of these enzymes, causing damage to the cell. This can be the underlying mechanisms of the toxicity of Te compounds (Ba et al., 2010).

2.3. Inflammatory processes

As a component of many selenoproteins, Se participates in the regulation of the immune system and immune response, and is essential for immune functions. As for Se compounds, they enhance T-cell proliferation and the differentiation of (CD)4 + T helper (Th) cells. Additionally, Se enhances the phagocytic action of macrophages (due to cytotoxicity) and promotes the production of IgG and IgM antibodies. Se also influences the inflammatory-signaling and pathogen elimination roles of macrophages. It was revealed that Se can induce a phenotypic switch in macrophage activation from a pro-inflammatory phenotype via classical activation, towards the alternative activation of an anti-inflammatory phenotype. In addition, Se affects natural killer cells (NK) and cytotoxic T lymphocytes. It was demonstrated that SeNPs prevent the phosphorylation of IkB-α, therefore avoiding the release of NF-κB. Moreover, they can inhibit inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression (Menon and Shanmugam, 2020; Avery and Hoffmann, 2018). Se compounds and selenoproteins exhibit anti-inflammatory activity due to the adequate expression of selenoproteins (Menon and Shanmugam, 2020). Se deficiency reduces antioxidant defenses, hence provoking an increased susceptibility to infections, and also increasing the risk of emergence of some cancers (Avery and Hoffmann, 2018).

Moreover, insufficient Se intake and suppressed selenoprotein expression have been implicated in higher levels of inflammatory cytokines in the gastrointestinal tract, the uterus, mammary gland tissues and many others (Avery and Hoffmann, 2018). Chronic inflammatory diseases in the digestive system, as well as certain cancers associated with inflammatory processes, can be modulated by Se levels. Interestingly, dietary supplementation with sodium selenite significantly increased the expression of the genes encoding selenoproteins and interferon γ-mediated responses (Avery and Hoffmann, 2018). Additionally, high Se concentrations above 5 mM were implicated in a direct reversible inhibition of NF-κB binding to DNA, modulation of the gene expression of pro-inflammatory cytokines, the triggering of apoptotic and cytotoxic processes in hyperactivated immune cells, as well as a direct antimicrobial effect (Manzanares et al., 2015). Current results suggested that selenoprotein S, a transmembrane protein typically present in the ER and plasma membranes, plays a crucial role in inflammation. This protein is responsible for removing misfolded proteins from the ER lumen, exerting a cytoprotective effect from oxidative stress and ER-stress induced apoptosis (Hariharan and Dharmaraj, 2020). A recent study correlated the levels of Se and selenoprotein with proper hematopoiesis and the development of the immune system (Avery and Hoffmann, 2018).

The antioxidant and anti-inflammatory functions of Se can be associated with the functions of selenoproteins such as GPx, thioredoxin reductase (TrxR), and the selenoproteins P, S and W. GPx is the most abundant selenoprotein in the human body and it mediates the scavenging of excess free radicals generated during inflammatory processes. In addition, selenoprotein S modulates the action of inflammatory cytokines, whereas selenoprotein P is responsible for homeostasis (Hariharan and Dharmaraj, 2020). selenoproteins (mainly GPx) reduce the concentration of cellular peroxides (hydrogen peroxide and phospholipid peroxides), thus avoiding radical propagation reactions and damage to cellular molecules. This peroxide reduction is also reflected in a reduction in the inflammatory prostaglandins and leukotrienes through the cyclooxygenase and lipoxygenase pathways (Kim et al., 2021).

In traditional medicine, some of the natural raw pharmacognostic materials contain Se compounds and are used for the prevention and treatment of various inflammatory diseases. One of the most popular mushrooms found in Asian countries is *Hypsizygus marmoreus*, commonly used as nutritional supplement rich in immunomodulatory polysaccharides with antitumor, hypolipidemic, hypoglycemic, and antioxidant properties. Several studies reported an important role of Se polysaccharides as antiproliferative, antioxidant, and antidiabetic agents (Navarro-Alarcon and Cabrera-Vique, 2008; Liu et al., 2013).

AS101, an organotelluride compound, exerted a potent anti-inflammatory activity in animals, linked with its Te(IV) redox chemistry. It modulated the production of inflammatory cytokines and regulated iNOS transcription and expression in activated macrophages *via* targeting the NF-kB complex. It is suggested that Te(IV) derivatives can play a key role in thiol redox homeostasis in humans. This makes them an alternative approach for developing novel anti-inflammatory drugs (Brodsky et al., 2010).

2.4. Apoptosis induction

According to the currently accepted multi-step theory of carcinogenesis, cancer is a disease in which proper cell growth regulation and proliferation are aberrant. Cells may become malignant as they accumulate mutations in numerous genes that control cell proliferation and apoptosis. Through oncogene activation, malignant cells may become self-sufficient in growth signals. Oncogenes are genes encoding proteins that act as promoters of cell cycle progression, for example growth factors and their receptors (e.g., HER2), signal transduction proteins (e.g., RAS), transcription factors (e.g., MYC) or proteins that inhibit apoptosis (e.g., BCL-2) (Gacche and Assaraf, 2018; Sciarrillo et al., 2020; Shahar and Larisch, 2020; Nussinov et al., 2021; Pecoraro et al., 2021; Chen et al., 2022). By inactivating tumor suppressor genes, the cells may lose their ability to regulate the cell cycle (e.g. *RB*, *PTEN*), induce apoptosis or maintain their genetic stability (e.g. *BRCA1/BRCA2*) (Šimoničová et al., 2022). One of the most commonly mutated tumor suppressor gene in cancers is *p53* (Stiewe and Haran, 2018; Cao et al.,

2020), which maintains the genetic stability by activating DNA repair proteins, arresting the cell cycle, and initiating apoptosis, if the DNA damage is unrepairable (Croce, 2008).

As a result of these mutations, genomic instability and increased cell proliferation occurs, which give rise to malignant tumor expansion, consisting of heterogeneous cells that differ both in their morphology and functionality (e.g., proliferative and angiogenic potential, response to therapy) (Marusyk and Polyak, 2010). The cancer stem cell hypothesis assumes that there is a minority quiescent population in the tumorous tissue with self-renewal capabilities that maintain tumor growth and may differentiate into heterogeneous linages of cancer cells (Fulawka et al., 2014). Chemotherapy may kill the bulk of the tumor; however, tumor stem cells could survive and be responsible for relapse and drug resistance (Koren and Fuchs, 2016; Sharifzad et al., 2019; Erin et al., 2020) Therefore, targeting this subset of cells in tumors may be a better strategy to prevent relapse (Phi et al., 2018).

One of the most relevant properties of Se is its ability to induce apoptosis, which may explain the cancer-preventing effect of Se. The mechanism of Se-induced apoptosis is related to the chemical manifestations of Se and its metabolism, as well as the type of cancer. Thus certain Se compounds, such as SeO_2, play a role in the activation of caspase-3, whereas sodium selenite induces apoptosis in the absence of caspases. The regulation of mitochondrial function plays a role in the control of apoptosis and is also a target for Se compounds. Other apoptotic mechanisms are the regulation of the appearance of glutathione and ROS generation, which may serve as intracellular messengers in the regulation of signaling pathways or even in the regulation of kinases. There are some putative mechanisms that may explain the effect of Se on the cell cycle and apoptosis: it is well known that Se plays a critical role in these processes, but the mechanisms of action of Se are highly complex and not yet fully elucidated. These include the regulation of protein kinase signaling, the phosphorylation of p53, caspase activation, and the generation of ROS (Sanmartín et al., 2012).

The mitogen-activated protein kinases (MAPKs) are the family of kinases responsible for the transduction of signals from the cell membrane to the nucleus (Wada and Penninger, 2004; Nussinov et al., 2021). MAPKs are serine/threonine kinases contributing to the regulation of cell proliferation and apoptosis. In mammalian cells, at least four prototypical classes of MAPK cascades are present, such as the extracellular signal-related kinases (ERK1/2), Jun amino-terminal kinases (JNK1/2/3), p38-MAPK and ERK5 (Sun et al., 2015; Kholodenko and Birtwistle, 2009).

Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) is one of the signaling pathways that can influence cell cycle progression, cell proliferation and apoptosis (Shi et al., 2019). The PI3K/Akt and mammalian target of rapamycin (mTOR) signaling pathways are essential for tumor growth, and these pathways are often aberrantly regulated in most human cancers. Furthermore, these signaling pathways can contribute to the maintenance of cancer stem cells (CSCs), because the activation of the PI3K/Akt/mTOR signaling can result in an increased CSC phenotype (Sunayama et al., 2010).

This pathway has a role in cancer progression, hence targeting the PI3K/AKT signaling pathway is an attractive approach in medicinal chemistry. Akt controls cell survival by inhibiting pro-apoptotic signals (e.g., Bad, procaspase-9 and Forkhead box O (FOXO) transcription factors), which can lead to cell cycle progression. Furthermore, Akt prevents the liberation of cytochrome *c* from mitochondria, inhibiting the intrinsic pathway of apoptosis (Altomare and Testa, 2005; Nitulescu et al., 2018). Sodium selenite exerts its anticancer activity in colorectal cancer via the AKT/β-catenin pathway due to elevated ROS levels (Luo et al., 2012).

Se compounds can induce apoptosis, however the molecular targets vary based on the structure and metabolism of the derivatives and on the cell lines studied (Sanmartín et al., 2012). Isoselenocyanates caused a marked decrease in Akt3 signaling in cultured melanoma cells; however, high concentrations were needed for a therapeutic effect. A solution could be the development of potent analogs with an isothiocyanate backbone while increasing the alkyl chain length and replacing sulfur with Se (Nguyen et al., 2011). Phenylbutyl isoselenocyanate (ISC-4) acts as an Akt inhibitor in mice injected with wild-type HT-29 human colon cancer cells (Sharma et al., 2011). The treatment of PC-3 prostate cancer cells with 3,5-dimethoxyphenyl and 4-cyanophenyl methylseleno imidocarbamates inhibited Akt and ERK phosphorylation, resulting in inhibition of the PI3K and MAPK pathways (Plano et al., 2011). The quinoline imidoselenocarbamate EI201 arrested the Akt/mTOR pathway in PC-3, HT-29 and MCF-7 breast cancer cells *in vitro* (Ibáñez et al., 2012). Methylselenol triggered apoptotic events in a HT1080 human fibrosarcoma cell line and inhibited the extracellular-regulated kinase 1/2 (ERK1/2) signaling and cellular myelocytomatosis oncogene (c-Myc) expression (Zeng et al., 2009). Several Se compounds influenced members of MAPKs; for example, 2-[3-(4-methoxyphenyl)− 4-oxo-1,3-selenazolidin-2-ylidene]malononitrile demonstrated a strong superoxide anion-scavenging activity, triggered ERK1/2 phosphorylation and induced apoptosis in prostate cancer cells (Nishina et al., 2011).

Cyclin-dependent kinases (CDKs) are also attractive targets, as they can regulate the cell cycle and proliferation of tumor cells. Treatment with methylseleninic acid resulted in a G1 cell cycle arrest in association with the upregulation of cyclin-dependent kinase inhibitor (CDKI) proteins in prostate cancer cells (Wang et al., 2010).

Caspases are cysteine proteases whose principal function is the regulation of apoptosis (Koren and Fuchs, 2016; Shahar and Larisch, 2020). Their activation is regulated by both an extrinsic and intrinsic signaling pathway. The extrinsic pathway is based on the activation of Fas and tumor necrosis factor receptors (TNFRs), leading to the activation of caspase-8. The intrinsic pathway induces the mitochondrial release of cytochrome *c*, leading to the activation of caspase-9. Methylseleninic acid can target caspases by activating caspase-9 and caspase-8 in breast cancer cells (Li et al., 2008), whereas [2,5-bis (5-hydroxymethyl-2-selenienyl)− 3-hydroxymethyl-*N*-methylpyrrol] (D-501036) could activate caspases − 9 and − 3 in human cervical cancer cells (Shiah et al., 2007).

2.5. Autophagy modulation

Autophagy is an intracellular non-selective protein degradation process that has a vital role in basic protein turnover and in the removal of damaged organelles (Moretti et al., 2007; Jiang et al., 2021).

In cancer, autophagy has a dual role: as a tumor suppressor it inhibits tumor formation by maintaining cellular homeostasis and the integrity of organelles. However, in cancer cells, this activity can meet the high metabolic needs and protect against various stresses, thus promoting tumor growth and survival. Therefore, the application of autophagy inducers and inhibitors may be beneficial in cancer therapy (Yun and Lee, 2018). Various Se compounds can act both as inducers and inhibitors of autophagy. A novel orally available Se-purine small molecule, SLLN-15, was able to induce autophagy via blockade of the AKT-mTOR pathway, demonstrating anticancer activity in triple negative breast cancer models *in vitro* and in orthotopic models *in vivo* (Chang et al., 2019). A dihydroselenoquinazoline compound demonstrated the inhibitory activity of autophagy, contributing to apoptosis induction and to the sensitization of hormone therapy in MCF-7 breast cancer cells (Moreno et al., 2014).

Sodium selenite and its nano form demonstrated a cytotoxic effect in a dose-dependent manner, and were able to induce apoptosis in human colorectal cell lines HCT-119 and Caco2, and in human breast cancer cell lines MCF-7 and MDA-MB231; moreover the combination of nano-Se and nano-doxorubicin could overcome doxorubicin resistance in the drug-resistant cell lines (Abd-Rabou et al., 2020). The apoptosis-inducing and doxorubicin-sensitizing effect of Na-Se may be achieved as a result of autophagy inhibition and Plk3/Akt pathway modulation (Li et al., 2007; Ren et al., 2009).

2.6. MDR reversal: P-gp inhibition

The development of MDR constitutes a primary impediment to successful chemotherapy; MDR is one of the main attributes of cancer stem cells that is responsible for cancer progression and recurrence. For a long time, among various drug resistance mechanisms, efflux pumps belonging to the ATP-binding cassette (ABC) transporters were thought to be the most important contributors to MDR (Li et al., 2016; Zhitomirsky and Assaraf, 2016; Assaraf et al., 2019; Cho and Lim, 2020; Su et al., 2021; Wang et al., 2021). According to the tumor stem cell concept, cancer stem cells are naturally resistant to chemotherapy due to their capability to repair DNA, due to their quiescence and due to the intrinsic expression of ABC-transporters (Ferreira et al., 2016, Koren and Fuchs, 2016; Likus et al., 2016; Sharifzad et al., 2019). Thus targeting the MDR transporters may be important in combating cancer and in the prevention of relapses (Dean et al., 2005).

The most extensively characterized MDR transporters include P-glycoprotein (also known as ABCB1 or P-gp), multidrug-resistant protein 1 (also known as ABCC1 or MRP1) and breast cancer resistance protein (also known as ABCG2 or BCRP) (Fletcher et al., 2010). Previously, this mode of resistance was treated with a combination of several chemotherapeutics, which however significantly increased their toxicity (Cao et al., 2004). Currently, the approach is to search for efflux pump inhibitors that act in a synergistic mode with chemotherapeutic agents. To date, competitive inhibitors competing with a chemotherapeutic for an efflux pump binding site, non-competitive inhibitors (both allosteric or ATPase domain inhibitors), and efflux pump expression inhibitors have been described (Fig. 2). Moreover, as discussed below, the overall oxidation state of the cell and the number of reactive oxygen species (ROS) play an important role in the expression of transmembrane efflux pumps as well as in the total amount of ATP available for transport (Pelicano et al., 2004; Cui et al., 2018). Since the transmembrane extrusion of chemotherapeutics is energy dependent, it offers another approach to inhibiting this process by searching for inhibitors of nutrient-importing transporters (Rask-Andersen et al., 2013). Such transporters belong to the solute carrier transporters (SLC) family, which are responsible for the uptake of nutrients including glucose. Such SLC transporter inhibitors induce cell starvation and block energy-dependent processes such as chemotherapeutic drug expulsion (Li and Shu, 2014). Both organic and inorganic Se compounds are found across all types of possible MDR inhibitors.

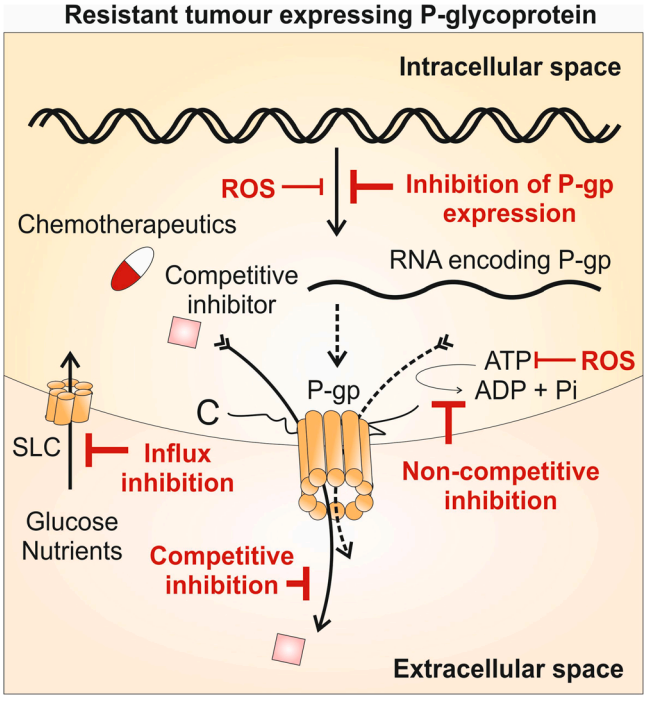


Fig. 2. The mechanism of transmembrane efflux pump (e.g. P-glycoprotein) inhibition: i) competitive inhibitor (e.g. verapamil) competes with a chemotherapeutic drug for an efflux pump binding capacity, ii) non-competitive inhibitors, allosterically bind to the active site of a pump and prevent chemotherapeutic drug binding or inhibit the ATPase activity, iii) inhibitors modulate the expression of transmembrane efflux pumps, iv) inhibitors downregulate the expression of solute carriers transporters (SLC) leading to nutrient deprivation in the tumor cell, v) reactive oxygen species (ROS) downregulate the expression of efflux pumps or reduce the total amount of ATP available for ATP-driven drug efflux.

Previously, Chakraborty et al., reported on the synergistic effect of combining diphenyl methyl selenocyanate and cisplatin, which generated ROS and modulated the antioxidant and detoxifying enzyme system in murine tumor cells, resulting in significant DNA damage and apoptosis (Chakraborty et al., 2015). It is well known that ROS contribute to cell killing as well as to the downregulation of P-gp (Cai et al., 2007). ROS oxidize NADH into NAD^+ and reduce the amount of ATP available for the transport mediated via efflux pumps (Wang et al., 2018a). Induction of apoptosis was also observed when SeNPs and irinotecan were combined for the treatment of colorectal cancer cells. Irinotecan is a chemotherapeutic agent that inhibits topoisomerase I, resulting in S-phase-specific cell killing (Gao et al., 2014). One of the main mechanisms by which cells acquire resistance to irinotecan is its export by efflux pumps, namely P-gp and MRP1 (Xu and Villalona-Calero, 2002). Both 5-methylselenocysteine and seleno-L-methionine significantly increased the cure rate of athymic nude mice bearing human squamous cell carcinoma of the head and neck and colon carcinoma resistant to irinotecan (Cao et al., 2004). 5-methylselenocysteine in combination with irinotecan demonstrated higher cure rates than the combination of iritecan with 5-fluorouracil. Other synergistic effects of Se compounds and chemotherapeutics have been demonstrated, e.g., by the combined application of selenite and imatinib (Abdel-Aziz et al., 2015), sodium selenite and cisplatin (Ohkawa et al., 1988), selenocystine and doxorubicin (Fan et al., 2014a), or selenocysteine and auranofin (Fan et al., 2014b). In all cases, apoptosis was induced by ROS. Apoptosis was associated with increased p53 mitogen-activated kinase phosphorylation, protein kinase B (Akt) dephosphorylation and poly(ADP-ribose) polymerase (PARP) cleavage (Cao et al., 2004). Selenomethionine was also demonstrated to inhibit the expression of P-gp in several renal cell carcinomas (Lai et al., 1993).

In addition to the indirect mechanism affecting efflux pump expression by ROS generation, numerous Se compounds are able to directly inhibit efflux pump activity. Depending on the chemical variation at the alkyl chain directly bound to the Se atom, selenoanhydrides and selenoesters exhibited P-gp efflux pump inhibition simultaneously with cytotoxic and pro-apoptotic effects in MDR mouse T-lymphoma cells and also in an MDR human colon adenocarcinoma cell line (Domínguez-Álvarez et al., 2016; Gajdács et al., 2017). The great advantage of these compounds is that they are not toxic themselves. While the effective concentration (IC_{50}) is usually at nanomolar range, the lethal concentration (LD_{50}) is at micromolar concentrations. The therapeutic window is therefore sufficiently wide, and the side effects of incorrect dosing are negligible. In addition, the non-toxic substances do not trigger the development of drug resistance. Verapamil, a calcium channel blocker, inhibits P-gp in a competitive manner; however, some Se compounds exhibit more pronounced activity than this known inhibitor. Phthalic selenoanhydride inhibited P-gp 3.6- and 4.3-fold more effectively than verapamil at the same concentration in MDR T-lymphoma (Domínguez-Álvarez et al., 2016) and colon adenocarcinoma cells (Gajdács et al., 2017), respectively. Methylketone selenoester, applied at a 10-fold lower concentration than verapamil, inhibited P-gp 3.4- and 4-fold more effectively than verapamil in MDR T-lymphoma and colon adenocarcinoma cells, respectively. The *tert*-butyl ketone selenoesters were less active than methyl ketone, but still 1.7–2.3-fold more active than verapamil at the same concentration. All the

above-mentioned compounds also significantly induced apoptosis in tested cells. In addition, methylketone selenoester with a 4-chlorophenyl moiety, methyl selenoester with a 3-$COSeCH_3$ moiety and methylketone selenoester with a 3,5-dimethoxyphenyl moiety have significant collateral sensitivity, with selectivity indexes equal to 10.0, 8.0 and 3.4, respectively (Domínguez-Álvarez et al., 2016; Gajdács et al., 2017). Collateral sensitivity is an alternative strategy for the clinical resolution of MDR, corresponding to the ability of compounds to kill MDR cells selectively over the parental cells from which they were derived (Pluchino et al., 2012). These compounds also have anticancer activity with therapeutic indices (ratio of IC_{50} for fibroblasts and IC_{50} for colon adenocarcinoma cells) equal to 9.7, 2.3 and 14.4, respectively. All the abovementioned compounds also significantly induced apoptosis (Gajdács et al., 2017). These selenocompounds also had a synergistic effect with doxorubicin on breast cancer cells overproducing P-gp (Csonka et al., 2019). Another study by Szemerédi et al., was focused on the derivatization of oxoselenoesters, resulting in sets of ketone-containing and cyano-containing selenocompounds (Szemerédi et al., 2021). Ketone-selenoesters were potent P-gp inhibitors that modulate its ATPase activity and induce apoptosis, 3-trifluoromethyl and 3-chloro-4-fluoro derivatives enhanced the activity of doxorubicin in a synergistic manner (Szemerédi et al., 2021).

Similarly, phenylselenoether-hydantoin hybrids were significantly more effective than the reference inhibitor verapamil (up to 2.6-fold at a 10-fold lower concentration) in human P-gp gene-transfected mouse lymphoma cells, upregulating p53 upon treatment in combination with doxorubicin (Ali et al., 2020). Pyrimidineselones also exhibited higher efflux pump inhibitory activity than verapamil (Żesławska et al., 2018).

Selenoflavones were also reported to possess potent efflux pump inhibitory activity in drug-resistant human colon adenocarcinoma cell lines without cytotoxicity, as well as having antimicrobial effects (Marć et al., 2020). Neither selenoflavone nor its bioisosteric analog exhibited cytotoxicity or antiproliferative activity against human embryonal lung fibroblasts up to a 100 μM concentration. However, both compounds inhibited P-gp in MDR colon adenocarcinoma cells, the analog even 1.4-fold more efficiently than verapamil at the same concentrations (Marć et al., 2020). Another heterocyclic Se compound demonstrating the ability to modulate MDR was a seleno-analog of tetramethylrosamine, a cationic rhodamine dye. Its incubation at 10 μM concentration with MDR Chinese hamster ovary cells doubled the intracellular accumulation of calcein AM when exposed to light (Gibson et al., 2004). The derivatization of selenorhodamine with thioamides even increased its photodynamic therapy (PDT) efficiency in combination with doxorubicin in colon adenocarcinoma cells (Hill et al., 2014). A pentacyclic Se-analog of tetramethylrosamine was an effective photosensitizer against MDR Chinese hamster ovary cells *in vitro* at 100 nM, completely blocking the ATPase activity of P-gp (Holt et al., 2006).

Three selenides containing a hydantoin moiety were potent inhibitors of P-gp efflux according to rhodamine assay, exhibiting higher activity than the reference verapamil at a 10-fold lower concentration. In addition, they demonstrated potent cytotoxic activity against L5178Y (a mouse T-lymphoma cell line) and its MDR subline, with low micromolar or submicromolar IC_{50} values in both cell lines (Ali et al., 2020).

Se also increased the effectiveness of antibody therapies. Trastuzumab (Herceptin) is a monoclonal antibody used for the treatment of HER2 (human epidermal growth factor receptor 2) positive breast cancer together with taxanes. However, patients often develop resistance to this treatment. Bapat et al., linked the redox selenide to the antibody, and through this conjugation increased the cytotoxicity of the antibody to resistant breast carcinoma JIMT-1 cells in a dose- and time-dependent manner (Bapat et al., 2021). This approach is an interesting option for delivering the Se and targeting it to breast tumors. Similarly, cadmium-telluride quantum dots demonstrated a synergistic effect with the flavonoid wogonin on the induction of apoptosis in drug-resistant human leukemia cells (Huang et al., 2016) and with daunorubicin in MDR hepatocellular carcinoma cells (Zhang et al., 2011).

Enantiomers of the Se hexapeptide inhibitor QZ59 were also used to understand the polyspecificity of the substrate-binding site of P-gp in 2014. The SSS enantiomer proved to be a competitive inhibitor of P-gp, in contrast to the RRR enantiomer, which acted as a non-competitive inhibitor (Martínez et al., 2014).

In addition, cisplatin can induce the expression of programmed death-ligand (PD-L1). This protein is expressed in immune and cancer cells to escape the activity of activated T-cells, hence the induction of its expression leads to resistance towards cisplatin. However, the addition of methylseleninic acid attenuates this expression, overcoming this PD-L1 resistance, which can have applications in the treatment of prostate and lung cancer (Hu et al., 2021a). Certain resistant cancers increase the expression of β-catenin, which is an oncogenic protein that promotes cell growth. A previous study (Saifo et al., 2010) revealed that methylseleninic acid inhibited the expression of this oncogenic protein in six human cancer cell lines, reversing this drug resistance and enabling the sensitization of these cell lines towards chemotherapeutic drugs such as docetaxel, paclitaxel, oxaliplatin, 5-fluorouracil and topotecan (Saifo et al., 2010).

2.7. Antimetastasis

Distant metastases are still the main cause of disease progression and death in cancer patients.The migration and invasion of the Epithelial-Mesenchymal Transition (EMT) is an important step in cancer (Sabbah et al., 2008; Erin et al., 2020). In the EMT process, malignant cells lose their apical-basal polarity and adherence junctions, acquire a mesenchymal phenotype and gain motility. Various extracellular signals contribute to this event, such as TGF-β secreted by tumor cells and fibroblasts, inflammatory cytokines (TNF-α, IL-6), HIF-1α and extracellular matrix (ECM) stiffness (Yeung and Yang, 2017). Several factors promote the survival and metastasis of disseminated tumor cells (DTCs). First, the detached cancer cells must evade apoptosis, resulting from the loss of cell matrix interaction (Douma et al., 2004). Then the DTCs must be able to infiltrate the tissue and reach the vasculature, which necessitates ECM remodeling and the formation of new blood vessels. This is promoted by matrix metalloproteases (MMPS), cytokines and growth factors, e.g. interleukins (ILs), tumor necrosis factor α (TNF-α), and vascular endothelial growth factor (VEGF) (Gupta et al., 2007; Kessenbrock et al., 2010). To survive the shear stress and immune clearance in the circulation system, circulating tumor cells form clusters with each other as well as with platelets and immunosuppressive immune cells (Wang et al., 2018b). Furthermore, various intracellular processes and pathways promote the survival of DTCs, such as the Akt and folate pathways, and by inducing reversible metabolic changes the tumor cells can avoid oxidative stress (Assaraf, 2006; Douma et al., 2004; Gonen and Assaraf, 2012; Assaraf et al., 2014; Raz et al., 2014; Piskounova et al., 2015; Raz et al., 2016). Colonization depends on the distant organ, to successfully proliferate in the distant organ, the tumor cells need to receive the appropriate signals, form new vessels, and evade immune surveillance, otherwise they may undergo growth arrest or dormancy (Steeg, 2006).

The redox balance also has an important role in metastasis formation; sublethal levels of ROS promote metastasis, while high levels of ROS suppress metastasis (Pelicano et al., 2004; Nishikawa, 2008; Cui et al., 2018). Se-compounds may be potent inhibitors of the metastatic process, presumably through their redox-active properties. Multiple Se-compounds, such as selenite, selenomethionine (SeMet), Se-methyl-selenocysteine (MSC), methylselenic acid (MSA), and methylselenocyanate (MeCN) demonstrated antimetastatic and anti-migratory effects in various *in vitro* and *in vivo* models. The antimetastatic effect of these compounds are attributed to the modulation of MMPs, IL-18, HIF-1α and VEGF signaling (Chen et al., 2013). Combining Se with additional compounds could enhance the selectivity and antitumor effect, while decreasing the toxicity of Se. For example, the combination of Se with the anticancer and anti-inflammatory

lentinan polysaccharide could demonstrate EMT, migration and invasion inhibition, while reducing the accumulation of Se in the liver and kidneys, thus decreasing the toxicity of Se. In the metastatic process, the cancerous cells' biomechanical properties change, they become more elastic in order to pass through the basement membrane. SeNPs, besides offering a tumor-selective delivery, have proven to be able to increase cell stiffness in human ovarian cancer cell lines, therefore lowering the metastatic potential of malignant cells (Toubhans et al., 2020).

The Wnt/ β-catenin pathway has been linked with EMT, tumor progression, cancer stem cells, metastasis and chemoresistance, therefore targeting this pathway may be vital for successful chemotherapy (Cui et al., 2012; DiMeo et al., 2009; Jiang et al., 2007). Sodium selenite could also activate JNK 1 and suppress β-catenin and its downstream mediators (Cyclin D1, CDK4, c-myc) both *in vitro* and *in vivo*, resulting in increased apoptosis of cancer cells and inhibition of intestinal carcinogenesis (Fang et al., 2010).

Very late antigen 4 (VLA-4) integrin has a vital role in the interaction between cells and the microenvironment. VLA-4 is considered to be a major player in the cellular immune response, embryogenesis and angiogenesis; however, it is also expressed by leukemic cells and some solid tumors, in the cancerous tissue VLA-4 contributes to several steps of tumor progression and metastasis. Furthermore, it is also involved in the cell adhesion-mediated drug resistance (Schlesinger and Bendas, 2015). Integrins are principal targets of Te compounds; organotelluranes exhibited antimetastatic effects both *in vitro* and *in vivo* murine melanoma models due to integrin inhibition (Silberman et al., 2016). Furthermore, the interaction between leukemic-cell VLA-4 and stromal fibronectin contributes to relapse after chemotherapy in some hematologic malignancies, because it delivers anti-apoptotic and proliferative signals to malignant cells and gives rise to drug resistance (Matsunaga et al., 2003). AS101 [ammonium trichloro (dioxoethylene-*O*,*O*') tellurate] is an organotellurium compound with immunomodulator activity and is being used in Phase II clinical trials with various potential clinical applications (Halpert and Sredni, 2014). AS101 is also a promising agent in the reversal of VLA-4-mediated drug resistance in acute myelogenous leukemia (AML), in a mouse xenograft of patient-derived AML cells with high VLA-4 activity, it demonstrated a chemosensitizing activity and was able to prolong the survival of mice receiving chemotherapy (Layani-Bazar et al., 2014). SAS ([octa-O-bis-(R,R)tartarate ditellurane]), another Te compound with immunomodulatory activity, exhibited promising effects in human multiple myeloma (MM) cell lines, SAS was capable of resensitizing myeloma cell lines by blocking the interaction between MM cells and fibronectin and inhibiting the expression of pAKT induced by stromal cells (Zigman-Hoffman et al., 2021).

2.8. Tumor selectivity

The main drawback of conventional chemotherapy is the lack of selective action on cancer cells; the cytotoxic effect on other rapidly dividing cells leads to undesired side effects such as myelosuppression, mucositis, alopecia, and organ dysfunction, resulting in the dose reduction, delay or discontinuation of chemotherapy. Another problem is the poor bio-accessibility of chemotherapeutic agents to the tumor, especially at the site of the hypoxic core, thus requiring a higher dose and resulting in the development of MDR. NPs may overcome these obstacles, as they can target cancer cells actively or passively (Shapira et al., 2011; Livney and Assaraf, 2013; Bar-Zeev et al., 2017; Engelberg et al., 2019; Lepeltier et al., 2020; Cohen et al., 2021; Engelberg et al., 2021; Su et al., 2021). Active targeting is achieved through modifying the surface of NPs, the selective uptake occurs as a consequence of ligand-receptor interaction or antibody-antigen recognition, such ligands include folic acid, transferrin and luteinizing-hormone releasing hormone. The passive targeting is based on the size of the NPs and on the unique properties of tumor microvasculature. Tumors have poorly defined lymphatic networks and leaky capillaries, therefore NPs that are designed to pass through the endothelial pores could accumulate selectively in the tumor interstitium. Another approach is making use of the acidic extracellular environment as a consequence of increased anaerobic metabolism in tumors. NPs can be designed to possess pH-sensitive drug-releasing abilities, hence providing a promising alternative to cancer drug delivery systems (Sutradhar and Amin, 2014).

Se-compounds demonstrated potent anticancer effects through ROS overproduction, inducing apoptosis or necrosis in various cancer cells when combined with other bioactive nanocarriers or NPs (Menon et al., 2018). β-Lactoglobulin, the most abundant whey protein in cow's milk, is often used as a bioactive carrier. Combining β-lactoglobulin with Se proved to be effective as an anticancer strategy in various cell lines *in vitro*. Se-β-lactoglobulin could influence the redox state of cells and induced apoptosis and autophagy, while sparing non-cancerous cells (Xu et al., 2019a; Yu et al., 2018; Zhao et al., 2018). Hydroxyapatite NPs doped with Se and loaded with an antitumor platinum complex were able to selectively inhibit the proliferation of PC3 prostate cancer cells and MDA-MB-231 breast cancer cells in co-culture with human bone marrow stem cells (Barbanente et al., 2020). It has also been demonstrated that folic acid (FA)-conjugated selenium nanoparticles (SeNPs) can be used as a cancer-targeting nano-drug delivery system for ruthenium polypyridyl (RuPOP) in cancer cells. FA-SeNPs sensitized MDR liver cancer cells by inhibiting ABC efflux transporters and by inducing apoptosis (Liu et al., 2015).

2.9. Adjuvant

The combination of cancer treatments – such as surgery, radiation, and chemotherapy, also known as multimodal treatment, is the best approach for some cancers, as it allows for an enhanced treatment efficacy with less untoward toxicity to healthy tissues and organs. Combination chemotherapy is considered to be superior to monotherapy in the treatment of many forms of cancer. The combination of antineoplastic agents with different mechanisms of action can reduce the risk of developing MDR. In addition, it permits drug dose optimization, thus reducing the appearance of intolerable side effects (Bayat Mokhtari et al.,2017).

Photothermal therapy (PTT) is a cancer treatment that can lead to the elimination of cancer cells by heat generated in tumor tissue exposed to near-infrared (NIR) light (Nomura et al., 2020). After PTT, tumor cells may be more responsive to radiation and chemotherapy. In preclinical models, the combination of Se-coated Te nanomaterials and PTT was effective on lung cancer and hepatocellular carcinoma (Chen et al., 2020).

SeNPs may increase the efficacy of irradiation, as was shown using *in vitro* MCF-7 breast cancer cells. Se-NPs acted synergistically with irradiation due to cell cycle arrest, the induction of autophagy and production of ROS (Chen et al., 2018). In addition, the PEG-SeNP nanosystem has proved to be a potent radiosensitizer when combined with X-rays, inducing apoptosis and enhancing ROS production in HeLa cervical cancer cells *in vitro* (Menon et al., 2018).

As for combination chemotherapy, *in vitro* effective Se compounds (one selenoanhydride and some selenoesters) were applied together with conventional chemotherapeutic drugs. Synergism was mostly observed for vincristine and doxorubicin, while some derivatives exhibited different levels of synergistic interactions with cyclophosphamide, methotrexate, topotecan and 5-fluorouracil in MDR mouse lymphoma cells (Spengler et al., 2019). Some selenocompounds produced a synergistic interaction with phenothiazines (promethazine, chlorpromazine and thioridazine) in MDR mouse lymphoma cells, indicating out that resistance modifiers could be applied in combination because of their adjuvant activities. Drugs with well-known pharmacological and toxicity profiles could be used in new indications according to the drug repositioning approach (Gajdács et al., 2020).

When used in combination with different anticancer agents against resistant malignant mesothelioma cell lines, sodium selenite enhanced

the cytotoxicity of these drugs, circumventing the resistance of these cell lines to taxol and doxorubicin. The highest enhancement was observed for the combination of selenite and bortezomib. Selenite also significantly promoted the activity of doxorubicin, gemcitabine, pemetrexed, and carboplatin (Szulkin et al., 2013). Selenite has also been used in combination assays *in vivo* with cisplatin, with the aim of avoiding the development of cisplatin resistance. It was observed that the combination with cisplatin enhanced the tumor growth inhibition compared to the one caused by cisplatin alone. Selenite alone or the combination of cisplatin with sodium sulfite did not enhance tumor growth inhibition. After two weeks, cisplatin administered alone started to lose its ability to inhibit tumor growth, but the co-administration with selenite prolonged the inhibitory effect, and thus the effectiveness of the treatment (Caffrey and Frenkel, 2012).

Selenomethionine, combined with doxorubicin and with different metals (Mn, Mg, Fe, Co, Ni), enhanced the cytotoxic activity of doxorubicin in a bacterial model that mimics the conditions of cancer cells. Additionally, when doxorubicin was administered in combination with the aforesaid metals, selenomethionine and ascorbic acid, the anticancer effect was strongly enhanced, and the cell growth was reduced to values very close to zero. Nevertheless, the growth inhibition observed with doxorubicin, the metals and ascorbic acid was higher than the one observed for selenomethionine alone (Matejczyk et al., 2018).

Many tumors developed resistance to the promising anticancer drug candidate ABT-737, developed by Abbott Laboratories. ABT-737 is a small-molecule drug which acts via the inhibition of Bcl-2 and Bcl-xL and induces apoptosis. To overcome such resistance, methylseleninic acid was administered in combination with ABT-737 in cytotoxicity assays in MDA-MB-231, HT-29 and DU145 cell lines. The selenocompound was able to sensitize these cells to ABT-737, restoring its anticancer activity against these aggressive cancer cell lines that developed resistance to it (Yin et al., 2012).

3. Chemistry of seleno-compounds and nanoparticles with applications in Cancer MDR

The biological properties of the Se compounds described above are a consequence of the exclusive chemical properties of this element, which are amazingly well exploited by the cells to control cellular redox homeostasis. For example, a hydrogen bound to Se is more acidic than when it is bound to sulfur (Reich and Hondal, 2016). This implies that at physiological pH the selenocysteine is ionized, whereas cysteine, the sulfur isostere of this selenoamino acid, is not. This fact is critical: exposing a charged atom such as Se with such readiness to react (relative to sulfur, it has higher nucleophilicity, higher electrophilicity, retains part of the hypervalency capacity and has a better leaving group ability) makes it highly reactive: it can readily react with the cellular thiols, altering the cellular thiolstat. These chemical properties, which lie beyond the scope of this review, were revised in more depth by Reich and Hondal, 2016. In this section, the synthesis and the preparative methods will be discussed for the relevant selenocompounds and SeNPs with noteworthy applications in the reversal of cancer MDR, according to a bibliographic search performed in Pubmed and focused on seleno-compounds with applications against MDR and reported this century. Compounds will be reviewed following a logical chemical order. Table 1 summarizes the applications against MDR of small-molecules containing Se in their structures, the chemistry of which is reviewed in this section.

3.1. Naturally occurring selenocompounds

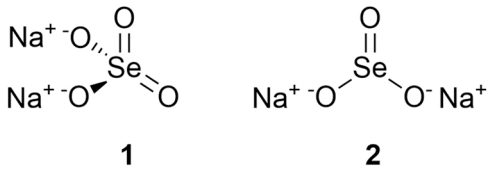
3.1.1. Selenate and selenite

Selenate, mainly in the form of sodium selenate (**1**, Na_2SeO_4, Scheme 1); and selenite, generally in the form of sodium selenite (**2**, Na_2SeO_3), are perhaps the most widespread forms in which Se can be found in nature (Pyrzyńska, 1998). These two Se-containing salts are the most important natural sources among inorganic compounds: the selenoamino acids selenomethionine and selenocysteine being the most relevant of the organic compounds. As a result, selenite and selenate can be found in various food sources, such as bread, cereals, fish, fruit, and vegetables (Fairweather-Tait et al., 2011).

Table 1
Selenium containing small-molecules and their anticancer activity.

	Activity	Ref.
Selenocompounds present in nature		
Selenate and Selenite	Chemosensitization	[1–5]
Selenomethionine	Chemosensitization	[6]
	ROS generation and apoptosis induction	[7]
Selenocysteine and its derivatives	Chemoprevention	[8]
	Apoptosis induction	[9]
	Chemosensitization	[10]
Selenides and diselenides		
Rhenium (I) diseleno-ether	Antitumor cytotoxicity	[11–14]
	Reduction of ROS, VEGF-A, TFG-β1, IGF-1	[15]
Hydantoinylalkyl phenyl selenides	Efflux pump inhibition and cytotoxicity	[16]
Selenocarbonyl compounds		
Methylseleninic acid	Chemosensitization	[17–19]
Quinoxaline bis (isoselenourea)	Apoptosis induction	[20]
Pyrimidineselones (exocyclic selenoureas)	Efflux pump inhibition and cytotoxicity	[21]
Selenoesters	Efflux pump inhibition and cytotoxicity	[22–24]
Selol	Efflux pump inhibition and cytotoxicity	[25]
Heterocycles containing selenium		
Phthalic selenoanhydride	Efflux pump inhibition and cytotoxicity	[26–28]
	Synergism with anticancer drugs	[29,30]
Ethaselen	Synergism with anticancer drugs	[31–34]
	Radiosensitization	[35]
Selenoflavones	Efflux pump inhibition and cytotoxicity	[36]
	Reduction of ROS and cytotoxicity	[37]
Iridium complexes containing a selenadiazole ligand	Chemosensitization, ROS production and apoptosis induction	[38]
Selenorhodamines	Photosensensitization, synergism with doxorubicin	[39]
Selenobarbituric acids	Anticancer cytotoxicity	[40]

References: [1] Choi et al., 2015; [2] Bao et al., 2015; [3] Szulkin et al., 2013; [4] Caffrey and Frenkel, 2012; [5] Björkhem-Bergman et al., 2002; [6] Matejczyk et al., 2018; [7] Virani et al., 2018; [8] Poluboyarinov et al. 2020; [9] Kang et al., 2014; [10] Björkhem-Bergman et al., 2002; [11] Kermagoret et al., 2011; [12] Collery et al., 2014; [13] Collery et al., 2015; [14] Collery et al., 2016; [15] Collery et al., 2019; [16] Ali et al., 2020; [17] Hu et al., 2021a; [18] Saifo et al., 2010; [19] Yin et al., 2012; [20] Alcolea et al., 2019; [21] Żesławska et al., 2018; [22] Domínguez-Álvarez et al., 2016; [23] Gajdács et al., 2017; [24] Csonka et al., 2019; [25] Suchocki et al., 2007; [26] Domínguez-Álvarez et al., 2016; [27] Gajdács et al., 2017; [28] Csonka et al., 2019; [29] Spengler et al., 2019; [30] Gajdács et al., 2020; [31] Zhang et al., 2021; [32] Zheng et al., 2016; [33] Ye et al., 2017; [34] Fu et al., 2011; [35] Wang et al., 2011; [36] Marć et al., 2020; [37] Martins et al., 2015; [38] Huang et al., 2020; [39] Hill et al., 2014; [40] Daziano et al., 2012.



Scheme 1. Selenium inorganic salts: Sodium selenate (1) and sodium selenite (2).

3.1.2. Selenomethionine

The selenoamino acid selenomethionine (**3**, SeMet, Scheme 2) is a natural component of our cells, and it is the predominant form of Se in the diet. Its role in human health is to act as a reservoir of Se due to its random incorporation into proteins instead of methionine (Burk and Hill, 2015).

A cutting-edge anticancer proof-of-concept approach was obtained in studies by Virani et al., 2018 using SeMet. These researchers treated mice with a plasmid encoding for a mutated cystathionine gamma-lyase (CTH), together with other oncogenes and cancer suppressors. The wild CTH did not recognize SeMet, but this mutated enzyme was able to catalyze its conversion to methylselenol, which is cytotoxic, as it generates high intracellular concentrations of ROS that can trigger the apoptotic cascade. Hence this plasmid, together with SeMet administration, could be used as an enzyme prodrug strategy (Virani et al., 2018).

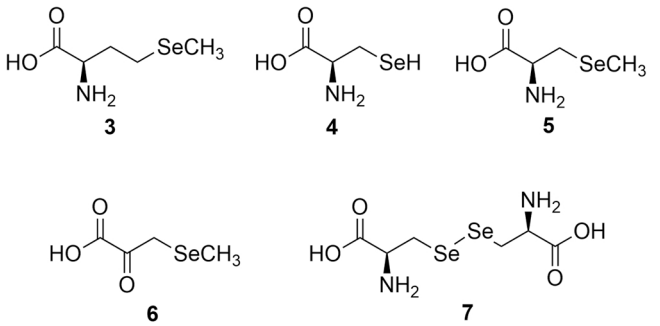
3.1.3. Selenocysteine and its derivatives

Selenocysteine (**4**, Scheme 2) is the second naturally occurring selenoamino acid, and it is very relevant for human health, as it is the key constituent of the selenoproteins, which are crucial for biological processes in the removal of free radicals, the formation or thyroid hormones and the regeneration of the cofactor thioredoxin (Fairweather-Tait et al., 2011; Rayman, 2012). Selenocysteine can be methylated to methylselenocysteine (MSC, **5**) by the action of methyltransferases (Urbančič et al., 2019), and later the MSC can be converted into methylselenopyruvate (MSP, **6**) by the action of transaminases or aminotransferases, such as for example the glutamine transaminase K (Lee et al., 2009). MSP is a mimic of butyrate, an inhibitor of histone deacetylase (HDAC), an enzyme whose inhibition could be a promising target in cancer research (Lee et al., 2009). Besides this, MSP is able to trigger Bcl-2-modifying factor (BMF)-mediated apoptosis in a pathway independent of p21 induction, circumventing the apoptosis suppression that is typical in resistant cancers (Kang et al., 2014). Selenocysteine can also be found naturally in the form of selenocystine (**7**), which consists of two selenocysteine amino acids bound via a diselenide bond. This selenocystine amino acid exhibits substantial anticancer and chemopreventive activities (Poluboyarinov et al. 2020).

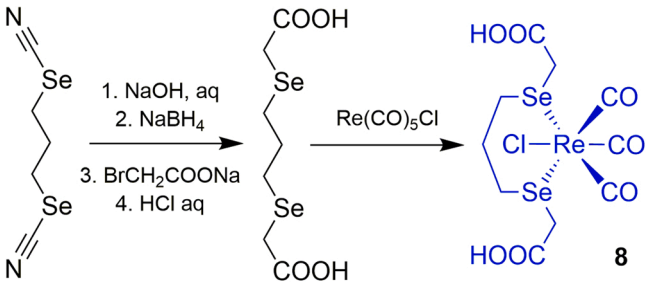
3.2. Selenides and diselenides

3.2.1. Rhenium (I) diseleno-ether

A rhenium (I) diseleno-ether (**8**, Scheme 3) has been extensively studied as an anticancer agent (Kermagoret et al., 2011; Collery et al., 2015, 2014, 2016, 2019). The synthesis of this Re-Se complex starts from propylene diselenocyanate (previously obtained by the treatment of Se with KCN in acetone, and subsequent substitution of the former selenocyanate ions over 1,3-dibromopropane), which is converted into the final rhenium (I) diselenoether complex through the reactions



Scheme 2. Selenoamino acids and derivatives. Selenomethionine (SeMet) (3), selenocysteine (4), methylselenocysteine (5), methylselenopyruvate (6) and selenocystine (7).



Scheme 3. Synthesis of Rhenium (I) diseleno-ether (**8**).

indicated in Scheme 3 (Kermagoret et al., 2011).

3.2.2. Hydantoinylalkyl phenyl selenides

The synthesis of three selenide derivatives (**9–11**, Scheme 4), with inhibitory activity of the P-gp efflux pump, which contains a hydantoin moiety in its structure, was quite straightforward and is shown in Scheme 4. Briefly, diphenyl diselenide was dissolved in a 1:1 water:THF mixture, and reduced with sodium borohydride. Then, the appropriate hydantoin derivative was added, dissolved in DCM, and the mixture was stirred for 24–48 until the substitution was complete (Ali et al., 2020).

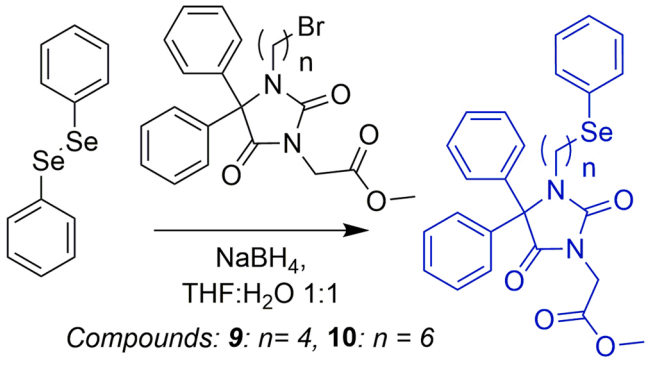
3.3. Selenocarbonyl compounds

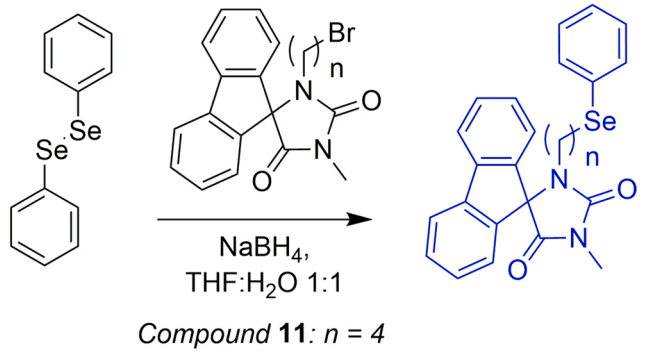
3.3.1. Methylseleninic acid

Methylseleninic acid (**12**, Scheme 5) is directly obtained from dimethylselenide (Scheme 5). The diselenide is dissolved in dichloromethane, cooled to 0ºC, and the hydrogen peroxide is added dropwise. The reagent oxidizes the diselenide, to form the desired methylseleninic acid (Kloc et al., 1989).

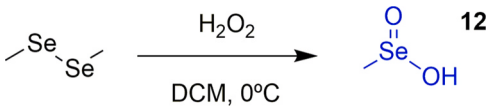
3.3.2. Quinoxaline bis(isoselenourea)

The quinoxaline bis(isoselenourea) (**13**, Scheme 6) has been reported

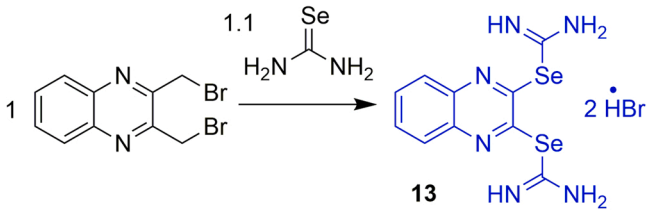




Scheme 4. Synthesis of hydantoinylalkyl phenyl selenides **9–11**.



Scheme 5. Synthesis of methylseleninic acid (**12**).



Scheme 6. Synthesis of the quinoxaline bis(isoselenourea), **13**.

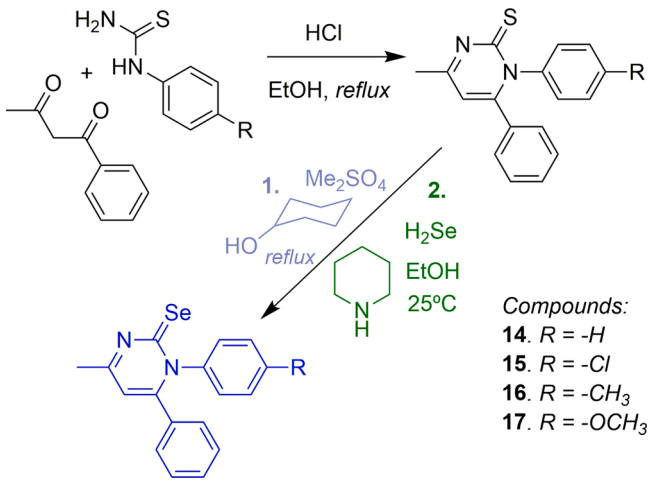
to be an effective compound against drug-resistant melanoma cells (Alcolea et al., 2019). To synthesize this compound, 2,3-bis(bromomethyl)quinoxaline was mixed with selenourea in the molar ratio 1:1.1 (Scheme 6), and the mixture was stirred for 2 h at room temperature until the precipitation of the desired compound (Alcolea et al., 2016).

3.3.3. *Pyrimidineselones (exocyclic selenoureas)*

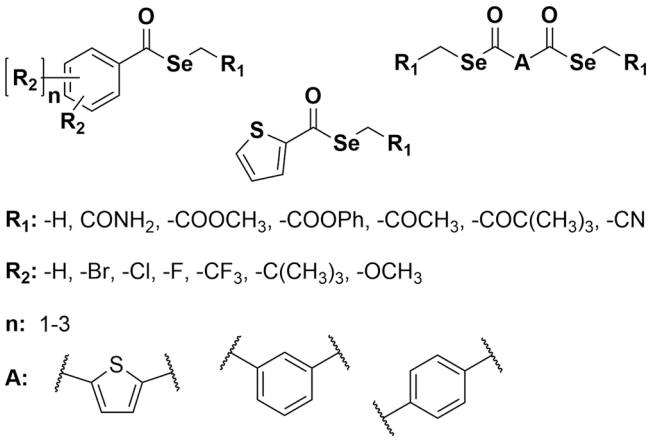
The cytotoxic and P-gp inhibitory activity of a series of 8 pyrimidineselones (the selenium isosteres of pyrimidone) and the sulfur isosteres of these Se-compounds have been reported (Żesławska et al., 2018). The four most active pyrimidineselones or pyrimidineselenones (**14–17**) were obtained by following a 3-step synthetic procedure, shown in Scheme 7 (Żylewska et al., 2003).

3.3.4. *Selenoesters*

Various series of selenoesters have been reported so far with activity against cancer and MDR cancer cells. Initially, 10 selenoesters were reported in several studies that evaluated different aspects related to their ability to reverse MDR tumor cell lines, via efflux pump inhibition (Domínguez-Álvarez et al., 2016; Gajdács et al., 2017; Csonka et al., 2019) or in combination with chemotherapy drugs (Spengler et al., 2019; Gajdács et al., 2020). Additionally, they also exhibit efflux pump inhibitory activity against antibiotic-resistant bacteria (Mosolygó et al., 2019). A second series has reported 15 additional selenoester derivatives (Szemerédi et al., 2021). These 25 compounds can be described with the formulas included in Scheme 8, in which R_2 can denote, in certain cases, different substituents on the same compound.



Scheme 7. Synthesis of pyrimidineselones **14–17**.



Scheme 8. Selenoesters with significant MDR-reversing activity.

The synthesis of these selenoesters follows a synthetic pathway developed in aqueous media that involves 3 reactions in the same pot, without purifying the intermediate compounds, as described in Scheme 9, for a simplified R_2-COSe-CH_2R_1 derivative (**18**, Scheme 9). After the final reaction, the compound precipitates or forms a non-miscible oil (Domínguez-Álvarez et al., 2014; Szemerédi et al., 2021).

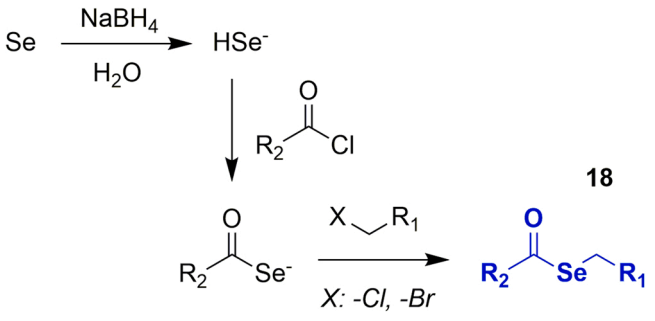
3.3.5. *Selol*

The University of Warsaw has developed a semi-synthetic group of compounds, named Selol (**19**, Scheme 10), which is a mixture of selenitetriglycerides that has been synthesized starting from sunflower oil as described by Jastrzebski et al. (1995). Selol exhibited cytotoxic activity against a panel of HL-60 acute promyelocytic leukemia cell lines, including cell sublines sensitive and resistant to vincristine or to doxorubicin. The cytotoxicity of Selol was higher against the drug-resistant cell lines than against their sensitive counterparts. Moreover, it inhibited P-gp efflux pump activity and caused DNA fragmentation (Suchocki et al., 2007).

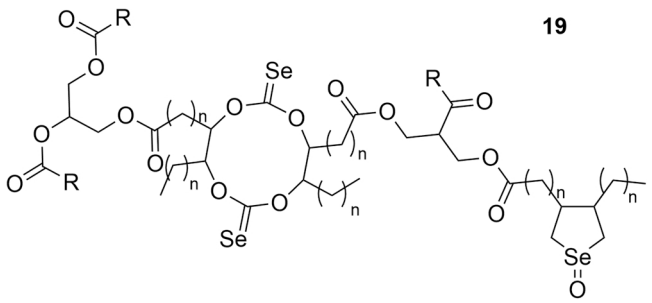
3.4. *Heterocycles containing selenium*

3.4.1. *Phthalic selenoanhydride*

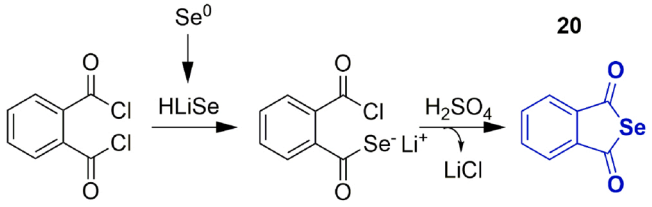
The phthalic selenoanhydride or benzo[*b*]selenophene-1,3-dione (**20**, Scheme 11), a Se isostere of phthalic anhydride, is a potent inhibitor of P-gp in different P-gp-overexpressing tumor cell lines (Domínguez-Álvarez et al., 2016; Gajdács et al., 2017; Csonka et al., 2019) and exhibits synergistic interactions with certain anticancer drugs when it is administered in combination with them (Spengler et al., 2019; Gajdács et al., 2020). The three-step one-pot synthesis of this compound is shown in Scheme 11. In short, lithium aluminum hydride reduces elemental Se in anhydrous THF to form lithium hydrogen selenide, which attacks phthaloyl chloride to form a monoselenated intermediate. The latter can undergo cyclization to form the desired selenoanhydride in the presence



Scheme 9. Synthesis of selenoesters, denoted with the general structure **18**.



Scheme 10. Approximate structure of Selol (**19**), which is a mixture of selenitetriglycerides.

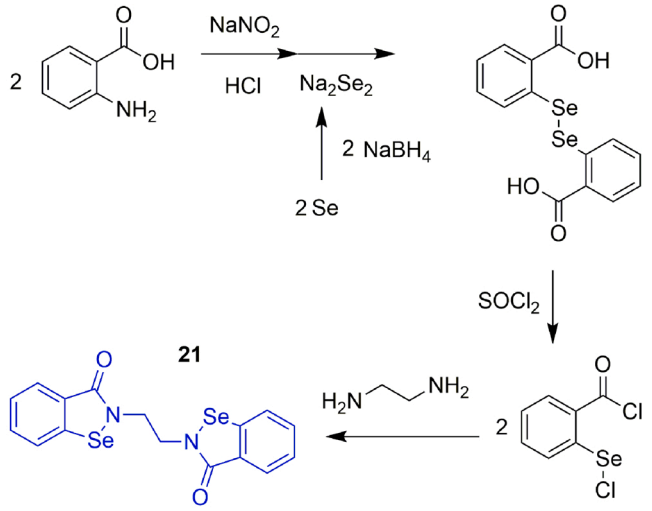


Scheme 11. Synthesis of the phthalic selenoanhydride (**20**).

of sulfuric acid (Domínguez-Álvarez et al., 2014). Phthalic selenoanhydride can also be obtained (although with significantly lower yields) when phthalic anhydride or *N*-hydroxyphthalimide are used as reagents instead of phthaloyl chloride. Similarly, the same compound can be synthesized using sodium borohydride in aqueous media instead of using H_4LiAl in dry tetrahydrofuran, but with a much lower yield (Kharma et al., 2019).

3.4.2. Ethaselen

A symmetrical derivative of ebselen, (1,2-[bis(1,2-benzisoselenazolone 3(2*H*)-ketone)] ethane (**21**, Scheme 12, for short known as ethaselen or BBSKE), was primarily designed as an inhibitor of thioredoxin reductase TrxR1 (He et al., 2012, Wang et al., 2012), an important selenoprotein involved in the regeneration of the cofactor thioredoxin, which is crucial for key cellular processes such as DNA synthesis and repair (Rose and Hoffmann, 2015). Interestingly, the presence of two Se atoms in the structure of this molecule and the ability of the benzoisoselenazone ring to be involved in ring-opening reactions, and the unique reactivity of the Se atom enables this compound to form selenylsulfide



Scheme 12. Synthesis of ethaselen (**21**).

(S-Se) and diselenide (Se-Se) bonds with specific aminoacids of this TrxR1 protein, as the Cys497 and the Sec498, respectively, forming a specific crosslink that enables the inhibition of this enzyme at nanomolar concentrations of ethaselen (Wang et al., 2012).

This heterocyclic selenazol has been deeply studied, revealing that it can enhance the anticancer activity of specific anticancer or chemotherapeutic drugs against various tumors or cancer cell lines: for example, oxaliplatin in gastric cancer cell lines (Zhang et al., 2021), sunitinib in colorectal cancer cell lines (Zheng et al., 2016), and cisplatin in a drug-resistant human erythroleukemia cell line (Ye et al., 2017) and in colon cancer cells (Fu et al., 2011). Similarly, it sensitized non-small cell lung cancer to radiotherapy (Wang et al., 2011). The synthesis of ethaselen is described in Scheme 12 (He et al., 2012, Ruberte et al., 2018).

3.4.3. Selenoflavones

Two selenoflavones (**22** and **23**, Scheme 13) with the selenium in an endocyclic position of the flavone ring have been studied as anticancer and as antimicrobial agents (Marć et al., 2020). These compounds were synthesized according to the synthetic pathway described in Scheme 13 (Alcaide et al., 2018).

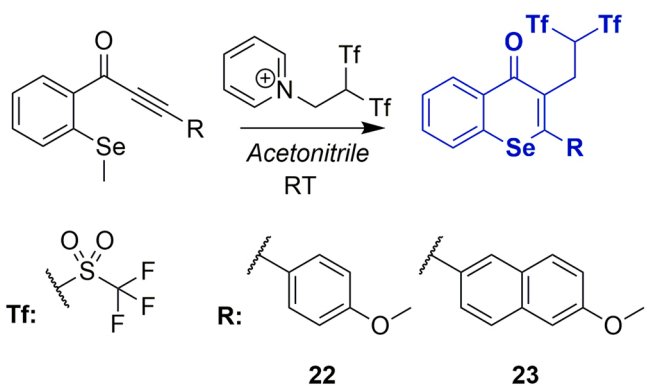
Likewise, another two selenoflavones (**24** and **25**, Scheme 14) with the Se in an exocyclic position of the flavone ring have also demonstrated promising applications in the fight against drug-resistant cancers (Martins et al., 2015). These selenoflavones were selenochrysin (**24**) and 3,7,3',4'-tetramethylselenoquercetin (**25**). The synthesis of these selenoflavones start from the natural flavones chrysin and quercetin, respectively. The compounds are obtained by the reaction of chrysin or the tetramethylated quercetin in a microwave with Woollins' reagent using acetonitrile as the solvent, as shown in Scheme 14 (Martins et al., 2015). This Woollins' reagent enables the direct replacement of a carbonyl oxygen with a Se atom and has been described as the Se isostere of the Lawesson's reagent used to replace carbonyl oxygen with sulfur (Battacharyya and Woollins, 2001).

3.4.4. Iridium complexes containing a selenadiazole ligand

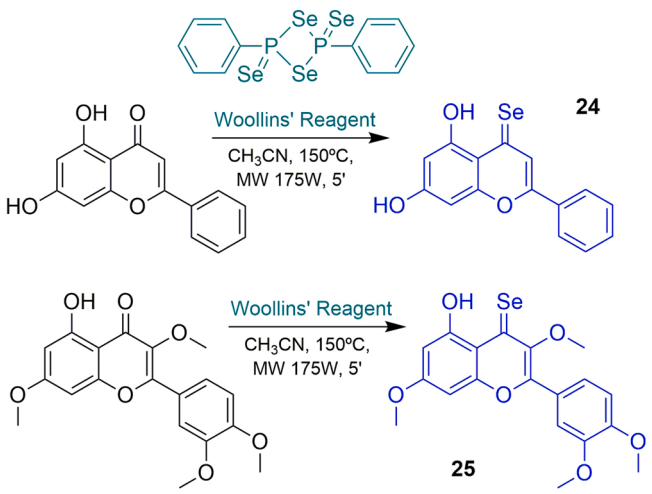
Combining an iridium complex and a selenodiazole moiety included in one of the ligands bound to this iridium atom enabled the construction of a fluorescent Ir(III) complex (**26**, Scheme 15) that could overcome cisplatin resistance in HeLa cells (Huang et al., 2020). Its synthesis is described in Scheme 15 (Huang et al., 2020).

3.4.5. Selenorhodamines

Rhodamines are fluorescent dyes that are *bona fide* transport substrates of the P-gp efflux pump and can have anticancer activity in non-resistant cancers. As they absorb light, they are excellent substrates for PDT, which is based on the irradiation of a tumor with a laser, when a photosensitizer is accumulated inside the tumor: the irradiation activates it and triggers its cytotoxicity (Hill et al., 2014). This study



Scheme 13. Synthesis of *Se*-endocyclic selenoflavones.



Scheme 14. Synthesis of *Se*-exocyclic selenoflavones **24** and **25**.

synthesized selenorhodamines (**27–30**, Scheme 16) starting from a selenoxanthone, containing a thioamide (**27**, **28**) or an amide (**29**, **30**) moiety (Hill et al., 2014); as described in a previous work (Kryman et al., 2014). These selenorhodamines were synthesized to evaluate whether they can act as photosensitizers, and it was found that the thioamide-containing derivatives demonstrated an increased inhibition of the P-gp efflux pump, as well as a more potent photosensitization. Furthermore, the thioamides **27** and **28** (but not the amides **29** and **30**) synergistically enhanced the activity of doxorubicin against Colo-26 cancer cells (Hill et al., 2014).

3.4.6. Selenobarbituric acids

An original approach to overcome drug resistance was utilized in a work that used selenobarbituric acid derivatives of merocyanine 540 (**31** selected as representative example, Scheme 17) to be photobleached photochemically with a white fluorescent light, demonstrating a remarkable cytotoxicity towards 5 of the 6 drug-resistant cell lines evaluated (Daziano et al., 2012). Interestingly, the thiobarbituric and barbituric isosteres of these active selenobarbituric derivatives did not exhibit cytotoxicity. The characterization of the photobleaching products revealed that this photochemical degradation formed within the subnanoparticles of elemental Se, which exerted their cytotoxicity through the formation of conjugates with proteins (Daziano et al., 2012). These compounds were synthesized according to a multi-step synthetic pathway described by Gunther et al., 1992.

3.5. Selenium nanoparticles (SeNPs)

Several SeNPs, or NPs containing Se in their structures (not only as the main element, also as a constituent of the coating or as a doping element, for example) have been reported to demonstrate a wide variety of applications against MDR cancers. Table 2 shows the applications against cancer MDR of the SeNPs whose chemistry is reviewed here.

3.5.1. Commercial quantum dots

Two commercial quantum dots (QD, NPs of cadmium selenide and zinc sulfide - CdSe/ZnS) from Suzhou Xingshuo Nano Technology Co., Ltd (Suzhou, China) coated with mercaptopropionic acid (MPA) or with glutathione (GSH) were evaluated as P-gp gene expression inhibitors in A549 cells, reducing it to half or less and being non-toxic at the tested concentrations. Suppression of P-gp gene expression was mediated by miR-34b and miR-185 miRNAs (Sun et al., 2020).

3.5.2. SeNPs stabilized with oxidized glutathione

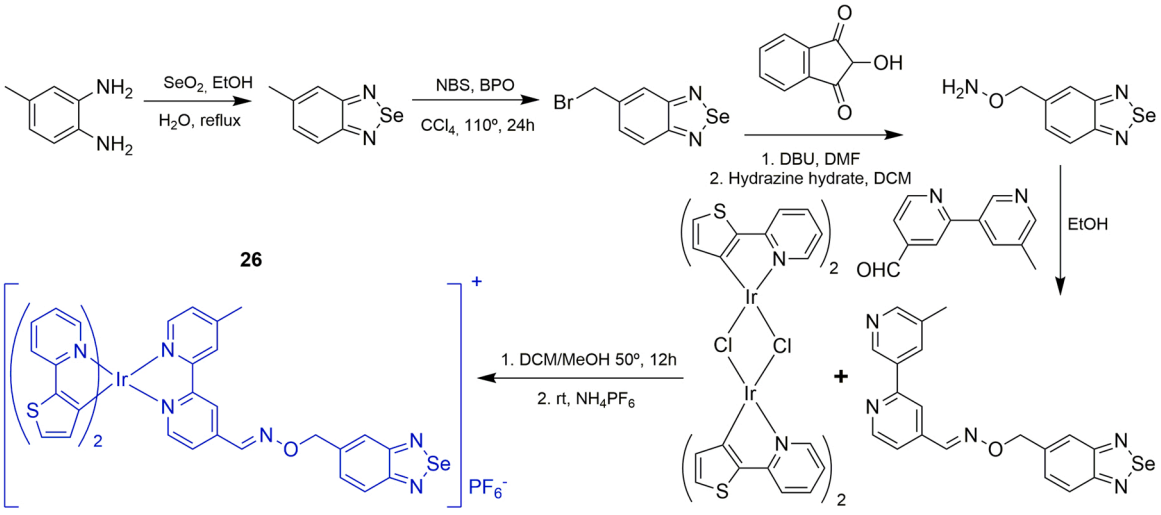
A study conducted with both SeNPs and doxorubicin-loaded poly (D, L-lactide-co-glycolide, PLGA) NPs (nano-DOX) compared their activities alone and in combination (Abd-Rabou et al., 2020). The administration of a combination of the two NPs enhanced their cytotoxicity and sensitized doxorubicin-resistant cell lines, making it possible to overcome the drug resistance of these cell lines to this chemotherapeutic anthracycline drug (Abd-Rabou et al., 2020). These SeNPs of elemental selenium and oxidized glutathione were obtained via a previously described procedure (Zhang et al., 2001).

3.5.3. Galactosamine-borneol-coated SeNPs

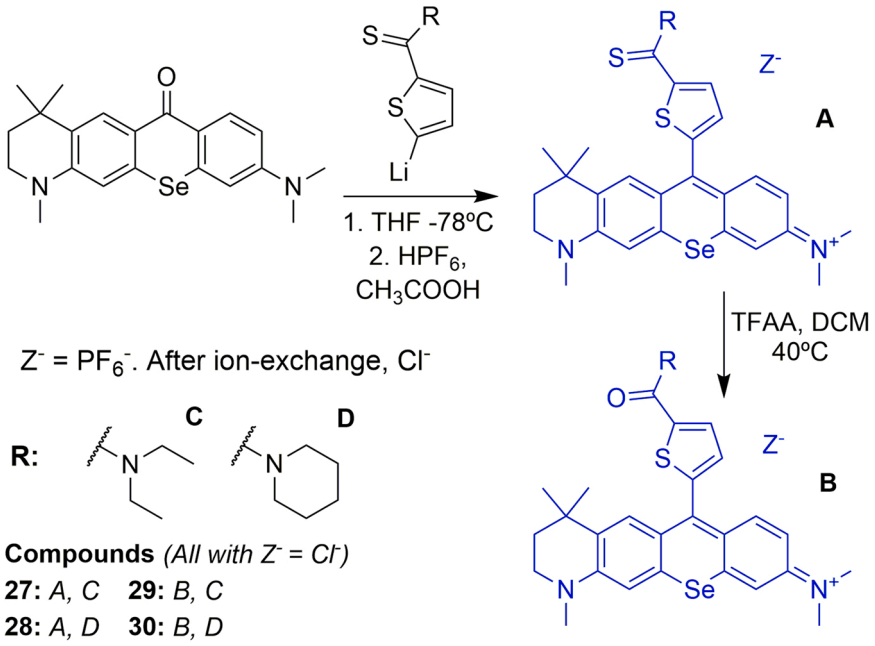
Galactosamine-borneol-coated SeNPs (Gal/Bor@SeNPs) inhibited the ABC family of transporter protein expression in several cancer cell lines (HepG2, R-HepG2 and LO2 cell lines) and served as a nanocarrier to deliver an anticancer drug cargo of ferric tris(2-phenylimidazo[4,5-*f*][1,10]phenantroline) and $Fe(PiP)_3$ to cancer cells (Zeng et al., 2015). Additionally, these SeNPs induced cancer cell apoptosis and activated ROS-mediated signaling pathways (Zeng et al., 2015).

3.5.4. Folic acid conjugated SeNPs

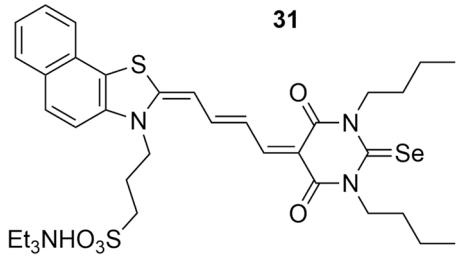
Decorating SeNPs with ligands such as folic acid (FA), which can be recognized by cancer cells overexpressing folate receptor α (Gonen and



Scheme 15. Synthesis of the iridium complex with a ligand bearing a selenadiazole (**26**). NBS: N-bromosuccinimide, BPO: benzoyl peroxide, DBU: 1,8-diazabicyclo [5.4.0]undec-7-ene, DMF: dimethylformamide, DCM: dichloromethane.



Scheme 16. Synthesis of selenorhodamines (**27–30**). TFAA: trifluoroacetic acid.



Scheme 17. Example of selenobarbituric acid (**31**).

Assaraf, 2012; Assaraf et al., 2014), is a novel and interesting strategy to selectively deliver different types of SeNPs to these cancer cells, as shown by several studies (Xuan et al., 2020, Luesakul et al., 2018, Liu et al., 2015).

The delivery of drugs to MDR cells that overexpress folate receptors in their plasma membrane could be achieved through loaded liposomes (Lips) bound to SeNPs coated with a FA conjugate with chitosan (CS), to form a FA-CS-SeNPs-Lips. These SeNPs increased the uptake of fluorescein by HeLa cells and demonstrated cytotoxic activity, with an IC_{50} below 30 μM. SeNPs were obtained by the reduction of sodium selenite with ascorbic acid in the presence of FA-CS conjugates (Xuan et al., 2020).

A similar approach was previously followed to deliver doxorubicin to a resistant NCI-ADR-RES cell line, enhancing the activity of doxorubicin towards these cells 10-fold. These SeNPs were coated with a conjugate of FA with *N*-trimethyl chitosan (DOX-SeNPs@TMC-FA). SeNPs were also prepared by the reduction of sodium selenite with ascorbic acid(Luesakul et al., 2018).

Likewise, Liu and co-workers (Liu et al., 2015) designed SeNPs coated with a chitosan-FA conjugate and loaded with a ruthenium polypyridyl complex (Liu et al., 2015), whose synthesis and apoptosis-inducing activity were described in a previous work (Chen et al., 2010). These FA-SeNPs demonstrated potent cytotoxicity (IC_{50} of 0.24 μM) against a drug-resistant HepG2 subline, towards which non-encapsulated DOX exhibited an IC_{50} value of 2.84 μM. Additionally, the expression levels of different ABC efflux transporters were significantly decreased, in a dose-dependent manner with respect to the concentration of FA-SeNPs tested. Finally, these SeNPs activated ROS-mediated signaling pathways, and induced apoptotic cell death. Their acute lethal effect was investigated in a mouse model, revealing that its DL_{50} is above 900 μM, much higher than the more toxic Se-compounds selenite and selenomethionine (Liu et al., 2015). SeNPs were obtained by the reduction of sodium selenite with ascorbic acid (Huang et al., 2013), and appropriately mixed with the chitosan-FA conjugates and with the ruthenium complex to yield FA-SeNPs(Chen et al., 2010).

3.5.5. *SeNPs as siRNA carriers*

MIL-101, a metallic organic framework (MOF), can be used to load drugs, protecting them from degrading enzymes and enabling the loading and release of small interfering RNAs (siRNAs). Therefore, SeNPs and ruthenium NPs (RuNPs) were prepared and embedded in a MIL-101 together with siRNA that silenced MDR gene expression (Chen et al., 2017). Both Se- or Ru-containing MOFs protected the siRNAs from the action of nucleases, thus increasing their activity, enabling the silencing of MDR genes in MCF-7 cells; this resulted in augmenting their cytotoxic activity, hence triggering apoptotic pathways in these paclitaxel-resistant cells (Chen et al., 2017).

In a previous work by the same research group (Chen et al., 2015), SeNPs were first coated with L- or D-Arginine (L-SeNPs or D-SeNPs), and afterwards with a ruthenium (II) complex, to obtain Ru@L-SeNPs and Ru@D-SeNPs, respectively. These SeNPs could be loaded with pDNA or siRNA, enabling their use as carriers to transfect cells, protecting them from the action of nucleases. Their loading with siRNAs targeting MDR gene expression reduces P-gp protein levels significantly. Additionally, these SeNPs enhanced the expression of *p53*, suppressed *Bcl-2*, increased the expression of *Bax*, and also altered other relevant genes and proteins in oncology. The Ru@L-SeNPs-siRNA effectively inhibited tumor growth in an *in vivo* experiment in mice bearing A549R tumor xenografts. SeNPs were obtained by the reduction of Na_2SeO_3 (in the presence of L- or D-arginine) with $NaBH_4$ (Chen et al., 2015).

A third study with SeNPs as carriers of siRNA was reported by Zheng et al., 2015. In this case, these researchers prepared SeNPs coated with polyamidoamine (PAMAM) dendrimers, and, particularly, 5-PAMAM dendrimers (G5), thus obtaining G5@SeNPs that could be loaded with siRNAs and/or with cisplatin (DDP). These SeNPs were less toxic than

Table 2
Selenium nanoparticles (SeNPs) and their anticancer activity.

SeNPs	Activity	Synthesis	SeNPs Features	Ref.
Commercial Quantum Dots (QD)	Efflux pump inhibition	Commercial (Cadmium selenide, Zinc sulfide)	QD-MPA: r = 11.7 nm, Z = −31,9 mV QD-GSH: r = 10.08 nm, Z = −31,8 mV	[1]
SeNPs stabilized with oxidized glutathione	Chemosensitization	Na_2SeO_3, glutathione. With BSA, pH 7.2	Size: 66.4–100 nm DOX-loaded: 210–330 nm	[2]
Galactosamine-borneol-coated (Gal/Bor@SeNPs)	Efflux pump inhibition and apoptosis induction	Gal, TGA, Na_2SeO_3, AA, Bor	D: from 30 to 80 nm	[3]
Folic acid conjugated SeNPs	Apoptosis induction and anticancer cytotoxicity	Na_2SeO_3, AA; FA-CS conjugates, Lips	FACS-SeNPs: d= 69.5 nm FACS-SeNPs-Lips: d= 186.6 nm, Z = 42.63 mV	[4]
		Na_2SeO_3, AA, TMC-FA conjugate, DOX	D: 50 nm pH 7.4; 110 nm at pH 5.3. Z = 46.7 mV	[5]
		Na_2SeO_3, AA. Synthesis: [6]	Diameter: 180 nm	[7]
SeNPs as siRNA carriers	Chemosensitization and apoptosis induction	Na_2SeO_3, $NaBH_4$, Ru^{3+} ions, SiRNA	Sizes: Se@MIL-101: 160 nM Ru@MIL-101: 180 nM	[8]
		Na_2SeO_3, $NaBH_4$, arginine, Ru complex, SiRNA	D: around 100 nM. Positive Z (19–36 mV)	[9]
	Efflux pump inhibition and apoptosis induction	Na_2SeO_3, $NaBH_4$, G5, SiRNAs, Cisplatin	G5 @SeNPs 31.2 nm. With SiRNA, 326,2 nm.	[10]
Hybrids of niosomes and bio-synthesized SeNPs	Reduction of ROS, efflux pump inhibition	Na_2SeO_3, PBS, BSA, cholesterol, surfactants	Size: 119–149 nm. Negative Z	[11]
Se-doped minerals and/or NPs	Chemosensitization and anticancer cytotoxicity	Na_2SeO_3, phosphoric acid, calcium acetate, NH_4OH.	Sizes: 200 and 300 nm (HA and Se-doped HA, respectively)	[12,13]
		$CaCl_2$, Na_2SeO_3, ATP, Urea	CaP: D= 200 nm Se-CaP: D= 150 nm	[14]
NPs with diselenide bonds	ROS generation and chemosensitization	Na_2SeO_3, $NaBH_4$, $BrCH_2CH_2OH$, CHTA, mPEG5000-NH_2	Polymer MW: 20,000 D= 120 nm	[15]
	Photosensitization, efflux pump inhibition and apoptosis induction	See Scheme, 18.	Sizes: DOX-loaded: 84.4 nm. Unloaded 76.2 nm, with a 2–10 nm height.	[16]
		Like previous one, replacing PAMAM by Poloxamer 188	Size: 20–60 nm. Z = 3.99 mV. Height: 2 nm	[17]
Nanovehicles for Se-compounds delivery	Chemosensitization,apoptosis induction and anticancer cytotoxicity	Na_2SeO_3, $NaBH_4$, 3-chloropropionic acid, PTX, EDC•HCl, DMAP	Hydrodynamic diameter of micelles: 150–600 nm	[18]

Table abbreviations: r: radius. Z: Zeta potential. MPA: mercaptopropionic acid. GSH: glutathione. Na2SeO3: sodium selenite. BSA: bovine serum albumin. DOX: doxorubicin. Gal: galactosamine. Bor: borneol. TGA: thioglycolic acid. AA: ascorbic acid. D: diameter. FA: folic acid. CS: chitosan. Lips: liposomes. TMC: trimethyl chitosan. NaBH4: sodium borohydride. MIL-101: a metallic organic framework. G5, PAMAM: polyamidoamine dendrimers. HA: hydroxyapatite. ATP: adenosine 5′-triphosphate disodium salt hydrate. CaP: calcium phosphate biomineral microspheres. BrCH2CH2OH: 2-bromoethanol. mPEG5000-NH2: N-capped polyethylene glycol. CHTA: 1,2,4,5-cyclohexanetetracarboxylic dianhydride. PTX: paclitaxel. DMAP: 4-dimethylamino pyridine. EDC•HCl: 1-Ethyl-3-(3′-dimethylaminopropyl) carbodiimide hydrochloride.
References: [1] Sun et al., 2020; [2] Abd-Rabou et al., 2020; [3] Zeng et al., 2015; [4] Xuan et al., 2020; [5] Luesakul et al., 2018; [6] Chen et al., 2010; [7] Liu et al., 2015; [8] Chen et al., 2017; [9] Chen et al., 2015; [10] Zheng et al., 2015; [11] Gharbavi et al., 2020; [12] Barbanente et al. 2020; [13] Barbanente et al. 2021; [14] Hu et al., 2021 b; [15] Wei et al., 2020; [16] Wang et al., 2018c; [17] Wang et al., 2019; [18] Xu et al., 2021.

the dendrimer alone. They induce apoptosis in both A549 cells and cisplatin-resistant A549/DDP cells, exerting a strong inhibition of the expression of MDR efflux pumps in A549/DDP-resistant cells, and reduced the size of tumors in *in vivo* experiments (Zheng et al., 2015). SeNPs were synthesized by the reduction of sodium selenite with ice-cold sodium borohydride. The Z potential was positive due to the cationic dendrimers, with the exception of the 1:1 complexes with siRNA, which exhibited a negative Z potential (Zheng et al., 2015).

3.5.6. *Hybrids of niosomes and bio-synthesized SeNPs*

A novel approach was followed by Gharbavi and collaborators (Gharbavi et al., 2020) to prepare niosomes whose surface was coated with BSA-synthesized SeNPs (NISM-B@SeNPs). These SeNPs demonstrated antioxidant and cytotoxic activities, as well as a capacity to reduce the expression of the *MDR-1* gene, which encodes the P-gp efflux pump. The SeNPs used to coat these niosomes were prepared using a solution of sodium selenite (Na_2SeO_3) in PBS and incubation with bovine serum albumin (BSA) at 121°C in autoclave with vigorous stirring at 15–20 psi, for 20–45 min (Gharbavi et al., 2020; Kalishwaralal et al., 2016).

3.5.7. *Se-doped minerals and/or NPs*

An interesting strategy in the preparation of active NPs against cancer is based on using a salt, metal or mineral, which is doped with Se. A few studies have explored this approach in MDR (Hu et al., 2021b, Barbanente et al., 2020), based on Se-doped calcium phosphate biomineral and in Se-doped hydroxyapatite NPs, respectively.

Calcium phosphate biomineral resembles the bones, as it has the same components, but lacks the 30% content of collagen. Consequently, it is highly compatible for use as a carrier in drug delivery systems (LeGeros, 2008, Ignjatović et al., 2014). Se-doped calcium phosphate biomineral microspheres were prepared and evaluated as nanocarriers of doxorubicin (DOX@Se-CaP). They exhibited cytotoxic activity in a concentration-dependent manner with respect to the proportion of Se in the biomineral and were found to have higher cytotoxicity against cancer and cancer-resistant cell lines than DOX or Se-CaP alone. Additionally, these microspheres reversed the MDR of MG63/DXR, a doxorubicin-resistant osteosarcoma cell line; and exerted a very significant reduction (>6-fold) in tumor size in mice after a 6-day treatment, when compared to the control group (Hu et al., 2021b).

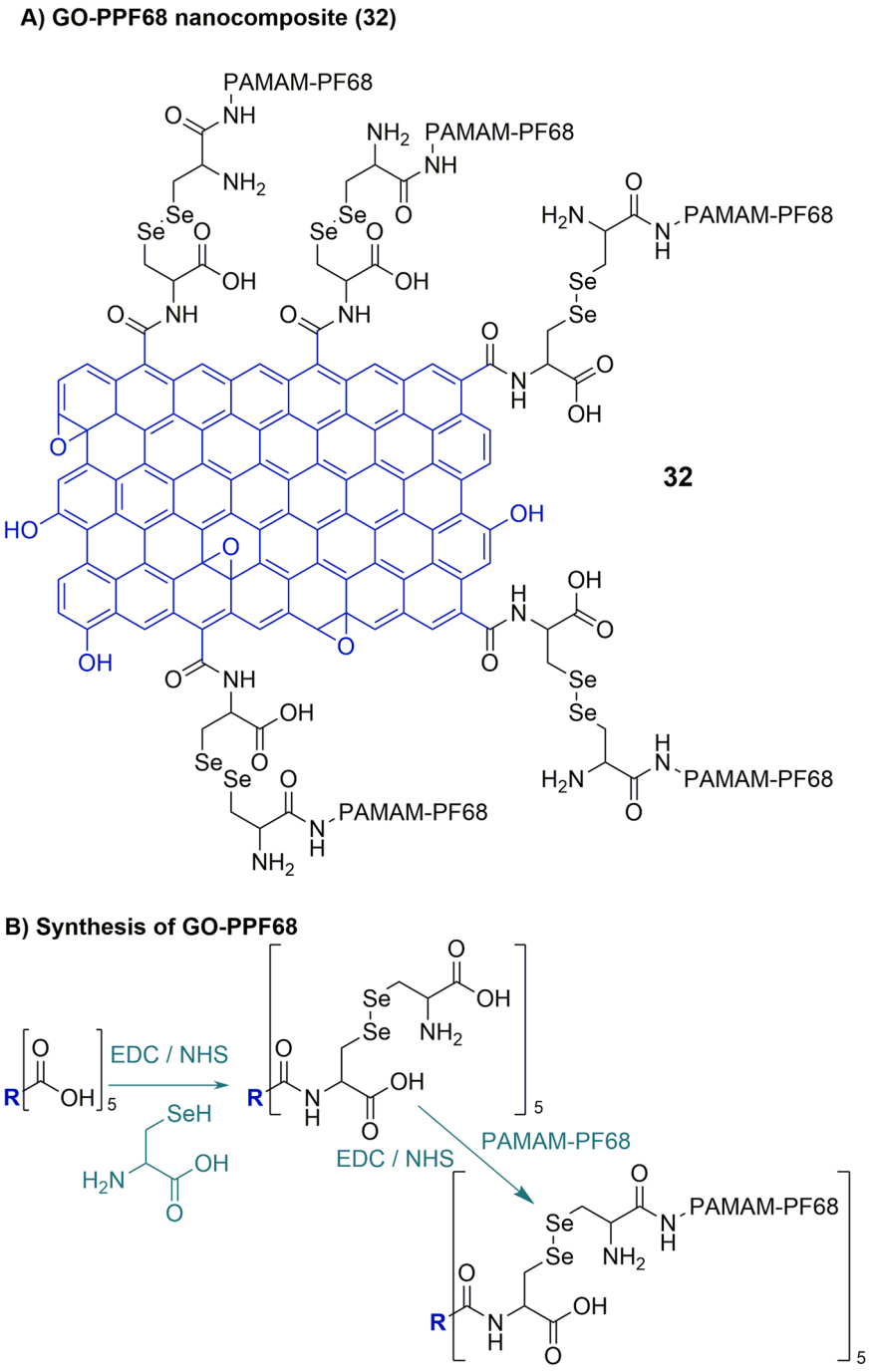
Se-doped hydroxyapatite NPs (HASe NPs) were prepared in different proportions Se/(Se+P), of 1, 10 and 25 wt% in a second study (Barbanente et al., 2020). These Se-HA NPs were prepared by precipitation from a solution of phosphoric acid (H_3PO_4) and sodium selenite (Na_2SeO_3) by the dropwise addition of calcium acetate ($Ca(CH_3COO)_2$). These HASe NPs were loaded with [Pt(dihydrogenpyrophosphate)(cis-1, 4-diaminocyclohexane)] (onwards PtPP) to form PtPP-HASe NPs. It was found that in Pt-loaded Se-doped HA the release of Se was more favored than that of PtPP, especially at acidic pH and in the HASe with the highest Se content. The cytotoxic activity towards PC-3 prostate and

MDA-MB-231 breast cancer cell lines of these PtPP-HASe NPs was enhanced when the co-release of both PtPP and Se took place (Barbanente et al., 2020). A second study of this group, in this case without Pt loading and with higher Se concentration in the Se-doped HA (up to 40 wt% in Se/(Se+P) formula), encountered similar release and cytotoxicity results, but also higher cytotoxicity towards normal cells with the treatment of the HASe than of sodium selenite alone (Barbanente et al., 2021).

3.5.8. *Construction of NPs using Se-Se bonds*

A different approach is using a standard polymer, for example polyethylene glycol (PEG) and forming larger particles via diselenide bonds, to obtain NPs that can be used as carriers; a strategy that has been utilized in several studies (Wei et al., 2020; Wang et al., 2018c, 2019).

Wei et al. (2020) constructed a polyethylene glycol (PEG)-based polymer (P1) with a diselenide bond (DSB): $mPEG_{5000}$-(CHTA-DSB-CHTA)-$mPEG_{5000}$, being CHTA 1,2,4,5-cyclohexanetetracarboxylic dianhydride and $mPEG_{5000}$, polyethylene glycol. These NPs were loaded with a cisplatin-derived drug, based on the coupling of modified fatty acids to the cisplatin. These particles (both loaded and unloaded) were tested against sensitive and drug-resistant cancer lines, revealing that they could effectively reverse the drug resistance to cisplatin; and a gene expression screening revealed that the expression of several crucial genes in oncology was significantly modified. Additionally, these particles altered the redox balance of cancer cells, depleting GSH and boosting the formation of ROS (Wei et al., 2020).



Scheme 18. Graphene-diselenide-polyamidoaminepluronic acid nanocomposite **32** (A). In B), its synthesis. R denotes all the graphene part (in blue in A)) of the molecule. PF68: pluronic; PAMAM: polyamidoamine dendrimer; EDC: n-(3-dimethylaminopropyl-*N*′-ethylcarbodiimide) hydrochloride; NHS: n-hydroxysuccinimide.

In a different study, Wang et al. (2018c) reported a nanocomposite (**32**) obtained through cross-linking between graphene oxide (GO) and polyamidoamine-pluronic F68 (PPF68) via a diselenide bond, as shown in Scheme 18. This GO-PPF68 nanocomposite was used to encapsulate DOX together with indocyanine (ICG), a near-infrared (NIR) photosensitizer. (Wang et al., 2018c). The presence of ICG enabled acceleration of the release of the encapsulated DOX through laser irradiation with NIR, this release being pH-dependent. The nanocomposite was cytotoxic against both MCF-7 and MCF-7/ADR-resistant cells. Additionally, the presence of the graphene oxide enabled the release of DOX when the ROS concentration in the cells increased. Finally, the nanocomposite reduced the expression of the *ABCB1* gene and its encoded P-gp protein; enhanced apoptosis via the increase in the expression of PARP, and inhibited tumor growth in *in vivo* experiments in mice (Wang et al., 2018c). A second study by the same group replaced the pluronic (PF68) end of the PAMAM dendrimer with Poloxamer 188. These NPs were also cytotoxic towards MCF-7 cells and its resistant subline MCF-7/ADR, and significantly reduced the expression of P-gp, hence overcoming MDR (Wang et al., 2019).

3.5.9. Delivery nanocarriers loaded with selenocompounds

To complete this overview of the use of selenium nanoparticles in drug delivery, we review the use of other nanovehicles to deliver selenocompounds.

In this field, Xu et al., 2021 have reported a PEG-based polymer cystine–(polyethylene glycol)$_2$-*b*-(poly(2-methacryloyloxyethyl ferrocene-carboxylate)$_2$), [denoted (Cys–(PEG45)$_2$-*b*-(PMAOEFC)$_2$)], that could be loaded with different forms of doxorubicin through a labile Schiff base structure that assembles itself as a globular micelle, enabling the release of doxorubicin. This complex was also loaded with paclitaxel and with a paclitaxel dimer crosslinked with 3,3'- diselenodipropionic acid (PTX-SeSe-PTX). This complex demonstrated a noteworthy cytotoxicity against HeLa cells when loaded in the (Cys–(PEG45)$_2$-*b*-(PMAOEFC)$_2$) nanovehicle. This nanocarrier enhanced the drug accumulation in the tumor, promoted a higher release of the drugs, and induced apoptotic events. This construction could be used to deliver chemotherapy drugs to resistant tumors, circumventing the MDR of these tumors (Xu et al., 2021).

4. Chemistry of telluro-compounds and nanoparticles with applications in Cancer MDR

Tellurium has been less investigated than selenium so far, but still the number of compounds with anticancer applications is high, so like with selenium, this section will focus on those compounds with applications against resistant cancers. In the majority of cases, the tellurocompounds are active in the form of nanoparticles or quantum dots; in contrast to selenium, where a wide variety of synthetic organic selenocompounds have shown activity towards resistant cancers. Table 3 summarizes the applications against MDR of the tellurocompounds reviewed in this work, and Table 4 provides an overview of the tellurium nanoparticles and Te-quantum dots whose chemistry is reviewed in this section.

4.1. Elemental tellurium as NPs

Unlike Se, tellurium is somewhat alien to biological systems. Elemental Te in the form of nanoparticles (TeNPs) has been reported to serve as an excellent multifunctional agent. *Aloe vera*-based TeNPs have been reported to exhibit excellent anticancer activities. These amorphous NPs demonstrated anticancer activity against melanoma cells (ATCC CRL-1619) at concentrations between 5 and 100 μg/mL after 72 h of exposure (Medina-Cruz et al., 2021). This activity is closely linked to elevated levels of ROS, which results in enormous damage to the nucleic acids, lipids, and proteins at the molecular level, as well as membranes and organelles at the macro level within the cell. Moreover, at higher concentrations, powerful oxidants add insult to injury by severely damaging vital macromolecules throughout the membranes and cytoplasm (Valencia and Morán, 2004). The combination of all these oxidants along with ROS triggers apoptosis, which ultimately leads to cell death.

Table 3
Tellurocompounds and their anticancer activity.

Tellurocompounds	Activity	References
Inorganic tellurocompounds		
Potassium tellurite	ROS generation and anticancer cytotoxicity	Sandoval et al., 2010
Organic tellurocompounds		
Diphenyl ditelluride	ROS generation, anticancer cytotoxicity and apoptosis induction	Vij and Hardej, 2012
DP41	ROS generation, anticancer cytotoxicity and apoptosis induction	Du et al., 2014
SAS and AS101	Chemosensitization	Layani-Bazar et al., 2014 Zigmann et al., 2021

In another study, the cytotoxic activity of mycosynthesized TeNPs was compared with inorganic tellurite. Interestingly, TeNPs provided excellent selective cytotoxic activity with an IC_{50} value of 39.83 μg/mL against a breast cancer MCF-7 cell line, whilst similar biogenic particles provided no cytotoxic effect against normal L929 cell lines at concentrations of 50 μg/mL or less. In sharp contrast, potassium tellurite (K_2TeO_3) exhibited higher cytotoxicity against the normal L929 cell line with an IC_{50} value of 76.33 μM (which corresponds to 9.739 μg/mL of elemental Te), while no IC_{50} value was observed against the breast cancer MCF-7 cell line at concentrations of 100 μM (which corresponds to 12.76 μg/mL of elemental Te) or less. All of these observations were found after 48 h of drug incubation. Higher overall antioxidant and anticancer activities were observed for the biogenic nanostructured TeNPs than for potassium tellurite (Vahidi et al., 2021).

4.2. Inorganic tellurium compounds

4.2.1. Tellurite

Although the toxicity of tellurite is not as strong as elemental Te, this simple inorganic substance cannot be considered to be totally harmless. Several *in vitro* studies revealed that tellurite oxidatively damages the membranes and causes the depletion of GSH, resulting in hemolysis (De Meio and O'Leary, 1975). Moreover, it suppresses the functionality of several NAD^+-dependent oxidoreductases in mitochondria (Siliprandi and Storey, 1973). Furthermore, this simple yet effective inorganic compound induces toxicity in a cervical cancer cell line (HeLa) and TLT cells in a time and concentration-dependent manner. In TLT cells, the toxicity resulted from elevated levels of ROS and decreased levels of ATP and GSH, which ultimately led to necrosis. Furthermore, exposure to tellurite caused phosphorylation of both the H2AX histone and the initiation factor eIF2α, which provide a hint about the tellurite-induced DNA damage and translational arrest (Sandoval et al., 2010). The notion that tellurite induces cell death in cancer and normal cells via oxidative stress is affirmed by another study conducted by Sandoval and coworkers, (Sandoval et al., 2012). Recent studies highlight the capability of this oxyanion (TeO_3^{2-}) to provoke the phosphorylation of eIF2α, stress granules (SGs) assembly and their correlation with DNA damage in human bone osteosarcoma epithelial U2OS cells. Intriguingly, tellurite stimulates the assembly of both cytoplasmic as well as nuclear stress granules (SGs) in response to OS and DNA damage, which is a relatively novel aspect of the response to cellular stress (Gaete-Argel et al., 2021).

4.2.2. Te-based quantum dots

A colloidal quantum dot (QD) is a form of nanocrystal (diameters in the range of 1–20 nm) comprised of a semiconducting material. Te-based QDs have recently been extensively employed to understand the different mechanisms underlying MDR and overcome it.

Table 4
Tellurium nanoparticles (TeNPs), Te-based quantum dots (QD) and their anticancer activity.

TeNPs and Te-based QD	Activity	Synthesis	Features (for TeNPs/QD)	Ref.
Aloe vera based TeNPs	ROS generation and apoptosis induction	Biosynthesis (*Aloe vera)*	Size: 20–60 nm	[1]
Mycosynthesized TeNPs	Anticancer cytotoxicity	Biosynthesis (*Penicillium chrysogenium)*	Size: 50.2 nm	[2]
Te-based quantum dots	Chemosensitization and efflux pump inhibition	$Cd(ClO4)_2{\cdot}H_2O$, MPA, Al_2Te_3	Size: 2.3 nm	[3]
		$Cd(ClO4)_2{\cdot}H_2O$, Cys, Al_2Te_3, DNR, GA	Cys-CdTe Size: 3.2 nm DNR-GA-Cys-CdTe size: 7.2 nm	[4]
		$Cd(ClO4)_2{\cdot}H_2O$, MPA, Al_2Te_3, wogonin	Diameter: 3–5 nm	[5]
		$NaBH_4$, cadmium acetate, Te, thioglycolic acid.	Diameter: 2.3–3.5 nm	[6]
		$NaBH_4$, $CdCl_2$, Te, thioglycolic acid.	Diameter: 5.1 nm	[7]
		Commercial QD	Diameter: 4.2 nm	[8]
Copper telluride ($Cu_{2-x}Te$) nanocubes (NCs)	Photosensitization	Tri-*n*-butylphosphine telluride, $CuCl_2$, DPP, octadecene	Size: 35–40 nm	[9]

Table abbreviations: MPA: mercaptopropionic acid. Cys: cysteine. DNR: daunarubicin. GA: gambogic acid. DPP: diphenylphosphine.
References: [1] Medina-Cruz et al., 2021; [2] Vahidi et al., 2021; [3] Zhou et al., 2010; [4] Zhou et al., 2016; [5] Huang et al., 2016; [6] Xu et al., 2019b; [7] Chen et al., 2016; [8] Tian et al., 2019; [9] Poulose et al., 2016.

Zhou and collaborators produced water-soluble CdTe (QDs) whose surface was negatively charged with 3-mercaptopropionic acid (MPA)-QDs to improve the drug profile, specifically to increase the transport of drug molecules to the target cancer cells. The results of the study affirmed the effectiveness of the MPA-CdTe QDs in facilitating the interaction of daunorubicin (DNR) with leukemia cells and the efficiency of biolabeling in cancer cells (Zhou et al., 2010).

In another study, cysteamine-modified cadmium tellurium (Cys-CdTe) QDs were developed and co-loaded with DNR) and gambogic acid (GA) NPs (DNR-GA-Cys-CdTe NPs) in order to decrease the side effects and the MDR of these agents against malignant lymphoma. These DNR-GA-Cys-CdTe NPs provided pH-responsive and dose-dependent antiproliferative activity against Raji/DNR cells. Flow cytometry confirmed the accumulation of DNR inside the cells, whilst Western blots affirmed the down-regulation of P-gp in Raji/DNR cells. These findings confirmed that DNR-GA-Cys-CdTe NPs could considerably decrease the MDR of Raji/DNR cells (Zhou et al., 2016).

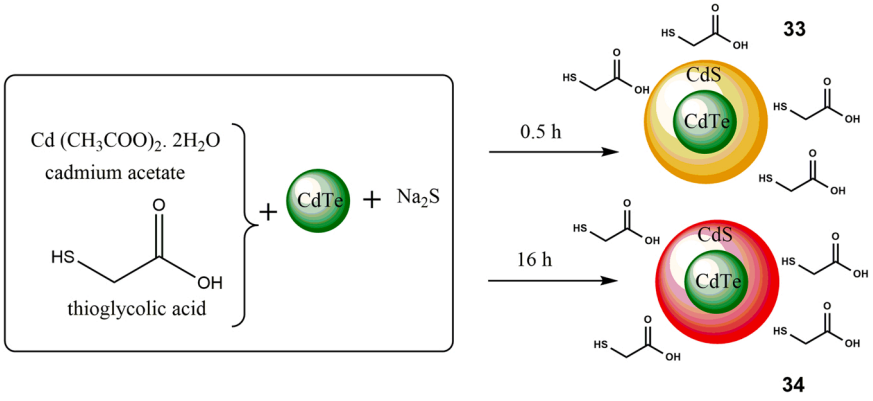
Similarly, Huang et al., combined wogonin (5,7-dihydroxy-8-methoxyflavone) with cadmium-telluride QDs (CdTe-QDs), and confirmed their synergic effect against drug-resistant human leukemia KA cells as revealed by flow cytometry, electron microscopy and micro-CT imaging. The synergistic effect was observed both *in vitro* as well as *in vivo*, and was made possible due to the interaction of wogonin with KA cells without any obstacles (Huang et al., 2016).

Tellurium has been utilized to produce water-soluble core-shell CdTe QDs which were green in color. Ning Xu et al., produced QDs of CdTe (green) and CdS (orange red) with enhanced fluorescence quantum yield, reducing the biological toxicity profile of QDs, and enhancing their fluorescence lifetime. These two core-shell QDs were subsequently combined with anticancer drugs (5-FU) and P-gp inhibitors (Tamoxifen, TAM) to produce novel fluorescent bioprobes, CdTe/CdS (λ_{em} = 545 nm)−5-FU (**33**, Scheme 19) and Bio-CdTe/CdS (λ_{em} = 600 nm)-TAM (**34**), respectively. The simultaneous utilization of these two fluorescent probes in human breast cancer cells MDA-MB-231/MDR affirmed the efficacy of anticancer drugs when applied together with P-gp inhibitors. The fluorescence imaging revealed that P-gp inhibitors accumulated at the surface of the cell membrane, whilst the anticancer drug was retained inside the cancer cells (Xu et al., 2019b).

The interest in the field of Te-based QDs attracted the attention of several scientists to explore the drug-resistance mechanisms in different models. The major players of drug resistance include ABC efflux transporters, including P-gp and multidrug resistance-associated proteins (MRPs).

Chen et al., produced CdTe QDs which were monodispersed and provided green fluorescence with a maximum excitation at 530 nm. Intriguingly, when such QDs were exposed to the human hepatocellular carcinoma cell line (HepG2), human kidney cell line 2 (HK-2), and Madin-Darby canine kidney (MDCK) cells, they resulted in a noteworthy toxicity due to the accumulation of all three cell lines. The incorporation of specific inhibitors and inducers of P-gp and MRPs significantly affected the cellular accumulation of these QDs and their subsequent toxicity in HepG2 and HK-2 cells and slightly in MDCK cells. Interestingly, CdTe QDs significantly affected the activity of ABC efflux transporters compared to $CdCl_2$ (Chen et al., 2016).

Tian et al., exploited a zebra fish model to determine oxidative stress signaling, alterations in the gene expression of ABC transporters and nuclear receptors. The treatment of zebrafish embryos with mercaptopropionic acid (MPA)CdTe QDs and MPA-CdSCdTe QDs resulted in delayed hatching and the induction of MRP1 and MRP2 transporters in a concentration-dependent manner. These findings reveal the protective



Scheme 19. Synthesis of quantum dots **33** and **34**. The details of the synthesis can be found in the same study (Xu et al., 2019b). The scheme is adapted and modified from Xu et al., (Xu et al., 2019b).

role of such efflux pumps induced by CdTe QDs. Moreover, exposure to QDs activated nuclear receptors, such as aryl hydrocarbon receptor (AHR) 1b, pregnane X receptor (PXR), and peroxisome proliferator-activated receptor (PPAR)-β. The interaction with QDs resulted in the induction of nuclear factor E2 related factor 2 (NRF2), decreased levels of GSH as well as SOD), resulting in an overall increased oxidative stress. Intriguingly, PXR and NRF2 were altered more significantly than MRPs. Collectively, these results affirm the contribution of MRP1 and MRP2 efflux transporters to the detoxification of QDs in zebrafish embryos (Tian et al., 2019).

4.2.3. *Copper telluride ($Cu_{2-X}Te$) nanocubes (NCs)*

This is another interesting inorganic telluride which has demonstrated efficacy against drug-resistant cancer cells in the form of nanocubes. Of the various cancers, hypermethylated cancers are extremely difficult to treat. Such malignant cells are characterized by abnormal methylated DNA. Poulose et al., reported the synthesis and efficacy of multifunctional copper telluride ($Cu_{2-X}Te$) nanocubes (NCs) as strong anticancer agents when utilized as photothermal and photodynamic agents. Moreover, such NCs provided photoacoustic and X-ray contrast imaging characteristics which may pave the way towards image-guided therapeutic studies (Poulose et al., 2016).

4.3. *Organic tellurocompound with MDR-reversing activity: Octa-O-bis-(R,R)-tartarate ditellurane (SAS)*

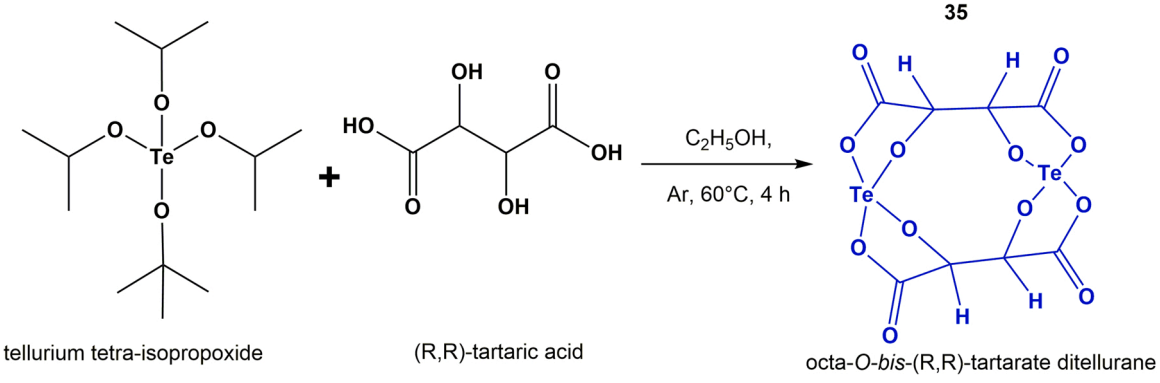
Octa-*O-bis*-(R,R)-Tartarate Ditellurane (**35**, SAS, Scheme 20) is an organotellurium compound comprised of two tellurium atoms, each of which is surrounded by four oxygen atoms from two carboxylates and two alkoxides of two tartaric acids. This organo-tellurium compound has been reported to serve as a multi-functional agent. It has been reported to interact with the thiol residues of the cysteine and thereby provide their biological activities. The chemical interaction of Te (IV) with thiols results in the formation of disulfides, which leads to conformational changes that affect the biological activities at the target site (Sredni et al., 2007). SAS has recently been evaluated to target drug-resistant cancer cells.

The literature reveals that when human multiple myeloma (MM) cells were exposed to SAS, it blocked the physical interaction of cells with fibronectin. Moreover, this exposure enhanced the re-sensitization of the cells to the chemotherapeutic drugs, and this re-sensitization was coupled to the blocking of phosphorylated Akt in MM cells by the mesenchymal stem cells. These findings highlight the significance of these molecules in the possible treatment of drug-resistant MM (Zigman-Hoffmann et al., 2021).

5. Final remarks and conclusions

Here we have explored the different applications of seleno- and telluro-containing compounds and NPs or quantum dots with reported anticancer activities. Firstly, the distinct mechanisms and activities have been reviewed, in the section '*2. Biochemistry of seleno- and telluro-compounds*'. Se and the compounds that contain this element are known chemopreventive agents, thanks to the participation of Se in antioxidant cellular defense, as a component of selenoproteins. However, this effect is not limited to them, and the chemopreventive activity of more seleno- and tellurocompounds has been reported, as reviewed here. The readiness for redox reactions of the Se (and of the tellurium) reveals that the compounds containing these chalcogens exert a marked influence on the redox-state of the cells. Additionally, certain specific seleno- and tellurocompounds are involved in the modulation of inflammatory processes and in the triggering of the cellular pathways leading to apoptosis and autophagy. As for the applications of seleno- and telluro-compounds and NPs against resistant cancers, many derivatives containing these chalcogen elements in their structure are able to reverse cancer MDR via the inhibition of efflux pumps that are overexpressed in resistant cancers to recognize the chemotherapy drugs and expel them out of the cells, preventing them from exerting their anticancer action. Thanks to these novel derivatives, this drug resistance modality can be circumvented. That may be one of the mechanisms underlying the synergistic effects shown by certain seleno- and telluro-compounds when they are administered in combination with standard anticancer drugs to treat drug-resistant tumors (but there must be additional mechanisms involved). Finally, the most active selenocompounds are able to block, perhaps through the modulation of ROS levels, the metastatic migration of aggressive tumors to other locations in the body. Many of the above-mentioned anticancer activities are based on specific Se/Te derivatives, which are selective towards drug-resistant cancer cells, in spite of the infamous toxicity that these chalcogens may have. This selectivity must be exploited in future studies to design more effective treatments with fewer and less severe side-effects.

Secondly, the selenocompounds and SeNPs with applications against drug-resistant cancers have been comprehensively revised in the section '*3. Chemistry of Seleno-compounds and nanoparticles with applications in Cancer MDR*', indicating a summary of their anticancer activity against drug-resistant cancers and of their synthesis (for the selenocompounds) or preparation and characterization (for the SeNPs). In this group of Se-containing compounds, promising derivatives have been explored, such as sodium selenite, selenoamino acids and derivatives, rhenium (I) diselenoethers, hydantoinylalkyl phenyl selenides, methylseleninic acid, quinoxaline bis(isoselenoureas), pyrimidine selones, selenoesters, selol, selenoanhydrides, ethaselen, exocyclic and endocyclic selenoflavones, iridium-selenodiazole complexes, selenorhodamines, selenobarbituric acids, as well as a wide variety of both SeNPs as well as NPs containing Se atoms embedded in their structure or coating. Besides these promising starting results, Se and selenocompounds are privileged scaffolds with promising applications against cancers and against resistant cancers, which deserve to be studied more intensively in the future.



Scheme 20. Synthesis of octa-*O-bis*-(R,R)-tartarate ditellurane (SAS, **35**).

Lastly, the reported tellurium-containing derivatives, NPs and quantum dots with applications against drug-resistant cancers have been approached in a similar manner in the section '*4. Chemistry of Telluro-compounds and nanoparticles with applications in Cancer MDR*'. In this case, this section is shorter, as less research on Te-compounds has been published, compared to the bibliography available for Se-compounds. Here, we have presented the chemistry and the anticancer activity against drug-resistant cancers of elemental tellurium NPs and quantum dots, tellurite, copper telluride nanocubes and an octa-bis-tartarate ditellurane. Fewer studies with tellurium can be found in the literature, but they are still of particular interest, making tellurium and tellurocompounds also worthy of being studied in depth like Se and selenocompounds in dedicated future studies.

In summary, both Se- and tellurium-containing compounds (including salts, natural compounds such as selenoaminoacids, synthetic compounds, NPs and quantum dots) have revealed remarkable biological activities that may be of use in the search for novel anticancer agents, or for adjuvants to circumvent drug resistance that emerges upon treatment with current chemotherapeutic regimens. The results reviewed in this paper open up possible approaches in the fight against cancer, and in particular, in the fight against drug-resistant cancers. Some of the compounds reviewed here are worthy of being studied in more in-depth studies (*in vivo* experiments or ADMETox assays: Absorption, Distribution, Metabolism, Excretion and Toxicity) to evaluate their suitability as novel potential anticancer drug candidates or adjuvants. Additionally, the ensemble of these compounds constitutes an interesting library of agents that could be of benefit for medicinal chemists to conduct reliable SARs (Structure-Activity Relationships) that could enable the design of more potent and selective seleno- and telluro-compounds against cancer. It is important that these researchers pay particular attention to address the issue of the potential toxicity of these compounds: perhaps the main drawback of the use of seleno-and telluro-compounds in oncology (and, in extension, in medicinal chemistry) is the concern about their potential toxicity. Thus, biomedical researchers need to design not only active compounds, but also safe and selective derivatives. If this approach is successful, it would enable the design, synthesis, and evaluation of novel Se- and tellurium derivatives with the ability to overcome the different modalities of drug resistance acquired by cancer cells to evade the action of current treatments used in clinical oncology.

Conflicts of interest

The authors declare no potential conflicts of interest.

Acknowledgments

The study was supported by the projects SZTE ÁOK-KKA 2018/270-62-2 of the University of Szeged, Faculty of Medicine and GINOP-2.3.2–15-2016–00038 (Hungary), Agencia Estatal Consejo Superior de Investigaciones Científicas (CSIC, Spain, mobility project LINKA20285). This research was funded by the mobility project from the Czech Ministry of Education, Youth and Sports INTER-COST, grant number LTC19007. This article is based upon work from COST Action 17104 <STRATAGEM> , supported by COST (European Cooperation in Science and Technology, http://www.cost.eu, assessed on 30 December 2021). The study was also supported by two associations from the province of Zamora, Spain: "Asociación Cultural Trevinca" and "Iniciativas Ropelanas". B.R. was supported by the project EFOP-3.6.3-VEKOP-16–2017-00009 (Hungary). N.S. was supported by the New National Excellence Program (ÚNKP).

References

Abd-Rabou, A.A., Ahmed, H.H., Shalby, A.B., 2020. Selenium overcomes doxorubicin resistance in their nano-platforms against breast and colon cancers. Biol. Trace Elem. Res. 193, 377–389.
Abdel-Aziz, A.K., Azab, S.S., Youssef, S.S., El-Sayed, A.M., El-Demerdash, E., Shouman, S., 2015. Modulation of imatinib cytotoxicity by selenite in HCT116 colorectal cancer cells. Basic Clin. Pharmacol. Toxicol. 116, 37–46.
Alcaide, B., Almendros, P., Lázaro-Milla, C., Delgado-Martínez, P., 2018. Divergence in ynone reactivity: atypical cyclization by 3,4-difunctionalization versus rare bis (cyclization). Chem.- A Eur. J. 24, 8186–8194.
Alcolea, V., Plano, D., Karelia, D.N., Palop, J.A., Amin, S., Sanmartín, C., Sharma, A.K., 2016. Novel seleno- and thio-urea derivatives with potent *in vitro* activities against several cancer cell lines. Eur. J. Med. Chem. 113, 134–144.
Alcolea, V., Karelia, D.N., Pandey, M.K., Plano, D., Singh, P., Palop, J.A., Amin, S., Sanmartín, C., Sharma, A.K., 2019. Identification of a novel quinoxaline-isoselenourea targeting the STAT3 pathway as a potential melanoma therapeutic. Int. J. Mol. Sci. 20, 521.
Alcolea, V., Pérez-Silanes, S., 2020. Selenium as an interesting option for the treatment of Chagas disease: a review. Eur. J. Med. Chem. 206, 112673.
Ali, W., Álvarez-Pérez, M., Marć, M.A., Salardón-Jiménez, N., Handzlik, J., Domínguez-Álvarez, E., 2018. The anticancer and chemopreventive activity of selenocyanate-containing compounds. Curr. Pharmacol. Rep. 4, 468–481.
Ali, W., Spengler, G., Kincses, A., Nové, M., Battistelli, C., Latacz, G., Starek, M., Dąbrowska, M., Honkisz-Orzechowska, E., Romanelli, A., Rasile, M.M., Szymańska, E., Jacob, C., Zwergel, C., Handzlik, J., 2020. Discovery of phenylselenoether-hydantoin hybrids as ABCB1 efflux pump modulating agents with cytotoxic and antiproliferative actions in resistant T-lymphoma. Eur. J. Med. Chem. 200, 8186–8194.
Altomare, D.A., Testa, J.R., 2005. Perturbations of the AKT signalling pathway in human cancer. Oncogene 24, 7455–7464.
Assaraf, Y.G., 2006. The role of multidrug resistance efflux transporters in antifolate resistance and folate homeostasis. Drug Resist. Updates 9, 227–246.
Assaraf, Y.G., Leamon, C.P., Reddy, J.A., 2014. The folate receptor as a rational therapeutic target for personalized cancer treatment. Drug Resist. Updates 17, 89–95.
Assaraf, Y.G., Brozovic, A., Gonçalves, A.C., Jurkovicova, D., Linē, A., Machuqueiro, M., Saponara, S., Sarmento-Ribeiro, A.B., Xavier, C.P.R., Vasconcelos, M.H., 2019. The multi-factorial nature of clinical multidrug resistance in cancer. Drug Resist. Updates 46, 100645.
Avery, J.C., Hoffmann, P.R., 2018. Selenium, selenoproteins, and immunity. Nutrients 10, 1203.
Ba, L.A., Döring, M., Jamier, V., Jacob, C., 2010. Tellurium: an element with great biological potency and potential. Org. Biomol. Chem. 8, 4203–4216.
Bao, P., Chen, S.C., Xiao, K.Q., 2015. Dynamic equilibrium of endogenous selenium nanoparticles in selenite-exposed cancer cells: a deep insight into the interaction between endogenous SeNPs and proteins. Mol. BioSyst. 11, 3355–3361.
Bapat, P., Sewell, D.G., Boylan, M., Sharma, A.K., Spallholz, J.E., 2021. *In vitro* cytotoxicity of trastuzumab (Tz) and Se-trastuzumab (Se-Tz) against the Her/2 breast cancer cell lines JIMT-1 and BT-474. Int. J. Mol. Sci. 22, 4655.
Bar-Zeev, M., Livney, Y.D., Assaraf, Y.G., 2017. Targeted nanomedicine for cancer therapeutics: towards precision medicine overcoming drug resistance. Drug Resist. Updates 31, 15–30.
Barbanente, A., Nadar, R.A., Esposti, L.D., Palazzo, B., Iafisco, M., van den Beucken, J.J. J.P., Leeuwenburgh, S.C.G., Margiotta, N., 2020. Platinum-loaded, selenium-doped hydroxyapatite nanoparticles selectively reduce proliferation of prostate and breast cancer cells co-cultured in the presence of stem cells. J. Mater. Chem. B 8, 2792–2804.
Barbanente, A., Palazzo, B., Esposti, L.D., Adamiano, A., Iafisco, M., Ditaranto, N., Migoni, D., Gervaso, F., Nadar, R., Ivanchenko, P., Leeuwenburgh, S., Margiotta, N., 2021. Selenium-doped hydroxyapatite nanoparticles for potential application in bone tumor therapy. J. Inorg. Biochem. 215, 111334.
Bartolini, D., Sancineto, L., Fabro de Bem, A., Tew, K.D., Santi, C., Radi, R., Toquato, P., Galli, F., 2017. Selenocompounds in cancer therapy: an overview. Adv. Cancer Res. 136, 259–302.
Battacharyya, P., Woollins, J.D., 2001. Selenocarbonyl synthesis using Woollins reagent. Tetrahedron Lett. 42, 5949–5951.
Bayat Mokhtari, R., Homayouni, T.S., Baluch, N., Morgatskaya, E., Kumar, S., Das, B., Yeger, H., 2017. Combination therapy in combating cancer. Oncotarget 8, 38022–38043.
Berzelius, J.J., 1818. Chemische Entdeckungen im Mineralreiche, gematch zu Fahlun in Schweden: Selenium ein neuer metallartiger Körper, Lithon ein neues Alkali, Thorina eine neue Erde. Annalen der Physik 59, 229–254.
Björkhem-Bergman, L., Jönsson, K., Eriksson, L.C., Olsson, J.M., Lehmann, S., Paul, C., Björnsted, M., 2002. Drug-resistant human lung cancer cells are more sensitive to selenium cytotoxicity. Effects on thioredoxin reductase and glutathione reductase. Biochem. Pharmacol. 63, 1875–1884.
Brodsky, M., Halpert, G., Albeck, M., Sredni, B., 2010. The anti-inflammatory effects of the tellurium redox modulating compound, AS101, are associated with regulation of NFkappaB signaling pathway and nitric oxide induction in macrophages. J. Inflamm. 7, 3.
Burk, R.F., Hill, K.E., 2015. Regulation of selenium metabolism and transport. Ann. Rev. Nutr. 35, 109–134.
Caffrey, P., Frenkel, G.D., 2012. Selenite enhances and prolongs the efficacy of cisplatin treatment of human ovarian tumor xenografts. In vivo 26, 549–552.

Cai, Y., Lu, J., Miao, Z., Lin, L., Ding, J., 2007. Reactive oxygen species contribute to cell killing and P-glycoprotein downregulation by salvicine in multidrug resistant K562/A02 cells. Cancer Biol. Ther. 6, 1794–1799.
Cao, S., Durrani, F.A., Rustum, Y.M., 2004. Selective modulation of the therapeutic efficacy of anticancer drugs by selenium containing compounds against human tumor xenografts. Clin. Cancer Res. 10, 2561–2569.
Cao, X., Hou, J., An, Q., Assaraf, Y.G., Wang, X., 2020. Towards the overcoming of anticancer drug resistance mediated by p53 mutations. Drug Resist. Updates 49, 100671.
Castellucci Estevam, E., Witek, K., Faulstich, L., Nasim, M.J., Latacz, G., Domínguez-Álvarez, E., Kieć-Kononowicz, K., Demasi, M., Handzlik, J., Jacob, C., 2015. Aspects of a distinct cytotoxicity of selenium salts and organic selenides in living cells with possible implications for drug design. Molecules 20, 13894–13912.
Chakraborty, P., Roy, S.S., Bhattacharya, S., 2015. Molecular mechanism behind the synergistic activity of diphenylmethyl selenocyanate and Cisplatin against murine tumor model. Anticancer Agents Med. Chem. 15, 501–510.
Chang, C.H., Bijian, K., Wernic, D., Su, J., da Silva, S.D., Yu, H., Qiu, D., Asslan, M., Alaoui-Jamali, M.A., 2019. A novel orally available seleno-purine molecule suppresses triple-negative breast cancer cell proliferation and progression to metastasis by inducing cytostatic autophagy. Autophagy 15, 1376–1390.
Chen, T., Liu, Y., Zheng, W.J., Liu, J., Wong, Y.S., 2010. Ruthenium polypyridyl complexes that induce mitochondria-mediated apoptosis in cancer cells. Inorg. Chem. 49, 6366–6368.
Chen, Y.C., Prabhu, K.S., Mastro, A.M., 2013. Is selenium a potential treatment for cancer metastasis? Nutrients 5, 1149–1168.
Chen, Q., Yu, Q., Liu, Y., Bhavsar, D., Yang, L., Ren, X., Sun, D., Zheng, W., Liu, J., Chen, L.M., 2015. Multifunctional selenium nanoparticles: chiral selectivity of delivering MDR-siRNA for reversal of multidrug resistance and real-time biofluorescence imaging. Nanomed. Nanotechnol. Biol. Med. 11, 1773–1784.
Chen, M., Yin, H., Bai, P., Miao, P., Deng, X., Xu, Y., Hu, J., Yin, J., 2016. ABC transporters affect the elimination and toxicity of CdTe quantum dots in liver and kidney cells. Toxicol. Appl. Pharmacol. 15, 11–20.
Chen, Q., Xu, M., Zheng, W., Xu, T., Deng, H., Liu, J., 2017. Se/Ru-decorated porous metal-organic framework nanoparticles for the delivery of pooled siRNAs to reversing multidrug resistance in taxol-resistant breast cancer cells. ACS Appl. Mater. Interfaces 9, 6712–6724.
Chen, F., Zhang, X.H., Hu, X.D., Liu, P.D., Zhang, H.Q., 2018. The effects of combined selenium nanoparticles and radiation therapy on breast cancer cells *in vitro*. Artificial Cells. Artif. Cells Nanomed. Biotechnol. 46, 937–948.
Chen, S., Xing, C., Huang, D., Zhou, C., Ding, B., Guo, Z., Peng, Z., Wang, D., Zhu, X., Liu, S., Cai, Z., Wu, J., Zhao, J., Wu, Z., Zhang, Y., Wei, C., Yan, Q., Wang, H., Fan, D., Liu, L., Zhang, H., Cao, Y., 2020. Eradication of tumor growth by delivering novel photothermal selenium-coated tellurium nanoheterojunctions. Sci. Adv. 6, 6825.
Chen, S., Zhao, Y., Liu, S., Zhang, J., Assaraf, Y.G., Cui, W., Wang, L., 2022. Epigenetic enzyme mutations as mediators of anti-cancer drug resistance. Drug Resist. Updates 61, 100821.
Cho, Y., Lim, Y.K., 2020. Cancer stem cells as a potential target to overcome multidrug resistance. Front. Oncol. 10, 764.
Choi, A.-R., Jo, M.J., Jung, M.-J., Kim, H.S., Yoon, S., 2015. Selenate specifically sensitizes drug-resistant cancer cells by increasing apoptosis via G2 phase cell cycle arrest without P-GP inhibition. Eur. J. Pharmacol. 764, 63–69.
Chu, M., Pan, X., Zhang, D., Wu, Q., Peng, J., Hai, W., 2012. The therapeutic efficacy of CdTe and CdSe quantum dots for photothermal cancer therapy. Biomaterials 33, 7071–7083.
Cohen, L., Livney, Y.D., Assaraf, Y.G., 2021. Targeted nanomedicine modalities for prostate cancer treatment. Drug Resist. Updates 56, 100762.
Collery, P., Bastian, G., Santoni, F., Mohsen, A., Wei, M., Collery, T., Tomas, A., Desmaele, D., D'Angelo, J., 2014. Uptake and efflux of rhenium in cells exposed to rhenium diseleno-ether and tissue distribution of rhenium and selenium after rhenium diseleno-ether treatment in mice. Anticancer Res. 34, 1679–1689.
Collery, P., Mohsen, A., Kermagoret, A., Corre, S., Bastian, G., Tomas, A., Wei, M., Santoni, F., Guerra, N., Desmaële, D., d'Angelo, J., 2015. Antitumor activity of a rhenium (I)-diselenoether complex in experimental models of human breast cancer. Investig. New Drugs 33, 848–860.
Collery, P., Santoni, F., Ciccolini, J., Tran, T.N., Mohsen, A., Desmaele, D., 2016. Dose effect of rhenium (i)-diselenoether as anticancer drug in resistant breast tumor-bearing mice after repeated administrations. Anticancer Res. 36, 6051–6057.
Collery, P., Veena, V., Harikrishnan, A., Desmaele, D., 2019. The rhenium(I)-diselenoether anticancer drug targets ROS, TGF-beta1, VEGF-A, and IGF-1 in an *in vitro* experimental model of triple-negative breast cancers. Investig. New Drugs 37, 973–983.
Croce, C.M., 2008. Oncogenes and cancer. N. Engl. J. Med. 358, 502–511.
Csonka, A., Kincses, A., Nové, M., Vadas, Z., Sanmartín, C., Domínguez-Álvarez, E., Spengler, G., 2019. Selenoesters and selenoanhydrides as novel agents against resistant breast cancer. Anticancer Res. 39, 3777–3783.
Cui, J., Jiang, W., Wang, S., Wang, L., Xie, K., 2012. Role of Wnt/β-catenin signaling in drug resistance of pancreatic cancer. Curr. Pharm. Des. 18, 2464–2471.
Cui, Q., Wang, J.Q., Assaraf, Y.G., Ren, L., Gupta, P., Wei, L., Ashby Jr., C.R., Yang, D.H., Chen, Z.S., 2018. Modulating ROS to overcome multidrug resistance in cancer. Drug Resist. Updates 41, 1–25.
Daziano, J.P., Günther, W.H., Krieg, M., Tsujino, I., Miyagi, K., Anderson, G.S., Sampson, R.W., Ostrowski, M.D., Muir, S.A., Bula, R.J., Sieber, F., 2012. Photochemically generated elemental selenium forms conjugates with serum proteins that are preferentially cytotoxic to leukemia and selected solid tumor cells. Photochem. Photobiol. 88, 448–460.
Dean, M., Fojo, T., Bates, S., 2005. Tumour stem cells and drug resistance. Nat. Rev. Cancer 5, 275–284.
De Meio, R.H., O'Leary, D.J., 1975. Proceedings: Hemolysis by tellurium compounds: telluride and tellurate, effect on reduced glutathione. J. Am. Osteopathol. Assoc. 75, 430–431.
DiMeo, T.A., Anderson, K., Phadke, P., Fan, C., Perou, C.M., Naber, S., Kuperwasser, C., 2009. A novel lung metastasis signature links Wnt signaling with cancer cell self-renewal and epithelial-mesenchymal transition in basal-like breast cancer. Cancer Res. 69, 5364–5373.
Domínguez-Álvarez, E., Plano, D., Font, M., Calvo, A., Prior, C., Jacob, C., Palop, J.A., Sanmartín, C., 2014. Synthesis and antiproliferative activity of novel selenoester derivatives. Eur. J. Med. Chem. 73, 153–166.
Domínguez-Álvarez, E., Gajdács, M., Spengler, G., Palop, J.A., Marć, M.A., Kieć-Kononowicz, K., Amaral, L., Molnár, J., Jacob, C., Handzlik, J., Sanmartín, C., 2016. Identification of selenocompounds with promising properties to reverse cancer multidrug resistance. Bioorg. Med. Chem. Lett. 26, 2821–2824.
Douma, S., Van Laar, T., Zevenhoven, J., Meuwissen, R., Van Garderen, E., Peeper, D.S., 2004. Suppression of anoikis and induction of metastasis by the neurotrophic receptor TrkB. Nature 430, 1034–1039.
Du, P., Saidu, N.E., Intemann, J., Jacob, C., Montenarh, M., 2014. A new tellurium-containing amphiphilic molecule induces apoptosis in HCT116 colon cancer cells. Biochim. Biophys. Acta 1840, 1808–1816.
Engelberg, S., Netzer, E., Assaraf, Y.G., Livney, Y.D., 2019. Selective eradication of human non-small cell lung cancer cells using aptamer-decorated nanoparticles harboring a cytotoxic drug cargo. Cell Death Dis. 10, 702.
Engelberg, S., Lin, Y., Assaraf, Y.G., Livney, Y.D., 2021. Targeted nanoparticles harboring jasmine-oil-entrapped paclitaxel for elimination of lung cancer cells. Int. J. Mol. Sci. 22, 1019.
Engman, L., Persson, J., Vessman, K., Ekström, M., Berglund, M., Andersson, C.M., 1995. Organotellurium compounds as efficient retarders of lipid peroxidation in methanol. Free Radic. Biol. Med. 19, 441–452.
Erin, N., Grahovac, J., Brozovic, A., Efferth, T., 2020. Tumor microenvironment and epithelial mesenchymal transition as targets to overcome tumor multidrug resistance. Drug Resist. Updates 53, 100715.
Fan, C., Zheng, W., Fu, X., Li, X., Wong, Y.S., Chen, T., 2014a. Strategy to enhance the therapeutic effect of doxorubicin in human hepatocellular carcinoma by selenocystine, a synergistic agent that regulates the ROS-mediated signalling. Oncotarget 5, 2853–2863.
Fan, C., Zheng, W., Fu, X., Li, X., Wong, Y.S., Chen, T., 2014b. Enhancement of auranofin-induced lung cancer cell apoptosis by selenocystine, a natural inhibitor of TrxR1 *in vitro* and *in vivo*. Cell Death Dis. 5, 1191.
Fang, W., Han, A., Bi, X., Xiong, B., Yang, W., 2010. Tumor inhibition by sodium selenite is associated with activation of c-Jun NH2-terminal kinase 1 and suppression of beta-catenin signaling. Int. J. Cancer 127, 32–42.
Fairweather-Tait, S.J., Bao, Y., Broadley, M.R., Collings, R., Ford, D., Hesketh, J.E., Hurst, R., 2011. Selenium in human health and disease. Antioxid. Redox Signal. 14, 1337–1383.
Ferreira, J.A., Peixoto, A., Neves, M., Gaiteiro, C., Reis, C.A., Assaraf, Y.G., Santos, L.L., 2016. Mechanisms of cisplatin resistance and targeting of cancer stem cells: adding glycosylation to the equation. Drug Resist. Updates 24, 34–54.
Fletcher, J.I., Haber, M., Henderson, M.J., Norris, M.D., 2010. ABC transporters in cancer: more than just drug efflux pumps. Nat. Rev. Cancer 10, 147–156.
Fu, J.N., Li, J., Tan, Q., Yin, H.W., Xiong, K., Wang, T.Y., Ren, X.Y., Zeng, H.H., 2011. Thioredoxin reductase inhibitor ethaselen increases the drug sensitivity of the colon cancer cell line LoVo towards cisplatin via regulation of G1 phase and reversal of G2/M phase arrest. Investig. New Drugs 29, 627–636.
Fulawka, L., Donizy, P., Halon, A., 2014. Cancer stem cells–the current status of an old concept: literature review and clinical approaches. Biol. Res. 47, 66.
Gacche, R.N., Assaraf, Y.G., 2018. Redundant angiogenic signaling and tumor drug resistance. Drug Resist. Updates 36, 47–76.
Gaete-Argel, A., Velásquez, F., Márquez, C.L., Rojas-Araya, B., Bueno-Nieto, C., Marín-Rojas, J., Cuevas-Zúñiga, M., Soto-Rifo, R., Valiente-Echeverría, F., 2021. Tellurite promotes stress granules and nuclear SG-like assembly in response to oxidative stress and DNA damage. Front. Cell Dev. Biol. 9, 622057.
Gajdács, M., Spengler, G., Sanmartín, C., Marć, M.A., Handzlik, J., Domínguez-Álvarez, E., 2017. Selenoesters and selenoanhydrides as novel multidrug resistance reversing agents: a confirmation study in a colon cancer MDR cell line. Bioorg. Med. Chem. Lett. 27, 797–802.
Gajdács, M., Nové, M., Csonka, Á., Varga, B., Sanmartín, C., Domínguez-Álvarez, E., Spengler, G., 2020. Phenothiazines and selenocompounds: a potential novel combination therapy of multidrug resistant cancer. Anticancer Res. 40, 4921–4928.
Gao, F., Yuan, Q., Gao, L., Cai, P., Zhu, H., Liu, R., Wang, Y., Wei, Y., Huang, G., Liang, J., Gao, X., 2014. Cytotoxicity and therapeutic effect of irinotecan combined with selenium nanoparticles. Biomaterials 35, 8854–8866.
Gharbavi, M., Johari, B., Mousazadeh, N., Rahimi, B., Leilan, M.P., Eslami, S.S., Sharafi, A., 2020. Hybrid of niosomes and bio-synthesized selenium nanoparticles as a novel approach in drug delivery for cancer treatment. Mol. Biol. Rep. 47, 6517–6529.
Gibson, S.L., Hilf, R., Donnelly, D.J., Detty, M.R., 2004. Analogues of tetramethylrosamine as transport molecules for and inhibitors of P-glycoprotein-mediated multidrug resistance. Bioorg. Med. Chem. 12, 4625–4631.
Goler-Baron, V., Assaraf, Y.G., 2012. Overcoming multidrug resistance via photodestruction of ABCG2-rich extracellular vesicles sequestering photosensitive chemotherapeutics. PLOS One 7, 35487.
Gonen, N., Assaraf, Y.G., 2012. Antifolates in cancer therapy: structure, activity and mechanisms of drug resistance. Drug Resist. Updates 15, 183–210.

Gross, M., Stanciu, E., Kenigsbuch-Sredni, D., Sredni, B., Pinhasov, A., 2017. The immunomodulatory tellurium compound ammonium trichloro (dioxoethylene-O,O') tellurate reduces anxiety-like behavior and corticosterone levels of submissive mice. Behav. Pharmacol. 28, 458–465.
Gunther, W.H.H., Searle, R., Sieber, F., 1992. Photosensitizing merocyanine dyes based on selenobarbituric acid. Phosphorus, Sulfur Silicon Relat. Elem. 67, 417–424.
Gupta, G.P., Nguyen, D.X., Chiang, A.C., Bos, P.D., Kim, J.Y., Nadal, C., Gomis, R.R., Manova-Todorova, K., Massagué, J., 2007. Mediators of vascular remodelling co-opted for sequential steps in lung metastasis. Nature 446, 765–770.
Gupta, S.C., Hevia, D., Patchva, S., Park, B., Koh, W., Aggarwal, B.B., 2012. Upsides and downsides of reactive oxygen species for cancer: the roles of reactive oxygen species in tumorigenesis, prevention, and therapy. Antioxid. Redox Signal. 16, 1295–1322.
Halpert, G., Sredni, B., 2014. The effect of the novel tellurium compound AS101 on autoimmune diseases. Autoimmun. Rev. 13, 1230–1235.
Hariharan, S., Dharmaraj, S., 2020. Selenium and selenoproteins: it's role in regulation of inflammation. Inflammopharmacology 28, 667–695.
He, J., Li, D., Xiong, K., Ge, Y., Jin, H., Zhang, G., Hong, M., Tian, Y., Yin, J., Zeng, H., 2012. Inhibition of thioredoxin reductase by a novel series of bis-1,2-benzisoselenazol-3(2H)-ones: organoselenium compounds for cancer therapy. Bioorg. Med. Chem. 20, 3816–3827.
Hill, J.E., Linder, M.K., Davies, K.S., Sawada, G.A., Morgan, J., Ohulchanskyy, T.Y., Detty, M.R., 2014. Selenorhodamine photosensitizers for photodynamic therapy of P-glycoprotein-expressing cancer cells. J. Med. Chem. 57, 8622–8634.
Holt, J.J., Gannon 2nd, M.K., Tombline, G., McCarty, T.A., Page, P.M., Bright, F.V., Detty, M.R., 2006. A cationic chalcogenoxanthylium photosensitizer effective *in vitro* in chemosensitive and multidrug-resistant cells. Bioorg. Med. Chem. 14, 8635–8643.
Hu, W., Ma, Y., Zhao, C., Yin, S., Hu, H., 2021a. Methylseleninic acid overcomes programmed death-ligand 1-mediated resistance of prostate cancer and lung cancer. Mol. Carcinog. 60, 746–757.
Hu, J., Jiang, Y., Tan, S., Zhu, K., Cai, T., Zhan, T., He, S., Chen, F., Zhang, C., 2021b. Selenium-doped calcium phosphate biomineral reverses multidrug resistance to enhance bone tumor chemotherapy. Nanomed. Nanotechnol. Biol. Med. 32, 102322.
Huang, Y., He, L., Liu, W., Fan, C., Zheng, W., Wong, Y.S., Chen, T., 2013. Selective cellular uptake and induction of apoptosis of cancer-targeted selenium nanoparticles. Biomaterials 34, 7106–7116.
Huang, B., Liu, H., Huang, D., Mao, X., Hu, X., Jiang, C., Pu, M., Zhang, G., Zeng, X., 2016. Apoptosis induction and imaging of cadmium-telluride quantum dots with wogonin in multidrug-resistant leukemia K562/A02 cell. J. Nanosci. Nanotechnol. 16, 2499–2503.
Huang, W., Chen, Z., Hou, L., Feng, P., Li, Y., Chen, T., 2020. Adjusting the lipid-water distribution coefficient of iridium(III) complexes to enhance the cellular penetration and treatment efficacy to antagonize cisplatin resistance in cervical cancer. Dalton Trans. 49, 11556–11564.
Ibáñez, E., Agliano, A., Prior, C., Nguewa, P., Redrado, M., González-Zubeldia, I., Plano, D., Palop, J.A., Sanmartín, C., Calvo, A., 2012. The quinoline imidoselenocarbamate EI201 blocks the AKT/mTOR pathway and targets cancer stem cells leading to a strong antitumor activity. Curr. Med. Chem. 19, 3031–3043.
Ignjatović, N.L., Ninkov, P., Sabetrasekh, R., Lyngstadaas, S.P., Uskoković, D.P., 2014. *In vitro* evaluation of a multifunctional nano drug delivery system based on tigecycline-loaded calcium-phosphate/ poly-DL-lactide-co-glycolide. Bio-Med. Mater. Eng. 24, 1647–1658.
Jastrzebski, Z., Czyzewska-Szafran, H., Fijatek, Z., Suchocki, P., Fitak, B.A., 1995. Toxicity studies of a new selenium compound, Selol, in rats. Drugs Exp. Clin. Res. 21, 217–220.
Jiang, Y.G., Luo, Y., He, D.L., Li, X., Zhang, L.L., Peng, T., Li, M.C., Lin, Y.H., 2007. Role of Wnt/beta-catenin signaling pathway in epithelial-mesenchymal transition of human prostate cancer induced by hypoxia-inducible factor-1alpha. Int. J. Urol. 14, 1034–1039.
Jiang, T., Chen, X., Ren, X., Yang, J.M., Cheng, Y., 2021. Emerging role of autophagy in anti-tumor immunity: Implications for the modulation of immunotherapy resistance. Drug Resist. Updates 56, 100752.
Kalishwaralal, K., Jeyabharathi, S., Sundar, K., Muthukumaran, A., 2016. A novel one-pot green synthesis of selenium nanoparticles and evaluation of its toxicity in zebrafish embryos. Artif. Cells Nanomed. Biotechnol. 44, 471–477.
Kang, Y., Nian, H., Rajendran, P., Kim, E., Dashwood, W.M., Pinto, J.T., Boardman, L.A., Thibodeau, S.N., Limburg, P.J., Löhr, C.V., Bisson, W.H., Williams, D.E., Ho, E., Dashwood, R.H., 2014. HDAC8 and STAT3 repress BMF gene activity in colon cancer cells. Cell Death Dis. 5, 1476.
Kermagoret, A., Morganta, G., d'Angelo, J., Tomas, A., Roussel, P., Bastian, G., Collery, P., Desmaële, D., 2011. Synthesis, structural characterization and biological activity against several human tumor cell lines of four rhenium(I) diseleno-ethers complexes: $Re(CO)_3Cl(PhSe(CH_2)_2SePh)$, $Re(CO)_3Cl(PhSe(CH_2)_3SePh)$, $Re(CO)_3Cl(HO_2C–CH_2Se(CH_2)_2SeCH_2–CO_2H)$ and $Re(CO)_3Cl(HO_2C–CH_2Se(CH_2)_3SeCH_2–CO_2H)$. Polyhedron 30, 347–353.
Kessenbrock, K., Plaks, V., Werb, Z., 2010. Matrix metalloproteinases: regulators of the tumor microenvironment. Cell 141, 52–67.
Kharma, A., Misak, A., Grman, M., Brezova, V., Kurakova, L., Baráth, P., Jacob, C., Chovanec, M., Ondrias, K., Domínguez-Álvarez, E., 2019. Release of reactive selenium species from phthalic selenoanhydride in the presence of hydrogen sulfide and glutathione with implications for cancer research. N. J. Chem. 43, 11771–11783.
Kholodenko, B.N., Birtwistle, M.R., 2009. Four-dimensional dynamics of MAPK information processing systems. Wiley Interdiscip. Rev. Syst. Biol. Med. 1, 28–44.
Kim, S.J., Choi, M.C., Park, J.M., Chung, A.S., 2021. Antitumor effects of selenium. Int. J. Mol. Sci. 22, 11844.
Kloc, K., Młochowski, J., Syper, L., 1989. Oxidation of organic diselenides with hydrogen peroxide to alkane- and areneseleninic acids and selenium-containing heterocycles. Liebigs Annalen der Chemie 8, 811–813.
Koren, E., Fuchs, Y., 2016. The bad seed: Cancer stem cells in tumor development and resistance. Drug Resist. Updates 28, 1–12.
Kryman, M.W., Schamerhorn, G.A., Hill, J.E., Calitree, B.D., Davies, K.S., Linder, M.K., Ohulchanskyy, T.Y., Detty, M.R., 2014. Synthesis and properties of heavy chalcogen analogues of the Texas reds and related rhodamines. Organometallics 33, 2628–2640.
Lai, T., Collins, C.M., Hall, P., Morgan, A.P., Smith, P.J., Stonebridge, B.R., Symes, M.O., 1993. Verapamil enhances doxorubicin activity in cultured human renal carcinoma cells. Eur. J. Cancer 29A, 378–383.
Layani-Bazar, A., Skornick, I., Berrebi, A., Pauker, M.H., Noy, E., Silberman, A., Albeck, M., Longo, D.L., Kalechman, Y., Sredni, B., 2014. Redox modulation of adjacent thiols in VLA-4 by AS101 converts myeloid leukemia cells from a drug-resistant to drug-sensitive state. Cancer Res. 74, 3092–3103.
Lee, J.I., Nian, H., Cooper, A.J., Sinha, R., Dai, J., Bisson, W.H., Dashwood, R.H., Pinto, J. T., 2009. Alpha-keto acid metabolites of naturally occurring organoselenium compounds as inhibitors of histone deacetylase in human prostate cancer cells. Cancer Prev. Res. 2, 683–693.
LeGeros, R.Z., 2008. Calcium phosphate-based osteoinductive materials. Chem. Rev. 108, 4742–4753.
Lepeltier, E., Rijo, P., Rizzolio, F., Popovtzer, R., Petrikaite, V., Assaraf, Y.G., Passirani, C., 2020. Nanomedicine to target multidrug resistant tumors. Drug Resist. Updates 52, 100704.
Li, S., Zhou, Y., Wang, R., Zhang, H., Dong, Y., Ip, C., 2007. Selenium sensitizes MCF-7 breast cancer cells to doxorubicin-induced apoptosis through modulation of phospho-Akt and its downstream substrates. Mol. Cancer Ther. 6, 1031–1038.
Li, Z., Carrier, L., Rowan, B.G., 2008. Methylseleninic acid synergizes with tamoxifen to induce caspase-mediated apoptosis in breast cancer cells. Mol. Cancer Ther. 7, 3056–3063.
Li, Q., Shu, Y., 2014. Role of solute carriers in response to anticancer drugs. Mol. Cell. Ther. 2, 15.
Li, W., Zhang, H., Assaraf, Y.G., Zhao, K., Xu, X., Xie, J., Yang, D.H., Chen, Z.S., 2016. Overcoming ABC transporter-mediated multidrug resistance: Molecular mechanisms and novel therapeutic drug strategies. Drug Resist. Updates 27, 14–29.
Likus, W., Siemianowicz, K., Bieńk, K., Pakuła, M., Pathak, H., Dutta, C., Wang, Q., Shojaei, S., Assaraf, Y.G., Ghavami, S., Cieślar-Pobuda, A., Łos, M.J., 2016. Could drugs inhibiting the mevalonate pathway also target cancer stem cells? Drug Resist. Updates 25, 13–25.
Liou, G.Y., Storz, P., 2010. Reactive oxygen species in cancer. Free Radic. Res. 44, 479–496.
Liu, Y., Sun, J., Rao, S., Su, Y., Li, J., Li, C., Xu, S., Yang, Y., 2013. Antidiabetic activity of mycelia selenium-polysaccharide from Catathelasma ventricosum in STZ-induced diabetic mice. Food Chem. Toxicol. 62, 285–291.
Liu, T., Zeng, L., Jiang, W., Fu, Y., Zheng, W., Chen, T., 2015. Rational design of cancer-targeted selenium nanoparticles to antagonize multidrug resistance in cancer cells. Nanomed. Nanotechnol. Biol. Med. 11, 947–958.
Livney, Y.D., Assaraf, Y.G., 2013. Rationally designed nanovehicles to overcome cancer chemoresistance. Adv. Drug Deliv. Rev. 65, 1716–1730.
Luesakul, U., Puthong, S., Neamati, N., Muangsin, N., 2018. pH-responsive selenium nanoparticles stabilized by folate-chitosan delivering doxorubicin for overcoming drug-resistant cancer cells. Carbohydr. Polym. 181, 841–850.
Luo, H., Yang, Y., Huang, F., Li, F., Jiang, Q., Shi, K., Xu, C., 2012. Selenite induces apoptosis in colorectal cancer cells via AKT-mediated inhibition of β-catenin survival axis. Cancer Lett. 315, 78–85.
Manzanares, W., Langlois, P.L., Heyland, D.K., 2015. Pharmaconutrition with selenium in critically ill patients: what do we know? Nutr. Clin. Pract. 30, 34–43.
Marć, M.A., Kincses, A., Rácz, B., Nasim, M.J., Sarfraz, M., Lázaro-Milla, C., Domínguez-Álvarez, E., Jacob, C., Spengler, G., Almendros, P., 2020. Antimicrobial, anticancer and multidrug-resistant reversing activity of novel oxygen-, sulfur- and selenoflavones and bioisosteric analogues. Pharmaceuticals 13, 453.
Martínez, L., Arnaud, O., Henin, E., Tao, H., Chaptal, V., Doshi, R., Andrieu, T., Dussurgey, S., Tod, M., Di Pietro, A., Zhang, Q., Chang, G., Falson, P., 2014. Understanding polyspecificity within the substrate-binding cavity of the human multidrug resistance P-glycoprotein. FEBS J. 281, 673–682.
Martins, I.L., Charneira, C., Gandin, V., Ferreira da Silva, J.L., Justino, G.C., Telo, J.P., Vieira, A.J., Marzano, C., Antunes, A.M., 2015. Selenium-containing chrysin and quercetin derivatives: attractive scaffolds for cancer therapy. J. Med. Chem. 58, 4250–4265.
Marusyk, A., Polyak, K., 2010. Tumor heterogeneity: causes and consequences. Biochim. Biophys. Acta 1805, 105–117.
Matejczyk, M., Świderski, G., Świsłocka, R., Rosochacki, S.J., Lewandowski, W., 2018. Seleno-l-methionine and l-ascorbic acid differentiate the biological activity of doxorubicin and its metal complexes as a new anticancer drugs candidate. J. Trace Elem. Med. Biol. 48, 141–148.
Matsunaga, T., Takemoto, N., Sato, T., Takimoto, R., Tanaka, I., Fujimi, A., Akiyama, T., Kuroda, H., Kawano, Y., Kobune, M., Kato, J., Hirayama, Y., Sakamaki, S., Kohda, K., Miyake, K., Niitsu, Y., 2003. Interaction between leukemic-cell VLA-4 and stromal fibronectin is a decisive factor for minimal residual disease of acute myelogenous leukemia. Nat. Med. 9, 1158–1165.
Medina-Cruz, D., Vernet-Crua, A., Mostafavi, E., González, M.U., Martínez, L., Jones III., A.A.D., Kusper, M., Sotelo, E., Gao, M., Geoffrion, L.D., Shah, V., Guisbiers, G., Cholula-Díaz, J.L., Guillermier, C., Khanom, F., Huttel, Y., García-Martín, J.M., Webster, T.J., 2021. Aloe vera-mediated Te nanostructures: highly

potent antibacterial agents and moderated anticancer effects. Nanomaterials 11, 514.
Menon, S., Shrudhi Devi, K.S., Santhiya, R., Rajeshkumar, S., Venkat Kumar, S., 2018. Selenium nanoparticles: a potent chemotherapeutic agent and an elucidation of its mechanism. Coll. Surf. B Biointerfaces 170, 280–292.
Menon, S., Shanmugam, V.K., 2020. Chemopreventive mechanism of action by oxidative stress and toxicity induced surface decorated selenium nanoparticles. J. Trace Elem. Med. Biol. 62, 126549.
Misra, S., Boylan, M., Selvam, A., Spallholz, J.E., Björnstedt, M., 2015. Redox-active selenium compounds–from toxicity and cell death to cancer treatment. Nutrients 7, 3536–3556.
Moreno, E., Doughty-Shenton, D., Plano, D., Font, M., Encío, I., Palop, J.A., Sanmartín, C., 2014. A dihydroselenoquinazoline inhibits S6 ribosomal protein signalling, induces apoptosis and inhibits autophagy in MCF-7 cells. Eur. J. Pharm. Sci. 63, 87–95.
Moretti, L., Yang, E.S., Kim, K.W., Lu, B., 2007. Autophagy signaling in cancer and its potential as novel target to improve anticancer therapy. Drug Resist. Updates 10, 135–143.
Mosca, L., Ilari, A., Fazi, F., Assaraf, Y.G., Colotti, G., 2021. Taxanes in cancer treatment: activity, chemoresistance and its overcoming. Drug Resist. Updates 54, 100742.
Mosolygó, T., Kincses, A., Csonka, A., Tönki, Á.S., Witek, K., Sanmartín, C., Marć, M.A., Handzlik, J., Kieć-Kononowicz, K., Domínguez-Álvarez, E., Spengler, G., 2019. Selenocompounds as novel antibacterial agents and bacterial efflux pump inhibitors. Molecules 24, 1487.
Navarro-Alarcon, M., Cabrera-Vique, C., 2008. Selenium in food and the human body: a review. Sci. Total Environ. 400, 115–141.
Nguyen, N., Sharma, A., Nguyen, N., Sharma, A.K., Desai, D., Huh, S.J., Amin, S., Meyers, C., Robertson, G.P., 2011. Melanoma chemoprevention in skin reconstructs and mouse xenografts using isoselenocyanate-4. Cancer Prev. Res. 4, 248–258.
Nishikawa, M., 2008. Reactive oxygen species in tumor metastasis. Cancer Lett. 266, 54–59.
Nishina, A., Kimura, H., Kozawa, K., Sommen, G., Nakamura, T., Heimgartner, H., Koketsu, M., Furukawa, S., 2011. A superoxide anion-scavenger, 1,3-selenazolidin-4-one suppresses serum deprivation-induced apoptosis in PC12 cells by activating MAP kinase. Toxicol. Appl. Pharmacol. 257, 388–395.
Nitulescu, G.M., Van De Venter, M., Nitulescu, G., Ungurianu, A., Juzenas, P., Peng, Q., Olaru, O.T., Grădinaru, D., Tsatsakis, A., Tsoukalas, D., Spandidos, D.A., Margina, D., 2018. The Akt pathway in oncology therapy and beyond (Review). Int. J. Oncol. 53, 2319–2331.
Nomura, S., Morimoto, Y., Tsujimoto, H., Arake, M., Harada, M., Saitoh, D., Hara, I., Ozeki, E., Satoh, A., Takayama, E., Hase, K., Kishi, Y., Ueno, H., 2020. Highly reliable, targeted photothermal cancer therapy combined with thermal dosimetry using a near-infrared absorbent. Sci. Rep. 10, 9765.
Nussinov, R., Tsai, C.J., Jang, H., 2021. Anticancer drug resistance: an update and perspective. Drug Resist. Updates 59, 100796.
Ohkawa, K., Tsukada, Y., Dohzono, H., Koike, K., Terashima, Y., 1988. The effects of co-administration of selenium and cis-platin (CDDP) on CDDP-induced toxicity and antitumour activity. Br. J. Cancer 58, 38–41.
Olm, E., Fernandes, A.P., Hebert, C., Rundlöf, A.K., Larsen, E.H., Danielsson, O., Björnstedt, M., 2009. Extracellular thiol-assisted selenium uptake dependent on the x (c)- cystine transporter explains the cancer-specific cytotoxicity of selenite. Proc. Natl. Acad. Sci. USA 106, 11400–11405.
Pecoraro, C., Faggion, B., Balboni, B., Carbone, D., Peters, G.J., Diana, P., Assaraf, Y.G., Giovannetti, E., 2021. GSK3β as a novel promising target to overcome chemoresistance in pancreatic cancer. Drug Resist. Updates 58, 100779.
Pelicano, H., Carney, D., Huang, P., 2004. ROS stress in cancer cells and therapeutic implications. Drug Resist. Updates 7, 97–110.
Phi, L.T.H., Sari, I.N., Yang, Y.G., Lee, S.H., Jun, N., Kim, K.S., Lee, Y.K., Kwon, H.Y., 2018. Cancer stem cells (CSCs) in drug resistance and their therapeutic implications in cancer treatment. Stem Cells Int. 2018, 5416923.
Piskounova, E., Agathocleous, M., Murphy, M.M., Hu, Z., Huddlestun, S.E., Zhao, Z., Leitch, A.M., Johnson, T.M., DeBerardinis, R.J., Morrison, S.J., 2015. Oxidative stress inhibits distant metastasis by human melanoma cells. Nature 527, 186–191.
Plano, D., Ibáñez, E., Calvo, A., Palop, J.A., Sanmartín, C., 2011. Novel library of selenocompounds as kinase modulators. Molecules 16, 6349–6364.
Pluchino, K.M., Hall, M.D., Goldsborough, A.S., Callaghan, R., Gottesman, M.M., 2012. Collateral sensitivity as a strategy against cancer multidrug resistance. Drug Resist. Updates 15, 98–105.
Poluboyarinov, P.A., Elistratov, D.G., Moiseeva, I.J., 2020. Antitumor activity of selenium and search parameters for its new potentially active derivatives. Russ. J. Bioorg. Chem. 46, 989–1003.
Pons, D.G., Moran, C., Alorda-Clara, M., Oliver, J., Roca, P., Sastre-Serra, J., 2020. Micronutrients selenomethionine and selenocysteine modulate the redox status of MCF-7 breast cancer cells. Nutrients 12, 865.
Poulose, A., Veeranarayanan, S., Mohamed, M.S., Aburto, R.R., Mitcham, T., Bouchard, R.R., Ajayan, P.M., Sakamoto, Y., Maekawa, T., Kumar, D.S., 2016. Multifunctional $Cu_{2-x}Te$ nanocubes mediated combination therapy for multi-drug resistant MDA MB 453. Sci. Rep. 6, 35961.
Pyrzyńska, K., 1998. Speciation of selenium compounds. Anal. Sci. 14, 479–483.
Radomska, D., Czarnomysy, R., Radomski, D., Bielawska, A., Bielawski, K., 2021. Selenium as a bioactive micronutrient in the human diet and its cancer chemopreventive activity. Nutrients 13, 1649.
Rask-Andersen, M., Masuram, S., Fredriksson, R., Schiöth, H.B., 2013. Solute carriers as drug targets: current use, clinical trials and prospective. Mol. Asp. Med. 34, 702–710.
Rayman, M.P., 2000. The importance of selenium to human health. Lancet 356, 233–241.
Rayman, M.P., 2012. Selenium and human health. Lancet 379, 1256–1268.
Raz, S., Sheban, D., Gonen, N., Stark, M., Berman, B., Assaraf, Y.G., 2014. Severe hypoxia induces complete antifolate resistance in carcinoma cells due to cell cycle arrest. Cell Death Dis. 5, 1067.
Raz, S., Stark, M., Assaraf, Y.G., 2016. Folylpoly-γ-glutamate synthetase: a key determinant of folate homeostasis and antifolate resistance in cancer. Drug Resist. Updates 28, 43–64.
Reich, H.J., Hondal, R.J., 2016. Why nature chose selenium. ACS Chem. Biol. 11, 821–841.
Ren, Y., Huang, F., Liu, Y., Yang, Y., Jiang, Q., Xu, C., 2009. Autophagy inhibition through PI3K/Akt increases apoptosis by sodium selenite in NB4 cells. BMB Rep. 42, 599–604.
Rose, A.H., Hoffmann, P.R., 2015. Selenoproteins and cardiovascular stress. Thromb. Haemost. 113, 494–504.
Rooseboom, M., Vermeulen, N.P.E., Durgut, F., Commandeur, J.N.M., 2002. 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. 15, 1610–1618.
Ruberte, A.C., Plano, D., Encío, I., Aydillo, C., Sharma, A.K., Sanmartín, C., 2018. Novel selenadiazole derivatives as selective antitumor and radical scavenging agents. Eur. J. Med. Chem. 157, 14–27.
Sabbah, M., Emami, S., Redeuilh, G., Julien, S., Prévost, G., Zimber, A., Ouelaa, R., Bracke, M., De Wever, O., Gespach, C., 2008. Molecular signature and therapeutic perspective of the epithelial-to-mesenchymal transitions in epithelial cancers. Drug Resist. Updates 11, 123–151.
Saifo, M.S., Rempinski Jr., D.R., Rustum, Y.M., Azrak, R.G., 2010. Targeting the oncogenic protein beta-catenin to enhance chemotherapy outcome against solid human cancers. Mol. Cancer 9, 310.
Sandoval, J.M., Verrax, J., Vásquez, C.C., Buc Calderon, P., 2012. A comparative study of tellurite toxicity in normal and cancer cells. Mol. and Cell. Toxicol. 8, 327–334.
Sandoval, J.M., Levéque, P., Gallez, B., Vásquez, C.C., Buc Calderon, P., 2010. Tellurite-induced oxidative stress leads to cell death of murine hepatocarcinoma cells. Biometals 23, 623–632.
Sanmartín, C., Plano, D., Sharma, A.K., Palop, J.A., 2012. Selenium compounds, apoptosis and other types of cell death: an overview for cancer therapy. Int. J. Mol. Sci. 13, 9649–9672.
Sciarrillo, R., Wojtuszkiewicz, A., Assaraf, Y.G., Jansen, G., Kaspers, G.J.L., Giovannetti, E., Cloos, J., 2020. The role of alternative splicing in cancer: From oncogenesis to drug resistance. Drug Resist. Updates 53, 100728.
Schlesinger, M., Bendas, G., 2015. Contribution of very late antigen-4 (VLA-4) integrin to cancer progression and metastasis. Cancer Metastasis Rev. 34, 575–591.
Shahar, N., Larisch, S., 2020. Inhibiting the inhibitors: targeting anti-apoptotic proteins in cancer and therapy resistance. Drug Resist. Updates 52, 100712.
Shapira, A., Livney, Y.D., Broxterman, H.J., Assaraf, Y.G., 2011. Nanomedicine for targeted cancer therapy: towards the overcoming of drug resistance. Drug Resist. Updates 14, 150–163.
Sharifzad, F., Ghavami, S., Verdi, J., Mardpour, S., Mollapour Sisakht, M., Azizi, Z., Taghikhani, A., Łos, M.J., Fakharian, E., Ebrahimi, M., Hamidieh, A.A., 2019. Glioblastoma cancer stem cell biology: potential theranostic targets. Drug Resist. Updates 42, 35–45.
Sharma, A.K., Kline, C.L., Berg, A., Amin, S., Irby, R.B., 2011. The Akt inhibitor ISC-4 activates prostate apoptosis response protein-4 and reduces colon tumor growth in a nude mouse model. Clin. Cancer Res. 17, 4474–4483.
Shi, X., Wang, J., Lei, Y., Cong, C., Tan, D., Zhou, X., 2019. Research progress on the PI_3K/AKT signaling pathway in gynecological cancer (Review). Mol. Med. Rep. 19, 4529–4535.
Shiah, H.S., Lee, W.S., Juang, S.H., Hong, P.C., Lung, C.C., Chang, C.J., Chou, K.M., Chang, J.Y., 2007. Mitochondria-mediated and p53-associated apoptosis induced in human cancer cells by a novel selenophene derivative, D-501036. Biochem. Pharmacol. 73, 610–619.
Silberman, A., Kalechman, Y., Hirsch, S., Erlich, Z., Sredni, B., Albeck, A., 2016. The anticancer activity of organotelluranes: potential role in integrin inactivation. ChemBioChem 17, 918–927.
Siliprandi, D., Storey, D.T., 1973. Interaction of tellurite with the respiratory chain in rat liver mitochondria. FEBS Lett. 29, 101–104.
Šimoničová, K., Janotka, Ľ., Kavcová, H., Sulová, Z., Breier, A., Messingerova, L., 2022. Different mechanisms of drug resistance to hypomethylating agents in the treatment of myelodysplastic syndromes and acute myeloid leukemia. Drug Resist. Updates 61, 100805.
Smith, A.M., Duan, H., Mohs, A.M., Nie, S., 2008. Bioconjugated quantum dots for *in vivo* molecular and cellular imaging. Adv. Drug Deliv. Rev. 60, 1226–1240.
Soll, M., Chen, Q.C., Zhitomirsky, B., Lim, P.P., Termini, J., Gray, H.B., Assaraf, Y.G., Gross, Z., 2020. Protein-coated corrole nanoparticles for the treatment of prostate cancer cells. Cell Death Discov. 6, 67.
Spengler, G., Gajdács, M., Marć, M.A., Domínguez-Álvarez, E., Sanmartín, C., 2019. Organoselenium compounds as novel adjuvants of chemotherapy drugs-A promising approach to fight cancer drug resistance. Molecules 24, 336.
Sredni, B., Geffen-Aricha, R., Duan, W., Albeck, M., Shalit, F., Lander, H.M., Kinor, N., Sagi, O., Albeck, A., Yosef, S., Brodsky, M., Sredni-Kenigsbuch, D., Sonino, T., Longo, D.L., Mattson, M.P., Yadid, G., 2007. Multifunctional tellurium molecule protects and restores dopaminergic neurons in Parkinson's disease models. FASEB J. 21, 1870–1883.
Steeg, P.S., 2006. Tumor metastasis: mechanistic insights and clinical challenges. Nat. Med. 12, 895–904.
Stiewe, T., Haran, T.E., 2018. How mutations shape p53 interactions with the genome to promote tumorigenesis and drug resistance. Drug Resist. Updates 38, 27–43.

Su, Z., Dong, S., Zhao, S.C., Liu, K., Tan, Y., Jiang, X., Assaraf, Y.G., Qin, B., Chen, Z.S., Zou, C., 2021. Novel nanomedicines to overcome cancer multidrug resistance. Drug Resist. Updates 58, 100777.
Suchocki, P., Misiewicz, I., Skupinska, K., Waclawek, K., Fijalek, Z., Kasprzycka-Guttman, T., 2007. The activity of Selol in multidrug-resistant and sensitive human leukemia cells. Oncol. Rep. 18, 893–899.
Sun, Y., Liu, W.Z., Liu, T., Feng, X., Yang, N., Zhou, H.F., 2015. Signaling pathway of MAPK/ERK in cell proliferation, differentiation, migration, senescence and apoptosis. J. Recept. Signal Transduct. 35, 600–604.
Sun, Y., Zhang, J., Yin, H., Yin, J., 2020. MicroRNA-mediated suppression of P-glycoprotein by quantum dots in lung cancer cells. J. Appl. Toxicol. 40, 525–534.
Sunayama, J., Matsuda, K., Sato, A., Tachibana, K., Suzuki, K., Narita, Y., Shibui, S., Sakurada, K., Kayama, T., Tomiyama, A., Kitanaka, C., 2010. Crosstalk between the PI_3K/mTOR and MEK/ERK pathways involved in the maintenance of self-renewal and tumorigenicity of glioblastoma stem-like cells. Stem Cells 28, 1930–1939.
Sutradhar, K.B., Amin, L., 2014. Nanotechnology in cancer drug delivery and selective targeting. Int. Sch. Res. Notices 2014, 939378.
Szemerédi, N., Dobiasová, S., Salardón-Jiménez, N., Kincses, A., Nové, M., Habibullah, G., Sevilla-Hernández, C., Benito-Lama, M., Alonso-Martínez, F.J., Viktorová, J., Spengler, G., Domínguez-Álvarez, E., 2021. Cyano- and ketone-containing selenoesters as multi-target compounds against resistant cancers. Cancers 13, 4563.
Szulkin, A., Nilsonne, G., Mundt, F., Wasik, A.M., Souri, P., Hjerpe, A., Dobra, K., 2013. Variation in drug sensitivity of malignant mesothelioma cell lines with substantial effects of selenite and bortezomib, highlights need for individualized therapy. PLOS One 8, 65903.
Tian, J., Hu, J., Liu, G., Yin, H., Chen, M., Miao, P., Bai, P., Yin, J., 2019. Altered gene expression of ABC transporters, nuclear receptors and oxidative stress signaling in zebrafish embryos exposed to CdTe quantum dots. Environ. Pollut. 244, 588–599.
Tiekink, E.R.T., 2012. Therapeutic potential of selenium and tellurium compounds: opportunities yet unrealised. Dalton Trans. 41, 6390–6395.
Toubhans, B., Gazze, S.A., Bissardon, C., Bohic, S., Gourlan, A.T., Gonzalez, D., Charlet, L., Conlan, R.S., Francis, L.W., 2020. Selenium nanoparticles trigger alterations in ovarian cancer cell biomechanics. Nanomedicine 29, 102258.
Urbančič, D., Kotar, A., Šmid, A., Jukič, M., Gobec, S., Mårtensson, L.G., Plavec, J., Mlinarič-Raščan, I., 2019. Methylation of selenocysteine catalysed by thiopurine S-methyltransferase. Biochim.t Biophys. Acta ((BBA)) - Gen. Subj. 1863, 182–190.
Vahidi, H., Kobarfard, F., Alizadeh, A., Saravanan, M., Barabadi, H., 2021. Green nanotechnology-based tellurium nanoparticles: exploration of their antioxidant, antibacterial, antifungal and cytotoxic potentials against cancerous and normal cells compared to potassium tellurite. Inorg. Chem. Commun. 124, 108385.
Valencia, A., Morán, J., 2004. Reactive oxygen species induce different cell death mechanisms in cultured neurons. Free Radic. Biol. Med. 36, 1112–1125.
Valente, A., Podolski-Renic, A., Poetsch, A., Filipovic, N., López, O., Turel, I., Heffeter, P., 2021. Metal- and metalloid-based compounds to target and reverse cancer multidrug resistance. Drug Resist. Updates 58, 100778.
Vij, P., Hardej, D., 2012. Evaluation of tellurium toxicity in transformed and non-transformed human colon cells. Environ. Toxicol. Pharmacol. 34, 768–782.
Virani, N.A., Thavathiru, E., McKernan, P., Moore, K., Benbrook, D.M., Harrison, R.G., 2018. Anti-CD73 and anti-OX40 immunotherapy coupled with a novel biocompatible enzyme prodrug system for the treatment of recurrent, metastatic ovarian cancer. Cancer Lett. 425, 174–182.
Wada, T., Penninger, J.M., 2004. Mitogen-activated protein kinases in apoptosis regulation. Oncogene 23, 2838–2849.
Wang, Z., Lee, H.J., Chai, Y., Hu, H., Wang, L., Zhang, Y., Jiang, C., Lü, J., 2010. Persistent p21Cip1 induction mediates G(1) cell cycle arrest by methylseleninic acid in DU145 prostate cancer cells. Curr. Cancer Drug Targets 10, 307–318.
Wang, L., Fu, J.N., Wang, J.Y., Jin, C.J., Ren, X.Y., Tan, Q., Li, J., Yin, H.W., Xiong, K., Wang, T.Y., Liu, X.M., Zeng, H.H., 2011. Selenium-containing thioredoxin reductase inhibitor ethaselen sensitizes non-small cell lung cancer to radiotherapy. Anticancer Drugs 22, 732–740.
Wang, L., Yang, Z., Fu, J., Yin, H., Xiong, K., Tan, Q., Jin, H., Li, J., Wang, T., Tang, W., Yin, J., Cai, G., Liu, M., Kehr, S., Becker, K., Zeng, H., 2012. Ethaselen: a potent mammalian thioredoxin reductase 1 inhibitor and novel organoselenium anticancer agent. Free Radic. Biol. Med. 52, 898–908.
Wang, H., Gao, Z., Liu, X., Agarwal, P., Zhao, S., Conroy, D.W., Ji, G., Yu, J., Jaroniec, C. P., Liu, Z., Lu, X., Li, X., He, X., 2018a. Targeted production of reactive oxygen species in mitochondria to overcome cancer drug resistance. Nat. Commun. 9, 562.
Wang, W.C., Zhang, X.F., Peng, J., Li, X.F., Wang, A.L., Bie, Y.Q., Shi, L.H., Lin, M.B., Zhang, X.F., 2018b. Survival mechanisms and influence factors of circulating tumor cells. BioMed Res. Int. 2018, 6304701.
Wang, M., Wu, J., Li, Y., Li, F., Hu, X., Wang, G., Han, M., Ling, D., Gao, J., 2018c. A tumor targeted near-infrared light-controlled nanocomposite to combat with multidrug resistance of cancer. J. Controlled Release 288, 34–44.
Wang, M., Xiao, Y., Li, Y., Wu, J., Li, F., Ling, D., Gao, J., 2019. Reactive oxygen species and near-infrared light dual-responsive indocyanine green-loaded nanohybrids for overcoming tumour multidrug resistance. Eur. J. Pharm. Sci. 134, 185–193.
Wang, J.Q., Yang, Y., Cai, C.Y., Teng, Q.X., Cui, Q., Lin, J., Assaraf, Y.G., Chen, Z.S., 2021. Multidrug resistance proteins (MRPs): structure, function and the overcoming of cancer multidrug resistance. Drug Resist. Updates 54, 100743.
Weekley, C.M., Harris, H.H., 2013. Which form is that? The importance of selenium speciation and metabolism in the prevention and treatment of disease. Chem. Soc. Rev. 42, 8870–8894.
Wei, D., Yu, Y., Zhang, X., Wang, Y., Chen, H., Zhao, Y., Wang, F., Rong, G., Wang, W., Kang, X., Cai, J., Wang, Z., Yin, J.Y., Hanif, M., Sun, Y., Zha, G., Li, L., Nie, G., Xiao, H., 2020. Breaking the intracellular redox balance with diselenium nanoparticles for maximizing chemotherapy efficacy on patient-derived xenograft models. ACS Nano 14, 16984–16996.
Wieslander, E., Engman, L., Svensjö, E., Erlansson, M., Johansson, U., Linden, M., Andersson, C.M., Brattsand, R., 1998. Antioxidative properties of organotellurium compounds in cell systems. Biochem. Pharmacol. 55, 573–584.
Ye, S.F., Yang, Y., Wu, L., Ma, W.M., Zeng, H.H., 2017. Ethaselen: a novel organoselenium anticancer agent targeting thioredoxin reductase 1 reverses cisplatin resistance in drug-resistant K562 cells by inducing apoptosis. J. Zhejiang Univ. Sci. B 18, 373–382.
Yeung, K.T., Yang, J., 2017. Epithelial-mesenchymal transition in tumor metastasis. Mol. Oncol. 11, 28–39.
Yin, S., Dong, Y., Li, J., Fan, L., Wang, L., Lu, J., Vang, O., Hu, H., 2012. Methylseleninic acid potentiates multiple types of cancer cells to ABT-737-induced apoptosis by targeting Mcl-1 and Bad. Apoptosis 17, 388–399.
Yu, J., Dong, X., Wang, L., Ji, H., Liu, A., 2018. Antitumor effects of seleno-β-lactoglobulin (Se-β-Lg) against human gastric cancer MGC-803 cells. Eur. J. Pharmacol. 833, 109–115.
Yun, C.W., Lee, S.H., 2018. The roles of authophagy in cancer. Int. J. Mol. Sci. 19, 3466.
Xu, Y., Villalona-Calero, M.A., 2002. Irinotecan: mechanisms of tumor resistance and novel strategies for modulating its activity. Ann. Oncol. 13, 1841–1851.
Xu, X., Feng, Y., Chen, X., Wang, Q., Meng, T., Liu, A., 2019a. Antitumor effects of seleno-β-lactoglobulin on human breast cancer MCF-7 and MDA-MB-231 cells *in vitro*. Toxicol. In Vitro 61, 104607.
Xu, N., Piao, M., Arkin, K., Ren, L., Zhang, J., Hao, J., Zheng, Y., Shang, Q., 2019b. Imaging of water soluble CdTe/CdS core-shell quantum dots in inhibiting multidrug resistance of cancer cells. Talanta 201, 309–316.
Xu, J., Yan, X., Ge, X., Zhang, M., Dang, X., Yang, Y., Xu, F., Luo, Y., Li, G., 2021. Novel multi-stimuli responsive functionalized PEG-based co-delivery nanovehicles toward sustainable treatments of multidrug resistant tumor. J. Mater. Chem. B 9, 1297–1314.
Xuan, G., Zhang, M., Chen, Y., Huang, S., Lee, I., 2020. Design and characterization of a cancer-targeted drug co-delivery system composed of liposomes and selenium nanoparticles. J. Nanosci. Nanotechnol. 20, 5295–5304.
Zare, B., Nami, M., Shahverdi, A.R., 2017. Tracing TEllurium and Its Nanostructures in Biology. Biol. Trace Elem. Res. 180, 171–181.
Zeng, H., Wu, M., Botnen, J.H., 2009. Methylselenol, a selenium metabolite, induces cell cycle arrest in G1 phase and apoptosis via the extracellular-regulated kinase 1/2 pathway and other cancer signaling genes. J. Nutr. 139, 1613–1618.
Zeng, L., Chen, J., Ji, S., Chan, L., Zheng, W., Chen, T., 2015. Construction of a cancer-targeted nanosystem as a payload of iron complexes to reverse cancer multidrug resistance. J. Mater. Chem. B 3, 4345–4354.
Żesławska, E., Kincses, A., Unger, V., Tóth, V., Spengler, G., Nitek, W., Tejchman, W., 2018. Exocyclic sulfur and selenoorganic compounds towards their anticancer effects: crystallographic and biological studies. Anticancer Res. 38, 4577–4584.
Zhang, J.S., Gao, X.Y., Zhang, L.D., Bao, Y.P., 2001. Biological effects of a nano red elemental selenium. Biofactors 15, 27–38.
Zhang, G., Shi, L., Selke, M., Wang, X., 2011. CdTe quantum dots with daunorubicin induce apoptosis of multidrug-resistant human hepatoma HepG2/ADM cells: *in vitro* and *in vivo* evaluation. Nanoscale Res. Lett. 6, 418.
Zhang, H., Wu, J., Yuan, J., Li, H., Zhang, Y., Wu, W., Chen, W., Wang, C., Meng, S., Chen, S., Huo, M., He, Y., Zhang, C., 2021. Ethaselen synergizes with oxaliplatin in tumor growth inhibition by inducing ROS production and inhibiting TrxR1 activity in gastric cancer. J. Exp. Clin. Cancer Res. 40, 260.
Zhao, Y., Liu, Y., Wang, W., Wu, D., Shi, J., Liu, A., 2018. Apoptosis and autophagy induction of Seleno-β-lactoglobulin (Se-β-Lg) on hepatocellular carcinoma cells lines. J. Funct. Foods 49, 412–423.
Zheng, W., Cao, C., Liu, Y., Yu, Q., Zheng, C., Sun, D., Ren, X., Liu, J., 2015. Multifunctional polyamidoamine-modified selenium nanoparticles dual-delivering siRNA and cisplatin to A549/DDP cells for reversal multidrug resistance. Acta Biomater. 11, 368–380.
Zheng, X., Zhang, Y., Zhang, L., Xu, W., Ma, W., Sun, R., Zeng, H., 2016. Synergistic inhibition of sunitinib and ethaselen against human colorectal cancer cells proliferation. Biomed. Pharmacother. 83, 212–220.
Zhitomirsky, B., Assaraf, Y.G., 2016. Lysosomes as mediators of drug resistance in cancer. Drug Resist. Updates 24, 23–33.
Zhou, Y., Shi, L., Li, Q., Jiang, H., Lv, G., Zhao, J., Wu, C., Selke, Wang, X., 2010. Imaging and inhibition of multi-drug resistance in cancer cells via specific association with negatively charged CdTe quantum dots. Biomaterials 18, 4958–4963.
Zhou, Y., Wang, R., Chen, B., Sun, D., Hu, Y., Xu, P., 2016. Daunorubicin and gambogic acid coloaded cysteamine-CdTe quantum dots minimizing the multidrug resistance of lymphoma *in vitro* and *in vivo*. Int. J. Nanomed. 11, 5429–5442.
Zigman-Hoffman, E., Sredni, B., Meilik, B., Naparstek, E., Tartakovsky, B., 2021. Tellurium compound provides pro-apoptotic signaling in drug resistant multiple myeloma. Leuk. Lymphoma 62, 1146–1156.
Živanović, M.N., Košarić, J.V., Šmit, B., Šeklić, D.S., Pavlović, R.Z., Marković, S.D., 2017. Novel seleno-hydantoin palladium(II) complex - antimigratory, cytotoxic and prooxidative potential on human colon HCT-116 and breast MDA-MB-231 cancer cells. Gen.Physiol. Biophys. 36, 187–196.
Żylewska, A., Tejchman, W., Korohoda, M.J., Żylewski, M., 2003. Synthesis of 1,4,6-trisubstituted 2[1H]-Pyrimidine-selenones. Heterocycles 60, 2749–2760.