

Selenium – a fascinating antioxidant of protective properties

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Abstract

Selenium is a trace element which fulfils important functions in the organism. Its deficit may cause acute disorders, but an overdose can also lead to severe consequences. The functions of selenium in the organism are mainly connected with its antioxidant properties, as it is an essential part of important antioxidant enzymes. Disturbances of oxidant balance have been found to be involved in the activity of numerous harmful factors as well as in the pathogenesis of diverse illnesses. Selenium administration has proved to be effective against the toxicity of many agents and the side effects of drugs. However, the narrow range between therapeutic and toxic doses of selenium, as well as the dependence of its effect on the applied form, dose and method of treatment, makes the choice of the most effective supplement a very complex issue. Divergent forms of selenium are still being studied, including both inorganic and organic compounds as well as Se-enriched natural products. The newest research has also involved selenium nanoparticles. The aim of this review is to present the great potential of selenium for protecting the organism against a wide variety of environmental pollutants, drugs and physical factors.

Key words: oxidative stress, selenium, drug-related side effects, protective agents

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Introduction

Selenium belongs to trace elements essential for humans. In the body it is involved in numerous processes, among other things immune functions and antioxidant defense. Its deficit may result in cardiac, muscular, osseous, and immune disturbances.^{1,2} The biological functions of selenium result from the occurrence of the selenocysteine amino acid in proteins. The research has revealed that about a hundred selenoproteins can be found in mammal organisms.² The most important of them are the antioxidant enzymes – glutathione peroxidase and thioredoxin reductase, as well as selenoprotein P, responsible for the storage and transport of selenium.^{3–6} Selenium supplementation has been proved to be protective against a very wide range of harmful factors, both chemical, such as drugs exerting severe side effects, heavy metals, carcinogens, mycotoxins, or pesticides, and physical, such as heat stress or magnetic fields. However, the narrow range between therapeutic and toxic doses of selenium, as well as the dependence of its effect on the applied form, dose and method of treatment, make the choice of the most effective supplement a very complex issue.^{5,7–10}

The average lethal dose established in animal models for sodium selenite (7 mg Se/kg b.w.) is almost 20 times smaller than that obtained for selenium sulfides, and more than 900 times smaller than for elemental selenium.¹¹ According to the US National Academy of Sciences, for adults, 55 µg is the recommended daily selenium intake, whereas 400 µg is the threshold which should not be exceeded.⁷ The toxic dose for adults was established as more than 700 µg/day.¹² The symptoms of selenium toxicity include fatigue, disturbances in connective tissue as well as in cardiovascular, gastrointestinal, nervous, and respiratory systems.^{11,13} As the interest in selenium and its effects on human health is still growing, diverse compounds of selenium are still being studied, both inorganic and organic, Se-enriched natural products like probiotics, yeast and green tea, as well as selenium nanoparticles.^{3,8,10,14–18} Organic compounds have been widely studied recently due to the similarity of the activity of some of them (e.g., ebselen or diphenyl diselenide) to that shown by glutathione peroxidase.¹⁹ Diphenyl diselenide has also been proved to possess many beneficial pharmacological properties: anti-hyperglycemic, anti-hyperlipidemic, hepatoprotective, antiulcer, and antidepressant.^{19,20}

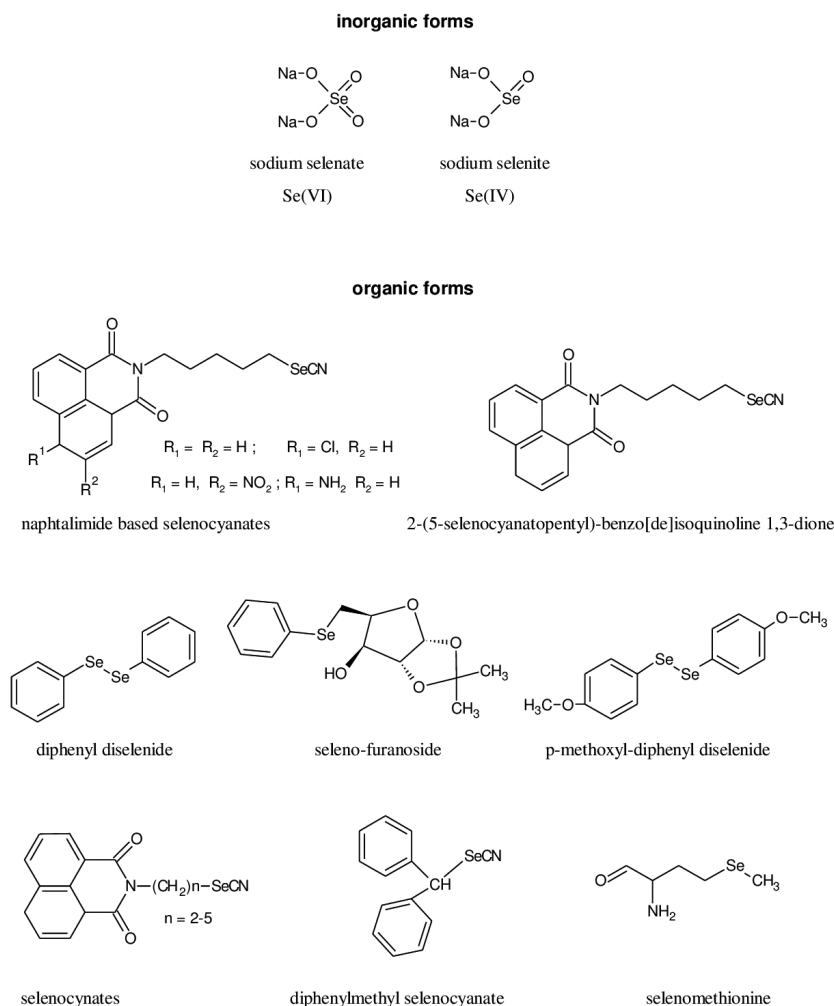


Fig. 1. The different forms of selenium used in scientific research

The aim of this review is to present the great potential of selenium for protecting the organism against the damage caused by environmental pollutants, drugs and physical factors, as well as the dependence of the selenium impact on the form and model of administration.

Comparison of the effect of different selenium forms on organisms

The effect of selenium on organisms shows strong dependence on its form. A distinct difference between organic and inorganic compounds has been found. The forms of selenium used are presented in Fig. 1.

Sodium selenite remains the most often studied inorganic form of selenium, containing Se(IV), but other forms are also commonly studied. A comparison of selenite and

selenate, containing Se(VI), was performed on the mycelia of *Pleurotus ostreatus* exposed to cadmium and silver (1.25 mg/L, 2.5 mg/L and 5 mg/L). Selenium (2.5 mg/L or 5 mg/L) prevented the malonyldialdehyde (MDA) increase caused by the metals, but while Se(IV) showed full effectiveness, Se(VI) was either less effective or even intensified the pro-oxidant processes.²¹

The research more and more often includes selenoorganic compounds – either naturally occurring forms or newly synthesized substances, e.g., selenomethionine, naphthalimide-based selenocyanates, 2-(5-selenocyanatopentyl)-benzo[de]isoquinoline-1,3-dione, diphenyl diselenide, selenofuranoside, p-methoxydiphenyl diselenide, selenocyanates, and diphenylmethyl selenocyanate.^{4–6,9,16,17,19,20,22–26} The results regarding the comparison of inorganic and organic compounds are not fully consistent, although the newest studies usually reveal

Table 1. Protective effect of selenium against cisplatin toxicity

Authors, citation number	Animals, way of administration, dose, time of exposure	Harmful effects of cisplatin	Selenium form, dose, method and time of administration	Effects of selenium co-administration	Effects of Se itself
Chakraborty et al. 2011 ⁹	mice intraperitoneally 5 mg/kg b.w. 5 days	kidney GST, GPx, CAT, SOD, GSH ↓; kidney TBARS, serum creatinine, blood urea nitrogen ↑	synthetic organic diphenylmethyl selenocyanate, 3 mg/kg b.w., oral gavage, 2 models: concomitant treatment (Se from day 1 to day 9, and cisplatin from day 1 to day 5); pretreatment (Se 7 days before cisplatin, and then from day 1 to day 9, cisplatin from day 1 to day 5)	kidney GPx, CAT, SOD, serum creatinine, blood urea nitrogen (±); kidney GSH, GST, TBARS (+); pretreatment model more effective	none
Yazici et al. 2014 ³⁰	rats intraperitoneally 16 mg/kg 3 days	drug-caused edema and subsequently retinal thickness increase	Na ₂ SeO ₃ 1.5 mg of Se/kg, oral gavage twice daily, for 5 days before drug and for 3 days concomitantly	selenium reduced the effects of cisplatin and showed the antiapoptotic influence	not studied
Rezvanfar et al. 2013 ³¹	rats intraperitoneally, single injection 7 mg/kg before Se	serum testosterone ↓; sperm abnormality ↑; blood and testis lipid peroxidation ↑; blood and testis peroxynitrite ↑; blood and testis SOD, CAT, GPx ↓	selenium nanoparticles 2 mg/kg/day, orally 10 days	serum testosterone (±); sperm abnormality (±); blood and testis lipid peroxidation (+); blood and testis peroxynitrite (+); blood and testis SOD, CAT, GPx (+)	none
Wilhelm et al. 2012 ²⁵	mice intraperitoneally, single injection 10 mg/kg on day 3	plasma urea and plasma creatinine ↑; kidney vitamin C, GSH, GST, GPx, GR, CAT, δ-ALA-D ↓	p-methoxyl-diphenyl diselenide 50 mg/kg or 100 mg/kg, orally 6 days	lower dose: plasma urea (±); plasma creatinine (0); kidney GSH, GST, GPx, GR, δ-ALA-D (±); kidney vitamin C, CAT (+) higher dose: plasma urea and plasma creatinine (±), kidney GSH, GST, GPx, GR, vitamin C, CAT (+) kidney δ-ALA-D (±)	none

↓ – decrease; ↑ – increase; (+) – full protection; (±) – partial protection; (0) – lack of protection; GST – glutathione S-transferase; GPx – glutathione peroxidase; CAT – catalase; SOD – superoxide dismutase; GSH – reduced glutathione; TBARS – thiobarbituric acid-reactive substances; GR – glutathione reductase; δ-ALA-D – δ-aminolevulinic dehydratase.

Table 2. Protective effect of selenium against toxicity of different drugs

Authors, citation number	Animals, way of administration, dose, time of exposure	Harmful effects of drug	Selenium form, dose, method and time of administration	Effects of selenium co-administration	Effects of Se itself
Gürgen et al. 2013 ³²	rats, cyclophosphamide intraperitoneally 75 mg/kg b.w. once a week, for 3 weeks	degeneration of the ovarian tissue; serum GSH ↓	40 ppm/day/rat, oral gavage 3 weeks	reducing the degeneration of ovarian tissue; serum GSH (±)	not studied
Ghosh et al. 2015 ⁵	mice, cyclophosphamide intraperitoneally 25 mg/kg b.w. 10 days or 25 days	pulmonary ROS, NO, lipid peroxidation ↑; GSH, GST, GPx, SOD, CAT ↓	a synthetic organic compound 2-(5-selenocyanatopentyl)-benzo[de]isoquinoline-1,3-dione 3 mg/kg b.w. (non-toxic dose), oral gavage, 2 models: 10 days or 25 days; 2 models: concomitant co-administration of selenium (10 days); Se-pretreatment (15 days before drug-exposure and subsequent co-administration)	oxidant parameters considerably improved by selenium; the pretreatment model was more effective, which was confirmed by histopathological studies of the lung: in co-administered animals moderate changes were observed, in the pretreatment model no distinct alterations were displayed compared with control	none
Danesi et al. 2006 ³³	rats adriamycin, single intraperitoneal dose 10 mg/kg b.w.	plasma reactive oxygen metabolites ↑; plasma total antioxidant activity ↓; reactive oxygen metabolites in heart ↑	pretreatment with dietary Na ₂ SeO ₃ or Se-enriched potato obtained by foliar Se-supplementation during growth 0.1 mg/kg 60 days	plasma reactive oxygen metabolites and total antioxidant activity (0); heart reactive oxygen metabolites: selenite (±), Se-enriched potato (+)	not studied
Saied and Hamza 2014 ³⁴	rats isotretinoin (a retinoid used in dermatology) gastric tube 7.5 mg/kg b.w. 28 days	ALT, AST, ALP, total cholesterol and triglycerides, TBARS ↑; HDL, GSH, SOD, CAT ↓	Na ₂ SeO ₃ 500 µg/kg/day, gastric tube, 28 days	ALT, ALP, TBARS, total cholesterol, triglycerides (±); SOD, CAT (0); AST, HDL, GSH (+)	SOD, CAT, HDL ↑
Mossa et al. 2014 ³⁵	rats aspirin 22.5 mg/kg b.w. 28 days	erythrocytes SOD, CAT, GPx ↓; erythrocytes MDA ↑	Na ₂ SeO ₃ 200 µg/kg b.w./day, orally 28 days	erythrocytes SOD, CAT, GPx, MDA (+)	none

↓ – decrease; ↑ – increase; (+) – full protection; (±) – partial protection; (0) – lack of protection. GSH – reduced glutathione; ROS – reactive oxygen species; NO – nitrogen oxide; GST – glutathione S-transferase; GPx – glutathione peroxidase; SOD – superoxide dismutase; CAT – catalase; ALP – alkaline phosphatase; AST – aspartate aminotransferase; ALT – alanine aminotransferase; HDL – high-density lipoproteins.

that the organic forms are more beneficial and less likely to induce their own toxic effects. In mice treated with either sodium selenite or naphthalimide-based synthetic organoselenocyanates (oral gavage; 1.2 mg/kg b.w. and 3 mg/kg b.w., respectively), selenite significantly decreased hemoglobin as well as increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), and hepatic lipid peroxidation. Organic selenium depressed AST and ALT as well as blood urea nitrogen and creatinine, indicating the potential hepatoprotective and nephroprotective effects of this form. Histopathological studies have confirmed these outcomes. The advantage of the organic form was also observed in the case of liver antioxidant parameters.²⁴

In one of the newest studies, sodium selenite, selenomethionine and selenium yeast were compared in vitro (1 µg/mL

in cell medium). In HepG2 cells exposed to lead nitrate (40 µg of Pb/mL or 80 µg of Pb/mL), DNA damage was reduced by organic selenium, whereas selenite not only was ineffective as a protective agent, but also intensified DNA injury.⁶

Four dietary selenium forms (selenite, lactate-protein complex, Se-protein, and Se-yeast), given to goats before (0.3 mg/day/goat) and after parturition (0.9 mg/day/goat), were studied as potential Se-supplements. Tissue selenium content in different organs of the younglings were the highest in the Se-yeast group, but the other organic forms were also more effective as supplements than selenite.²⁷

Sodium selenite was also compared with dextrin stabilized selenium nanoparticles (both forms used at doses 10–100 µg/mL). An in vitro investigation revealed that the viability of the nanoparticle-treated cells was much higher than in the case of those treated by selenite. In an in vivo

Table 3. Protective effect of selenium against cadmium toxicity

Authors, citation number	Animals, way of administration, dose, time of exposure	Cadmium-induced harmful effects	Selenium form, dose, method and time of administration	Effects of selenium co-administration	Effects of Se itself
Li et al. 2013 ¹⁴	chickens CdCl ₂ 150 mg/kg of diet 60 days	liver lipid peroxidation, NO level and nitric oxide synthase activity ↑; liver SOD, GPx ↓; the number of apoptotic cells ↑	dietary Na ₂ SeO ₃ 10 mg/kg, 60 days	liver lipid peroxidation, NO level, nitric oxide synthase activity, SOD, GPx (±); the number of apoptotic cells (±)	GPx ↑
El-Boshy et al. 2015 ³⁷	rats cadmium 40 mg/L in drinking water as CdCl ₂ 30 days	serum tumor necrosis factor α, interleukins IL-6, IL-10, IL-β, MDA ↑; serum interferon γ, GSH, GPx, CAT, SOD ↓; ALT and AST, urea and creatinine ↑	Na ₂ SeO ₃ 0.1 mg/kg b.w., orally	serum tumor necrosis factor α, IL-6, IL-10, interferon γ, MDA, GSH, GPx, CAT, SOD, ALT, AST, urea and creatinine (+); IL-β (0)	serum interferon γ (IFN-γ), GSH, GPx, CAT ↑; IL-10 ↓
Sk and Bhattacharya 2006 ²⁶	mice CdCl ₂ intraperitoneally 1 or 2 mg/kg b.w. 20 days	serum ALT and AST, hepatic microsomal lipid peroxidation ↑; liver cytosol GST, SOD, CAT, GSH ↓	synthetic selenocyanates 3 mg/kg b.w., by gavage 2 models: concomitant; pretreatment (selenium given 7 days before cadmium, and then throughout the experimental period of 20 days)	serum ALT and AST, hepatic microsomal lipid peroxidation, liver cytosol GST, SOD, CAT, GSH (±); pretreatment model more effective	not studied
Vargas et al. 2013 ¹⁷	mice CdCl ₂ , single intraperitoneal dose	ovary δ-aminolevulinatase dehydratase activity ↓	synthetic seleno-furanoside 100 μmol (32.9 mg)/kg subcutaneously	in CdCl ₂ 2.5 mg/kg group (±); in CdCl ₂ 5 mg/kg group (+)	none

↓ – decrease; ↑ – increase; (+) – full protection; (±) – partial protection; (0) – lack of protection. NO – nitrogen oxide; SOD – superoxide dismutase; GPx – glutathione peroxidase; MDA – malonyldialdehyde; GSH – reduced glutathione; CAT – catalase; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GST – glutathione S-transferase.

study, rats with arthritis showed depletion of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) in the liver, kidney and spleen as well as an increase in serum C-reactive protein. These disturbances were reversed by oral administration of nanoparticles (100 μg/kg b.w., 250 μg/kg b.w., 500 μg/kg b.w., or 750 μg/kg b.w.).²⁸ On the other hand, treatment with selenium nanoparticles (5–25 μg/mL) was reported to cause dose-dependent malformations in zebrafish embryos, whereas the same doses of sodium selenite did not show any harmful effects.²⁹

A comparison of Se-enriched probiotics and sodium selenite was performed on rats exposed to carbon tetrachloride. CCl₄ significantly increased serum ALT and AST, and disturbed liver oxidant balance. Both selenium forms alleviated the harmful effects, but the Se-enriched probiotics were more effective.³

Protecting effect of selenium against toxicity of different substances

Protective properties of selenium against toxicity of diverse drugs: Animal model research

Administration of drugs can be connected with side effects causing the impairment of organism functions. Selenium was found to protect against the toxicity of different drugs, including the chemotherapeutic agents – cisplatin and cyclophosphamide, antibiotics and dermatological medications as well as aspirin. The research also showed the pretreatment application to be more effective. The details of the studies performed and their results are presented in Tables 1 and 2.

Table 4. Protective effect of organic selenium against toxicity of aluminum, mercury and arsenic

Authors, citation number	Animals, way of administration, dose, time of exposure	Induced harmful effects	Selenium form, dose, method and time of administration	Effects of selenium co-administration	Effects of Se itself
Viezeliene et al. 2013 ³⁸	mice AlCl ₃ , intraperitoneally 25 mg Al ³⁺ /kg b.w. 16 h	serum interleukin IL-6 ↑; liver total GSH ↓	Na ₂ SeO ₃ , 1.25 mg of Se ⁴⁺ /kg b.w., intraperitoneally 16 h	IL-6 (±); liver total GSH (+)	liver total GSH ↑; serum IL-6 ↑
Lakshmi et al. 2015 ³⁹	rats AlCl ₃ 100 mg/kg, orally	brain CAT, GSH, GR, AChE ↓; MDA ↑	selenium 1 mg/kg, orally	brain CAT, AChE (±); GSH, GR, MDA (+)	brain GSH, GR ↑; MDA ↓
Agarwal and Behari 2007 ¹	rats mercuric chloride, intraperitoneally 0.4 mg/kg/day 20 days	brain, liver and kidney lipid peroxidation ↑; brain, liver and kidney GSH ↓; brain, liver and kidney Hg concentration ↑	Na ₂ SeO ₃ 0.2 mg/kg/day, intraperitoneally 4 h before mercury, 20 days	brain, liver and kidney lipid peroxidation and GSH, brain Hg (0); liver and kidney Hg concentration (-)	liver MDA ↑; kidney GSH ↓
Glaser et al. 2013 ¹⁹	mice methylmercury (MeHg), orally in drinking water 40 mg/L 21 days	GPx, respiratory chain enzymes in cortical mitochondrial preparations ↓; GR, TBARS in cortical mitochondrial preparations ↑; cerebral cortex Hg deposition ↑	diphenyl diselenide 5 μmol/kg, subcutaneously 21 days	TBARS, respiratory chain enzymes in cortical mitochondrial preparations (+); GPx, GR in cortical mitochondrial preparations (0); cerebral cortex Hg deposition (±)	GR ↑; TBARS ↓; cerebral cortex Hg deposition ↑
Prasad and Selvaraj 2014 ⁴⁰	human lymphocytes sodium arsenite NaAsO ₂ 10 μM 1 h	increased cell death; DNA damage	selenium nanoparticles 0.01 μg/μL 1 h	protecting from DNA damage and cell death	not studied
Xu et al. 2013 ⁴¹	rats sodium arsenite NaAsO ₂ , in drinking water 13 mg/L 20 weeks	liver MDA ↑; liver CAT, GPx, SOD ↓; serum ALT and AST ↑	Na ₂ SeO ₃ 17.0 mg/L, in drinking water 20 weeks	liver MDA (+); liver CAT, GPx, SOD (±); serum ALT and AST (+)	liver CAT ↓

↓ – decrease; ↑ – increase; (+) – full protection; (±) – partial protection; (0) – lack of protection; (-) – intensification of harmful effects. GSH – reduced glutathione; CAT – catalase; GR – glutathione reductase; AChE – acetylcholinesterase; MDA – malonyldialdehyde; GPx – glutathione peroxidase; TBARS – thiobarbituric acid-reactive substances; SOD – superoxide dismutase; ALT – alanine aminotransferase; AST – aspartate aminotransferase.

Protective properties of selenium against environmental contaminants and physical factors: Animal model research

Selenium has been studied in regard to its possible protective effect against numerous environmental pollutants, and the results obtained seem to be very promising. The harmful effects of toxic elements (cadmium, aluminum, mercury, arsenic, lead, chromium) and compounds, e.g., carbon tetrachloride, carcinogens (acrylamide, hydrocarbons), mycotoxins (patulin, aflatoxin), and pesticides (beta-cyfluthrin, diazinon, acephate) were found to be reversed or alleviated by selenium treatment. Sodium selenite was most often used, but organic forms were also studied. Some researchers applied very interesting, new natural forms like polysaccharides isolated from selenium-enriched Ziyang tea, or meat from lambs receiving Se-nanoparticles in drinking water.^{7,10} Synthetic organoselenium compounds also revealed their advantage over

inorganic forms. Diphenyl diselenide was proved effective against the toxicity of mercury in rodents, while selenite showed no efficacy.^{1,19} It was also found that the influence of selenium was dependent on its dose.^{10,36} The detailed information is collected in Tables 3–8.

In vitro studies of protective properties of selenium

The beneficial impact of different forms of selenium against the toxicity of diverse factors has also been confirmed by in vitro studies.

In neuronal cells exposed to the addictive drug methamphetamine, a decrease in GPx isoforms (GPx 1 and GPx 4), and the depletion of GPx activity and intracellular reduced glutathione (GSH) was observed. However, in cells cultured in Se-containing media (10 nM or 100 nM as sodium selenite), before and during methamphetamine exposure, these effects were alleviated, although in the case of GPx

Table 5. Protective effect of selenium against toxicity of lead and chromium

Authors, citation number	Animals, way of administration, dose, time of exposure	Induced harmful effects	Selenium form, dose, method and time of administration	Effects of selenium co-administration	Effects of Se itself
Han et al. 2014 ⁸	weaned rats PbCl ₂ , in drinking water 2 mmol/L 3 weeks	deteriorations of synaptic structural plasticity as well as impaired spatial learning and memory	Se-enriched yeast 6 µg/100 g b.w., by gavage 3 weeks after Pb exposure	Pb-induced effects were improved by the subsequent treatment with selenium	not studied
Baş et al. 2015 ⁴²	rats lead nitrate, by gavage 22.5 mg/kg b.w. (1/100 LD ₅₀) 28 days	MDA in erythrocytes and leucocytes ↑; SOD, CAT, GPx, GST in erythrocytes and leucocytes ↓; plasma antioxidant capacity ↓	Na ₂ SeO ₃ 1 mg/kg b.w., by gavage 28 days	MDA, SOD, CAT, GPx, GST in erythrocytes and leucocytes (±); plasma antioxidant capacity(±)	none
Soudani et al. 2011 ⁴³	rats K ₂ Cr ₂ O ₇ , in drinking water 700 ppm 3 weeks	heart SOD, CAT, GPx, MDA ↑; heart GSH, vitamin C, non-protein thiols, LDH activity ↓; plasma LDL, ALT, AST, bilirubin, total cholesterol, triglycerides, LDL-cholesterol ↑; plasma HDL-cholesterol ↓	dietary Na ₂ SeO ₃ 0.5 mg/kg 3 weeks	heart SOD, CAT, GPx, MDA, vitamin C, non-protein thiols, LDH (±); heart GSH, plasma ALT, AST, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (+); plasma bilirubin (±)	heart non-protein thiols ↑; heart SOD ↓
Soudani et al. 2012 ⁴⁴	rats K ₂ Cr ₂ O ₇ , in drinking water 700 ppm 3 weeks	cerebrum and cerebellum MDA, SOD, GPx, CAT, plasma LDH ↑; cerebrum and cerebellum GSH, non-protein thiols, vitamin C, AChE, LDH ↓	dietary Na ₂ SeO ₃ 0.5 mg/kg 3 weeks	cerebrum and cerebellum MDA, SOD, GSH, non-protein thiols, vitamin C, GPx, LDH, AChE, cerebellum CAT (±); cerebellum CAT (0); plasma LDH (+)	cerebrum non-protein thiols ↑
Hassanin et al. 2013 ¹⁸	rats K ₂ Cr ₂ O ₇ , single intraperitoneal dose 60 µg/kg b.w. in Cr + Se animals, Cr was given on day 3	serum thyroid hormones (free triiodothyronine and thyroxine), GSH ↓; serum CAT, SOD and MDA ↑; in thyroid: hyperplasia of intrafollicular epithelium, follicular segregation, increased interfollicular spaces, increased collagen deposition	selenium nanoparticles, intraperitoneally 0.5 mg/kg b.w. 5 days	serum thyroid hormones (free triiodothyronine and thyroxine) (±); serum GSH, CAT, SOD and MDA (+); alleviated histopathological changes	none

↓ – decrease; ↑ – increase; (+) – full protection; (±) – partial protection; (0) – lack of protection; MDA – malonyldialdehyde; SOD – superoxide dismutase; CAT – catalase; GPx – glutathione peroxidase; GST – glutathione S-transferase; GSH – reduced glutathione; LDH – lactate dehydrogenase; LDL – low-density lipoproteins; ALT – alanine aminotransferase; AST – aspartate aminotransferase; AChE – acetylcholinesterase.

Table 6. Protective effect of organic selenium against toxicity of carbon tetrachloride and other carcinogens

Authors, citation number	Animals, way of administration, dose, time of exposure	Induced harmful effects	Selenium form, dose, method and time of administration	Effects of selenium co-administration	Effects of Se itself
Ding et al. 2010 ⁴⁵	mice CCl ₄ , intraperitoneally 5 µL of a 20% solution in olive oil biweekly for 4 weeks	liver GPx ↓; liver MDA, serum ALT, liver fibrosis, liver α ₁ (I) collagen mRNA ↑	Na ₂ SeO ₃ 4 mg/L, in drinking water started 2 days before CCl ₄	liver GPx and MDA (+); liver fibrosis (±); serum ALT, liver α ₁ (I) collagen mRNA (0)	liver GPx ↑; liver MDA ↓
Wang et al. 2014 ¹⁰	mice CCl ₄ , intraperitoneally 0.3 µL of a 0.8% solution in peanut oil once	serum ALT, AST and LDH ↑; liver MDA ↑; liver SOD and GPx ↓	polysaccharides isolated from selenium-enriched Ziyang tea 100, 200 and 400 mg/kg b.w. intragastrically daily for 14 days before CCl ₄	serum ALT, AST and LDH (±); liver MDA, SOD: low dose (0), middle and high doses (±); liver GPx: all doses (±)	not studied
Ali et al. 2014 ⁴⁶	rats acrylamide, gastric intubation 15 mg/kg b.w./day 28 days	erythrocytes, leucocytes and hematocrit, serum Zn and ALP ↓; MDA, Na, Ca in retinas ↑; retinas GPx and K ↓	0.1 mg/kg b.w./day, gastric intubation for 28 days	all studied parameters (+)	none
Ungvári et al. 2014 ⁷	mice hydrocarbon DMBA, 7,12-dimethyl-bez(a) anthracene, single intraperitoneal dose 200 mg/kg b.w.	blood total antioxidant capacity, total white blood cells counts ↓; impaired granulopoiesis	meat from lambs receiving selenium nanoparticles in drinking water (0.1%)	blood total antioxidant capacity (+); total white blood cells counts (±); granulopoiesis (±)	blood total antioxidant capacity ↑; intensified granulopoiesis

↓ – decrease; ↑ – increase; (+) – full protection; (±) – partial protection; (0) – lack of protection; DMBA – 7,12-dimethylbenz(a)anthracene; GPx – glutathione peroxidase; MDA – malonyldialdehyde; ALT – alanine aminotransferase; AST – aspartate aminotransferase; LDH – lactate dehydrogenase; SOD – superoxide dismutase; ALP – alkaline phosphatase.

Table 7. Protective effect of organic selenium against toxicity of mycotoxins and substances used in agriculture

Authors, citation number	Animals, way of administration, dose, time of exposure	Induced harmful effects	Selenium form, dose, method and time of administration	Effects of selenium co-administration	Effects of Se itself
Song et al. 2014 ²²	mice patulin intraperitoneally 1 mg/kg once a week for 8 weeks	brain thiol group, GPx, GR, TrxR mRNA expressions ↓; brain oxidized glutathione, ROS generation, TBARS, protein carbonyls ↑	dietary Na ₂ SeO ₃ or selenomethionine 0.2 mg Se/kg	all studied parameters (+)	not studied
Liao et al. 2014 ⁴⁷	ducklings aflatoxin B ₁ , intragastically 0.1 mg/kg b.w. 14, 21, and 28 days	serum ALT and AST ↑; liver Bax and caspase-3 ↑; liver Bcl-2 ↓	Na ₂ SeO ₃ 1 mg of Se/kg b.w., intragastically, 5 min after aflatoxin for 14, 21, and 28 days	serum ALT and AST(+); liver caspase-3 (+); liver Bcl-2 and Bax (±)	not studied
Chen et al. 2013 ³⁶	broilers aflatoxin B ₁ , in diet 0.3 mg/kg 7, 14, and 21 days	peripheral blood T-cell subsets, serum interleukin IL-2 and interferon-γ (IFN-γ) ↓	dietary Na ₂ SeO ₃ 0.6, 0.8 and 1.0 mg Se/kg	peripheral blood T-cell subsets: low and middle doses (±), high dose (-); IL-2: low dose (±), middle dose (+), high dose (±); IFN-γ: low dose (±), middle dose (+), high dose (0)	not studied
Jebur et al. 2014 ⁴⁸	rats β-cyfluthrin, oral gavage 15 mg/kg b.w. (1/25 LD ₅₀) 30 days	liver TBARS, LDH ↑; liver GSH, GPx, GR, SOD, CAT, GST, AST, ALT, ALP ↓	Na ₂ SeO ₃ , oral gavage 200 µg Se/kg b.w. 30 days	TBARS, GSH, GPx, GR, SOD, CAT, LDH (+); AST, ALT, ALP (±); GST (0)	serum ALT, TBARS ↓; serum GSH, GPx, GR, CAT, GST ↑
El-Demerdash and Nasr 2014 ¹⁵	rats diazinon, oral gavage 10 mg/kg b.w. 30 days	serum TBARS, ALT, AST, ALP, LDH ↑; serum GSH, SOD, CAT, GST, GPx, GR, AChE, HDL-cholesterol ↓; serum total lipids, total cholesterol, triglycerides, LDL-cholesterol ↑	Na ₂ SeO ₃ , oral gavage 200 µg Se/kg b.w. 30 days	all studied parameters (±)	TBARS ↓; GSH, CAT, GST, GPx, GR ↑
Acker and Nogueira 2014 ²⁰	rats acephate, oral gavage 140 mg/kg once	plasma glucose, corticosterone, triglycerides ↑; liver tyrosine aminotransferase ↑; cerebral AChE ↓	synthetic organic diphenyl diselenide, oral gavage 10 or 30 mg/kg 1 h before acephate, once	plasma glucose (±); plasma corticosterone (0); plasma triglycerides (+); cerebral AChE (0); liver tyrosine aminotransferase: lower dose (0), higher dose (±)	none

↓ – decrease; ↑ – increase; (+) – full protection; (±) – partial protection; (0) – lack of protection; (-) – intensification of harmful effects; GPx – glutathione peroxidase; GR – glutathione reductase; TrxR – thioredoxin reductase; TBARS – thiobarbituric acid-reactive substances; ALT – alanine aminotransferase; AST – aspartate aminotransferase; LDH – lactate dehydrogenase; GSH – reduced glutathione; ALP – alkaline phosphatase; SOD – superoxide dismutase; CAT – catalase; AChE – acetylcholinesterase.

activity only the low dose, and in the case of GSH only the high one, were found to be effective.⁵¹

In vitro experiments have also shown the efficacy of selenium nanoparticles. This form was proved to prevent DNA damage and cell death in lymphocytes exposed to UVB radiation.⁵² Another study performed on cardiomyoblast H9c2 cells revealed the occurrence of changes in the antioxidant level as well as in mitochondrial functions during ischemia and reperfusion which were prevented by selenium in the form of selenium incorporated guar gum nanoparticles.⁵³

Natural selenium forms have also been found to show a protective effect under in vitro conditions. Two selenium-enriched medicines of herbal origin (IMOD and Angipars) (Rose Pharmed Biotechnology Co., Iran) were studied in an experiment performed on human lymphocytes. Both substances prevented the toxicity of an organophosphorus pesticide – chlorpyrifos. The beneficial influence included the amelioration of the chlorpyrifos-induced increase in TNF-α and reduction in cell apoptosis and necrosis.⁵⁴

Table 8. Protective effect of selenium against negative effects caused by pathological condition

Authors, citation number	Animals pathological condition	Harmful effects	Selenium form, dose, method and time of administration	Effects of selenium co-administration	Effects of Se itself
Akil et al. 2011 ⁴⁹	rats acute swimming exercise after the end of experiment period, once for 30 min	plasma MDA and lactate, erythrocyte GSH, serum SOD and GPx ↑	Na ₂ SeO ₃ 200 µg/day, intraperitoneally 4 weeks	plasma MDA and lactate (±); erythrocyte GSH, serum SOD and GPx further ↑	none
Prigol et al. 2009 ¹⁶	mice acute swimming exercise after Se-treatment, for 20 min; euthanized 1 h or 24 h after exercise	euthanized after 1 h: skeletal muscle MDA and vitamin C, lung MDA and CAT ↑; euthanized after 24 h: skeletal muscle MDA and vitamin C ↑	synthetic organic diphenyl diselenide pretreatment 5 mg/kg, orally 7 days	euthanized after 1 h: skeletal muscle and lung MDA (+); skeletal muscle vitamin C, lung CAT (±); euthanized after 24 h: skeletal muscle MDA (+); skeletal muscle vitamin C (±)	after 1 h: muscle MDA ↓ after 24 h: muscle MDA and vitamin C ↓; lung vitamin C ↑
Ghazi Harsini et al. 2012 ⁴	chicken heat stress 4 weeks	serum glucose, uric acid and copper, skeletal muscle MDA and SOD ↑; serum iron and zinc ↓	dietary selenomethionine 0.5 or 1 mg of Se/kg	lower dose: skeletal muscle MDA, serum glucose (±); serum uric acid, copper, iron and zinc (0); skeletal muscle SOD (-) higher dose: skeletal muscle MDA, serum glucose, copper and uric acid (±); serum iron and zinc (0); skeletal muscle SOD (-)	none
Ghodbane et al. 2011 ⁵⁰	rats static magnetic field 128 mT/1 h/day for the last 5 consecutive days of Se-administration	kidney and muscle GPx ↓; kidney, muscle and brain Se level ↓	Na ₂ SeO ₃ 0.2 mg/L, in drinking water for 4 weeks	kidney and muscle GPx (+); kidney, muscle and brain Se level (+)	liver and muscle GPx ↑

↓ – decrease; ↑ – increase; (+) – full protection; (±) – partial protection; (0) – lack of protection; (-) – intensification of harmful effects; MDA – malonyldialdehyde; CAT – catalase; SOD – superoxide dismutase; GPx – glutathione peroxidase; GSH – reduced glutathione.

Protective properties of selenium: Human model research

Diverse human studies have also revealed the beneficial effects of selenium supplementation.

In young children (4.4–5.4 years) in rural Bangladesh, an inverse relationship between the exposure to cadmium (evaluated by the assay of its urinary level) and glomerular filtration rate was found, particularly in girls. This effect was alleviated in subjects with higher urinary selenium, which led the authors to suggest that higher Se-status seemed to exert a protective influence against cadmium nephrotoxicity.⁵⁵

An interesting study on 933 mother-newborn pairs, performed in China, revealed that umbilical cord serum manganese was related to the risk of lower Neonatal Behavioral Neurological Assessment rank. However, this effect was alleviated in the cases where umbilical cord serum selenium was higher. The authors suggested that selenium supplementation might be considered in pregnant women, particularly in regions of low environmental selenium level.⁵⁶

Based on a study involving cancerous patients subjected to cisplatin therapy, Ghorbani et al. suggested that selenium might prevent the renal toxicity of the drug. They found that acute kidney failure occurred in 11.5% of patients treated with cisplatin, whereas in those pretreated with a single selenium tablet (400 mcg), no such cases were observed.⁵⁷ Similarly, Mix et al. observed some protective influence of selenium treatment (selenomethionine, 1 week before as well as during therapy) in patients with inoperable, stage III non-small cell lung cancer undergoing concurrent chemoradiation (radiation, paclitaxel and cisplatin).²³

Conclusions

In conclusion, the presented studies make it possible to suggest that selenium seems to be one of the most appealing agents to be examined in relation to its protective role against the toxic effects induced by different harmful factors, both chemical and physical. But it must be

emphasized that its effect depends on many factors, such as its chemical form as well as the applied dose and experimental model, so supplementation must be performed taking proper precautions to obtain the best results and avoid the toxicity of selenium itself.^{5,10,24,36}

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