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FOCUSED REVIEW

Advances in Research on the Toxicological Effects of Selenium

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Abstract

Selenium is a trace element necessary for the growth of organisms. Moreover, selenium supplementation can improve the immunity and fertility of the body, as well as its ability to resist oxidation, tumors, heavy metals, and pathogenic microorganisms. However, owing to the duality of selenium, excessive selenium supplementation can cause certain toxic effects on the growth and development of the body and may even result in death in severe cases. At present, increasing attention is being paid to the development and utilization of selenium as a micronutrient, but its potential toxicity tends to be neglected. This study systematically reviews recent research on the toxicological effects of selenium, aiming to provide theoretical references for selenium toxicology-related research and theoretical support for the development of selenium-containing drugs, selenium-enriched dietary supplements, and selenium-enriched foods.

Keywords Selenium (Se) · Toxicological effects · Mechanism · Functional agriculture

Abbreviations

ABA	Abscisic acid
AIDS	Acquired immunodeficiency syndrome
GSH-Px	Glutathione peroxidase
Nano-Se	Nano-selenium
MDA	Malondialdehyde
SOD	Superoxide dismutase
CAT	Catalase
POD	Peroxidase
ROS	Reactive oxygen species
SDG	Selenodiglutathione

Introduction

Selenium is a non-metallic element first discovered in the lead chamber mud of a sulfuric acid plant by Swedish chemist Jöns Jacob Berzelius in 1817. Schwarz et al. (1957) proved that selenium prevented dietary liver necrosis in rats and exudative diathesis in chickens. Rotruck et al. (1973) further confirmed its role as the active center of glutathione peroxidase (GSH-Px) in rats. In 1973, WHO declared it to be a trace element indispensable to human and animal life. Later, Awasthi et al. (1975) proved that selenium was a component of GSH-Px in human red blood cells. Since then, selenium has been deemed to be a trace element essential for human physiology, with selenium research entering a new era (Hybsier et al. 2017; Ullah et al. 2018). Biological effects of selenium have attracted considerable attention from experts in the medical and nutrition fields. Extensive reports have shown that selenium deficiency is related to a variety of diseases such as liver disease (Schwarz and Foltz 1957), Keshan disease (Fan and Kizer 1990), Kaschin-Beck disease (Peng and Yang 1991), kidney disease (Iglesias et al. 2013), cancer, cardio-cerebrovascular disease, acquired immunodeficiency syndrome (AIDS), and malignant malnutrition (Gladyshev et al. 1999; Xia et al. 2005), indicating that selenium plays an important role in human physiology. Selenium is known to have a protective effect as research has shown that it has several biological functions; it enhances immunity (Broome et al. 2004; Carlson et al. 2010), improves fertility (Ahsan et al. 2014), promotes the growth of livestock and poultry (Benton and Cook 1990; Marin-Guzman et al. 2000; Navarro-Alarcón et al. 2002; Kommisrud et al. 2005; Lubos et al. 2010; Shi et al. 2010; Roy et al. 2011; Hughes et al. 2012; Liu et al. 2014; Habibian et al. 2015; Aghwan et al.

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2016; Talukdar et al. 2016), protects the liver, prevents some diseases (cancer, diabetes, AIDS, and cardio-cerebrovascular disease), delays aging, improves moods, regulates thyroid function (Rowntree et al. 2004; Lin et al. 2014), is resistant to heavy metals (Rusetskaya and Borodulin 2015), is resistant to pathogenic microorganisms (fungi, bacteria, viruses, and parasites) (Beck et al. 1994; Huang and Chen 1996; Qiao and Zhao 1997; Yu et al. 1997; Shisler et al. 1998; Wei et al. 2005; Huang 2006; Jaspers et al. 2007; Verma et al. 2008; Stone et al. 2010; Yu et al. 2011; Wang et al. 2012; Beheshti et al. 2013; Dagmar et al. 2014; De Miranda et al. 2014; Huang et al. 2014; Mahmoudvand et al. 2014; Cihalova et al. 2015; Liu et al. 2015; Mojtaba et al. 2015; Cheng et al. 2016; Dkhil et al. 2016; Guisbiers et al. 2016; Taylor et al. 2016; Guisbiers et al. 2017; Lv et al. 2018), and has an antioxidant activity (Wolonciej et al. 2016; Zhang et al. 2016b). However, selenium cannot be synthesized in the body and stored for a long time. Instead, it must be taken up by the body from external sources to maintain its dynamic balance (Rayman et al. 2008). The beneficial dose range of selenium is considerably narrow, and thus, a slight overdose above the necessary nutrient level will result in toxicity. Therefore, excessive selenium supplementation is harmful to the organism and may cause selenosis or induce mutations in severe cases (Han et al. 2016; Long et al. 2020). In 1990, the Joint FAO/IAEA/WHO Expert Committee on Trace Elements in Human Nutrition explicitly listed selenium as an "essential trace element in the human body" (Wang 2012). Moreover, in 2005, the US Food and Nutrition Board recommended that adults should not consume more than 400-μg selenium per day (Lee et al. 2015). In recent years, with the increase in cases of selenosis in humans as well as animals, such as horses, cattle, and sheep, due to long-term occupational exposure to excessive selenium compounds or due to excessive selenium in soils and foods in some areas, selenium toxicity research has been drawing increased attention across the globe (Wang and Niu 2010; Kohshahi et al. 2019). In the following sections, the progress in research on the toxic mechanism of selenium has been briefly reviewed to provide a theoretical basis for research on the development and utilization of selenium resources, their ecological risk assessment, and toxicological analysis.

Physical and Chemical Properties of Selenium

Physical Properties of Selenium

In nature, selenium is mainly distributed in rocks, soils, lakes, oceans, atmosphere, water, and the biosphere (Ren and Guo 2004), but the distribution is not uniform among many countries, with many areas naturally lacking selenium. In organisms, selenium mainly exists as selenomethionine obtained through diet and selenocysteine in selenoproteins; the former cannot be synthesized in vivo and serves as an unregulated storage form of selenium, so that when the dietary supply of selenium is interrupted, selenomethionine can provide selenium to the body, and can be substituted for protein methionine; the latter is a biologically active compound and also an important component of selenoproteins. Selenoproteins are the main functional form of selenium in the body, and there are more than 30 types of known selenoproteins so far, including nearly 15 that can be obtained through in vitro purification, which has provided a new basis for studying the functions of selenoproteins and their relationship with diseases (Kryukov et al. 2003; Qing and Zhang 2012).

Generally, selenium exists either as an element or as compounds, with the latter being the prevalent form. Studies have shown that the chemical species and quantity of selenium are closely related to its biological function, with the absorption efficiency, biological effect, and toxicity of selenium varying among different chemical species (Mu et al. 2004; Yu et al. 2006). The selenium element exists as solid powder in red or gray, with six solid allotropes, of which three are crystalline and the other three are amorphous. Nano-selenium (Nano-Se) is an elemental form of selenium with a valence of 0 in red and has a nanoscale size (generally < 60 nm in diameter) and possesses excellent nanoproperties. Owing to the advantages of structural uniformity, small size, abundant unsaturated surface bonds, large surface area, high surface activity, wide range of safe concentrations, high bioavailability, and excellent bioactivity, Nano-Se has been widely used as a new selenium additive in livestock and poultry feed (Jia et al. 2005; Yoon et al. 2007; Zhang et al. 2008a, b; Zhou et al. 2009; Li et al. 2011, 2020; Hu et al. 2012; Forootanfar et al. 2014; Yang et al. 2016). Selenium compounds come in inorganic selenium compounds, such as selenate and selenite, and organic selenium compounds, such as selenium polysaccharides, selenoproteins, selenium-containing nucleic acids, alkylated selenium, and selenoamino acids and their derivatives. The use of inorganic selenium compounds have been rigorously forbidden owing to their high toxicity, low toxic thresholds close to the necessary nutrient level, and low utilization efficiency, with the US, Japan, and other countries having banned the addition of inorganic selenium compounds such as sodium selenite to foods (Kucukbay et al. 2010; Wang et al. 2011). In contrast, most organic selenium compounds are good sources of selenium and may serve as a biologically active form of selenium. Organic selenium compounds have the advantages of low toxicity, fewer side effects, environmental friendliness, high biological activity, and easy reuse by the body. Selenium polysaccharides, for example, have dual physiological functions of providing energy for the body and

supplementing the body with selenium at the same time, and are thus the best selenium supplement (Zhang et al. 2016a).

Chemical Properties of Selenium

Selenium is a non-metallic chemical element in Group VIA and period 4 of the periodic table, with an atomic number of 34, a proton number of 34, a neutron number of 45, a molar mass of 79, and a relative atomic mass of 78.96 (Berzelius et al. 1817). Its valence electron arrangement is $[Ar]3d^{10}4s^24p^4$, with six valence electrons, including two unpaired electrons with the ability to form two covalent bonds, and a lone pair of p electrons not involved in bonding (Bjørklund et al. 2017). Selenium is a multivalent element in the chalcogen group, also known as the oxygen family, and has physical and chemical properties similar to those of sulfur and tellurium, especially with high similarity to tellurium in terms of atomic size, bonding energy, ionization energy, and electron affinity. Selenium has valences of − 2, 0, + 1, + 2, + 4, and + 6. Selenium with a valence of − 2 mainly exists as organic selenides, H_2Se, and some metal selenides. Selenium with a valence of 0 is mostly elemental selenium, in black, gray, or red. Selenium with a valence of + 4 mainly exists as sodium selenite and selenium dioxide. Selenium with a valence of + 6 mainly exists as selenate.

Toxicology of Selenium

Toxicity of Selenium

Selenium has been considered a highly toxic element for more than 100 years since its discovery. For example, Franke (1934a, b) confirmed that selenium acts as a harmful toxic substance in mammal diets. In the same year, the US Department of Agriculture discovered that, in the agricultural experiment stations of Wyoming and South Dakota, animals consuming plants with high selenium content were subject to alkalosis and blind staggers. Currently, increasing importance has been attached to the safety assessment of drugs and chemicals, and selenosis is also divided into the classes of general toxicity versus specific toxicity. According to the time and dose of selenium intake, the general toxicity of selenium is mainly characterized as acute selenosis and chronic selenosis. Acute selenosis refers to acute toxicity caused by a large dose of selenium intake in a short period of time, which is mainly manifested as respiratory distress, ataxia, diarrhea, vomiting, abdominal pain, and even death. Chronic selenosis refers to cumulative toxicity caused by long-term low-dose intake of selenium, which is mainly manifested as fatigue, depression, garlic odor in breath, anemia, feed intake reduction, hair loss, onychomadesis, hoof rot, growth retardation, and liver cirrhosis (Ekermans and Schneider 1982; Ju et al. 2018). In addition, excessive selenium can induce specific toxicity, including genotoxicity (Biswas et al. 2000), embryotoxicity (Goldhaber 2003), reproductive toxicity (He et al. 2002), immunotoxicity (Brown and Arthur 2001), and cytotoxicity (Markus et al. 2004). Recent studies have shown that the toxicity of selenium depends on its chemical species, and the intensity of the toxic effects of selenium also varies with animal species, nutritional statuses, and drug administration routes (Mu et al. 2004; Chang et al. 2019). When the chemical species of selenium are concerned, inorganic selenium compounds, in general, are more toxic than organic selenium compounds, and organic selenium compounds are usually more toxic than Nano-Se (Mcadam and Orville 1987; Gao et al. 2003). Inorganic selenium compounds show almost the same toxicity, while selenium toxicity varies greatly among organic selenium compounds. For example, the toxicity of selenocysteine is greater than that of selenomethionine. Moreover, the same organic selenium compound may show different toxicity at different conformations, as is the case with L-selenomethionine having greater toxicity than D-selenomethionine (Wilber 1980; Brahser and Ogle 1993; Choy et al. 1993).

Mechanism of Selenium Phytotoxicity

Absorption and Accumulation of Selenium in Plants

The absorption of selenium by plants is affected by exogenous selenium species, sulfur elements, plant species and their tissues and organs, as well as growth stages (Garousi 2017). For example, different plant species have different selenium accumulation capabilities, with the highest selenium concentration usually existing in root and tuber crops as well as bulb crops, followed by field crops (including cereals, beans, and cruciferous plants) with the second highest concentration, and thereafter, leafy vegetables, seed vegetables, vegetable fruits, and tree fruits, in order of decreasing concentration (Mikkelsen et al. 1989; Hamilton and Beath 2002). Even for the same plant species, its absorption of selenium will vary with the chemical species of selenium (Arvy 1993; Zhang et al. 2003). For example, plants can absorb selenite faster than selenate. Plants absorb selenite through efficient sulfur transfer proteins and accumulate it mostly in the roots, while selenate is absorbed by plants, possibly through passive transport, and mainly accumulated in the tender shoots (Shrift and Ulrich 1969; Adel and Lytle 1998; Terry et al. 2000; White et al. 2004; Sors et al. 2005).

Mechanism of Selenium Phytotoxicity

At normal or low selenium levels, the selenium metabolite selenocysteine is transported from the chloroplast to the

cytoplasm to continue the metabolic reaction. Conversely, at abnormally high or excessive selenium levels, selenium can have a negative effect on most selenium-sensitive plants, such as non-selenium-accumulating plants. In such plants, excessive selenocysteine will replace cysteine to participate in protein synthesis, which weakens the resistance of plants and damages their chlorophyll and anti-oxidative enzyme systems, thereby causing toxic effects (De Souza et al. 2000; Tai and Li 2002; Laure et al. 2007; Yi and Si 2007; Xu et al. 2011; Yang and Yang 2014; Li et al. 2016; Hou et al. 2018). Under normal circumstances, plants have the ability to adjust and adapt to adverse external environment, for which abscisic acid (ABA) is a very important indicator. Tai and Li (2002) have shown that excessive selenium can reduce the content of ABA in plants, suggesting that excessive selenium can inhibit the plants' ability to resist external adverse factors by decreasing their self-regulatory function, which will eventually lead to symptoms of phytotoxicity. Lin et al. (2005) showed that a high concentration of selenium significantly inhibits the chlorophyll *a* content and the chlorophyll *a*/*b* ratio in rice, and produces a stress effect on the anti-oxidative enzyme system, which significantly increases GSH-Px and malondialdehyde (MDA), while significantly decreasing the activity of superoxide dismutase (SOD), catalase (CAT), and peroxidase (POD). Li et al. (2003) showed that the effect of selenium on the antioxidant activity of plants is consistent with the effect of selenium on the growth of plants, suggesting that excessive selenium can decrease the content of reducing substances in plants by damaging the endogenous antioxidant system in plants, which further weakens the ability of plants to scavenge reactive oxygen species (ROS), thereby inhibiting plant growth. Sharma et al. (2014) observed increased levels of oxidative stress markers proline, H_2O_2, and MDA in rice leaves during the tillering and flowering periods, grown in high-selenium soils in India, confirming once again that selenium can inhibit plant growth by interfering with the antioxidant defense system of plants, and the affected plants show decreased dry matter weight.

Mechanism of Selenium Toxicity in Animals

Absorption, Distribution, Metabolism and Excretion of Selenium in Animals

Absorption of selenium varies among animal species, and is affected by physiological characteristics, functional status, amount of intestinal contents, chemical species of selenium, residence time of selenium in the intestine, and selenium administration routes (Sun et al. 2017; Allarabi et al. 2019; Lv and Wang 2019; Wei et al. 2019). Under normal circumstances, selenium enters the animal's body mainly through the digestive tract, respiratory tract, skins, veins, or subcutis, after which it is absorbed in the stomach and intestine to enter the blood, where it combines with plasma proteins to become biologically active selenoproteins, which are then transported to various tissues and organs for utilization (Kang 2009; Cao et al. 2017). Although all cells and tissues in animals' bodies contain selenium, the selenium content varies among tissues and is dependent on the dietary selenium level. For example, selenium will be preferentially distributed in body parts with sufficient blood supply, after which it is selectively redistributed according to the affinity of organs. As a result, selenium is mostly distributed in the liver, kidney, heart, and pancreas, followed by muscles, bones, and blood with the second highest abundance, and fat tissues with the lowest abundance (Hu et al. 2004). There are multiple pathways for selenium metabolism in animals. Inorganic selenium and organic selenium are involved in different metabolic pathways because they are different species of selenium. For example, sodium selenite, an inorganic selenium compound, is usually involved in only one metabolic pathway, where, under certain conditions it is first reduced to hydrogen selenide and then transported to the liver to become part of the selenium pool, where it is incorporated into selenoproteins as selenocysteine, or forms methylated metabolites to be finally excreted. In contrast, the organic selenium compound selenomethionine is mainly involved in two metabolic pathways, namely the methionine pathway and the selenium pathway. Generally, selenomethionine is absorbed by the body through the Na^+-dependent neutral amino acid transport system in the small intestine, and then exists in a bound form in the liver, kidney, skeletal muscles, gastrointestinal mucosa, and pancreas to participate in protein synthesis (Eskil and Sten-Olof 1966; Vendeland et al. 1994; Shi et al. 2003). Under normal circumstances, selenium metabolized by animals is mainly excreted through urine and feces, but in the event of high selenium intake, exhalation also serves as one of the important routes for excreting selenium. In addition, selenium can be excreted through hair and sweat (Shi et al. 2003).

Mechanism of Selenium Toxicity in Animals

Studies have shown that selenium as a micronutrient works within a narrow beneficial range for animals, with the relationship between the biological effects and the concentrations of selenium following the well-known Weinberg's principle (Scott 1973; Chen and Hou 2015). Selenosis is divided into acute selenosis and chronic selenosis. The main cause of the disease is that, after high concentrations of selenium enter the body, there is a competitive relationship between selenium and sulfur owing to the similarity of selenium to sulfur, with selenium being prone to act as a substitute for sulfur in sulfur-containing amino acids, to become selenomethionine and selenocysteine, which disturbs protein expression and deactivates SH-enzymes (such

as succinate dehydrogenase and δ-aminolevulinic acid dehydratase), thereby hindering the biochemical reaction in the body and causing damage to tissues and organs. As a result, animals exhibit abnormal physiological functions such as growth inhibition, fertility decline, and immunosuppression (Spallholz et al. 1973; Kajander et al. 1991; Daniels 1996; Gu et al. 1998; Lemly 1998; Vickerman et al. 2002; Popham et al. 2005; Wang et al. 2007; Han and Hou 2012; Han et al. 2016). In addition, some studies have shown that selenosis in animals is mainly attributed to the fact that selenium methylation, the main detoxification pathway of selenium in the body, is inhibited. For example, Hasegawa et al. found that high doses of selenocysteine administered to mice can inhibit selenium methylation by deactivating methionine adenosyltransferase (an enzyme responsible for the synthesis of *S*-adenosyl methionine), which leads to the accumulation of hepatotoxic selenides, especially large quantities of hydrogen selenide, and eventually liver damage in animal bodies (Tatsuya et al. 1996).

Moreover, there is a controversial mechanism underlying selenosis in animal bodies, namely the oxidative stress mechanism. Studies have shown that many selenium compounds (such as selenites, selenium dioxide, and diselenides) that are prone to form Se_2^- or SeH^- anions can react with oxygen in the presence of thiols (such as glutathione and cysteine) to produce superoxide or ROS, which leads to redox cycling, cell cycle arrest, endoplasmic reticulum (ER) stress and apoptosis in animal bodies (Per et al. 1988; Seko et al. 1988; Yan and Spallholz 1993; Lanfear et al. 1994; Nakamuro et al. 1997; Wang et al. 2002; Mu et al. 2004; Spallholz et al. 2004; Wycherly et al. 2004; Rayman et al. 2008; Pacini et al. 2013). For example, Yao et al. (2015) indicated that selenium induced oxidative stress in chicken liver and the occurrence of oxidative stress can induce continuous ER stress through interfering with the oxidation of the internal environment of the ER, which process may be involved in the PERK, ATF6 and IRE1 pathways. Kim et al. (2004) illustrated that the oxidative-ER stress pathway participates in selenite-induced apoptosis in Chang liver cells. Hwang et al. (2007) showed that selenium treatment led to the activation of the ER stress signal through the phosphorylation of JNK and eIF2 protein and Zachariah et al. (2015, 2016) verified that high selenium induced endothelial dysfunction via endoplasmic reticulum stress. In contrast, some studies have revealed that selenodiglutathione (SDG), the primary metabolite of selenites, cannot induce oxidative stress similar to that induced by typical oxidants such as H_2O_2 (Harrison et al. 1997). However, as pointed out by Seko and Imura (1997), experimental designs adopted in earlier studies on proving that the production of ROS might be a mechanism of selenium toxicity are subject to a few shortcomings. In addition, some scholars believe that excessive selenium can damage cellular functions by affecting the level of vitamin A in the body (Chen et al. 1997; Mu et al. 2004), whereas others believe that excessive selenium can oxidize sulfhydryl groups to inhibit or damage some enzymes or functional proteins in the mitochondria, resulting in the inhibition of mitochondrial energy metabolism and blockage of the function (Deagen et al. 1987; Mu et al. 2004). Furthermore, few other scholars believe that excessive selenium can cause a large amount of intracellular Ca^{2+} to accumulate by disturbing the Ca^{2+} signaling pathway in the body, which in turn activates Ca^{2+}-dependent intracellular enzymes (such as endonucleases, transglutaminase, and calpain) and causes poisoning phenomena such as DNA breakage in the host cell chromatin, cytoplasmic protein cross-linking, and cytoskeleton destruction (Carson and Ribeiro 1993; Xu et al. 2002; Zhivotovsky and Orrenius 2011).

Mechanism of Selenium Toxicity in Microorganisms

Metabolism of Selenium in Microorganisms

Microorganisms play an important role in the geochemical cycling of selenium. Studies have shown that microorganisms can metabolize selenium through various pathways of transport, reduction, oxidation, assimilation, and methylation, to achieve selenium species transformation and self-detoxification (Nancharaiah and Lens 2015; Xu et al. 2017).

Mechanism of Selenium Toxicity in Microorganisms

Currently, increasing evidence shows that in addition to toxic effects on the growth and related physiological functions of animals and plants, selenium also has certain negative effects on microbial growth. It has been reported that Nano-Se has a significant antibacterial effect on *Staphylococcus aureus*, and it is speculated that Nano-Se may affect the growth of bacteria by inhibiting the formation of cell membranes (Tran and Webster 2011; Dagmar et al. 2014; Khiralla and El-Deeb 2015; Wang et al. 2015; Guisbiers et al. 2016). It is also reported that selenium can inhibit pathogenic bacteria such as *Salmonella* spp. and *E. coli*, but the specific mechanism remains unclear (Wang et al. 2015; Li et al. 2017). For viruses, numerous studies have shown that the replication of many viruses is affected by selenium, including DNA viruses, RNA viruses, and subviruses (Lv et al. 2018). For mouse mammary tumor virus and porcine parvovirus, studies have shown that methylselenic acid can inhibit the replication of mouse mammary tumor virus by regulating epigenetic markers (De Miranda et al. 2014), whereas sodium selenite, selenomethionine, and seaweed selenium polysaccharides inhibit the replication of porcine parvovirus by scavenging oxygen free radicals (Wei et al. 2005). For fungi, many studies have shown that selenium can antagonize the infection of fungi such as *Aspergillus*

Table 1 Species-related toxic effects of selenium

Species	Species-related toxic effects of selenium	References
Plant	(a) Excessive selenocysteine will replace cysteine to participate in protein synthesis, which damages their anti-oxidative enzyme systems	Yang and Yang (2014), Hou et al. (2018)
	(b) Excessive selenium can reduce the content of ABA in plants, decreasing their own resistance	Tai and Li (2002)
	(c) Destroying the plants' own protective enzyme system(taking GSH-Px for example), inhibiting the antioxidant capacity of plants	Lin et al. (2005), Li et al. (2003), Sharma et al. (2014)
Animal	(a) Selenium acts as a substitute for sulfur in sulfur-containing amino acids, which disturbs protein expression and deactivates SH-enzymes, thereby hindering the biochemical reaction in the body	Daniels (1996), Lemly (1998)
	(b) High doses of selenocysteine can inhibit selenium methylation by deactivating methionine adenosyltransferase	Tatsuya et al. (1996)
	(c) Selenium compounds that are prone to form Se_2^- or SeH^- anions can react with oxygen in the presence of thiols to produce superoxide or ROS, which leads to oxidative-stress	Nakamuro et al. (1997), Spallholz et al. (2004)
	(d) Excessive selenium damages cellular functions by affecting the level of vitamin A in the body	Chen et al. (1997), Mu et al. (2004)
	(e) Excessive selenium can oxidize sulfhydryl groups to inhibit or damage some enzymes or functional proteins in the mitochondria, resulting in the inhibition of mitochondrial energy metabolism and blockage of the function	Deagen et al. (1987), Mu et al. (2004)
	(f) Excessive selenium can disturbs the Ca^{2+} signaling pathway in the body, which causes poisoning phenomena such as DNA breakage in the host cell chromatin, cytoplasmic protein cross-linking, and cytoskeleton destruction	Carson and Ribeiro (1993), Xu et al. (2002), Zhivotovsky and Orrenius (2011)
Microorganism	(a) Nano-Se inhibits the formation of cell membranes and thereby affecting the growth of bacteria and fungi	Tran and Webster (2011), Khiralla and El-Deeb (2015), Wang et al. (2015), Guisbiers et al. (2017)
	(b) Methylselenic acid can inhibit the replication of mouse mammary tumor virus by regulating epigenetic markers	De Miranda et al. (2014)
	(c) Sodium selenite, selenomethionine, and seaweed selenium polysaccharides inhibit the replication of porcine parvovirus by scavenging oxygen free radicals	Wei et al. (2005)

flavus, *Magnaporthe oryzae*, *A. fumigatus*, and *Candida albicans* (Mojtaba et al. 2015; Yao et al. 2016; Guisbiers et al. 2017; Hosnedlova et al. 2017; Zhou 2018). For example, Guisbiers et al. (2017) have shown that Nano-Se can destroy the cell structure in *C. albicans* by replacing sulfur on the biofilm, thereby inhibiting the formation of biofilm, eventually inhibiting the fungal growth.

Summary and Prospects

This article reviewed the progress in research on the selenosis mechanism in plants, animals, and microorganisms (summarized in Table 1). Although selenosis may involve many different mechanisms, the mechanisms of selenium toxicity are far from being clear. Generally, the mechanisms of selenium toxicity may involve three main aspects: (i) oxidative stress, (ii) inhibition of biofilm formation, and (iii) disturbance of enzyme activity. The ever-growing understanding of selenium toxicity, especially in-depth research on the nutrition and toxicity mechanisms of various newly developed selenium-enriched foods, selenium-containing drugs, and selenium-enriched dietary supplements in different organisms, will provide theoretical support for the rational utilization of selenium resources, assessment of ecological risks, and appropriate use of selenium products.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Research Involving Human Participants and/or Animals Not applicable.

Informed Consent Not applicable.

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