

Insights into the mechanisms of arsenic-selenium interactions and the associated toxicity in plants, animals, and humans: A critical review

Waqar Ali, Hua Zhang, Muhammad Junaid, Kang Mao, Nan Xu, Chuanyu Chang, Atta Rasool, Muhammad Wajahat Aslam, Jamshed Ali & Zhugen Yang

To cite this article: Waqar Ali, Hua Zhang, Muhammad Junaid, Kang Mao, Nan Xu, Chuanyu Chang, Atta Rasool, Muhammad Wajahat Aslam, Jamshed Ali & Zhugen Yang (2020): Insights into the mechanisms of arsenic-selenium interactions and the associated toxicity in plants, animals, and humans: A critical review, *Critical Reviews in Environmental Science and Technology*

To link to this article: <https://doi.org/10.1080/10643389.2020.1740042>



Published online: 18 Mar 2020.



Submit your article to this journal [↗](#)



View related articles [↗](#)



Insights into the mechanisms of arsenic-selenium interactions and the associated toxicity in plants, animals, and humans: A critical review

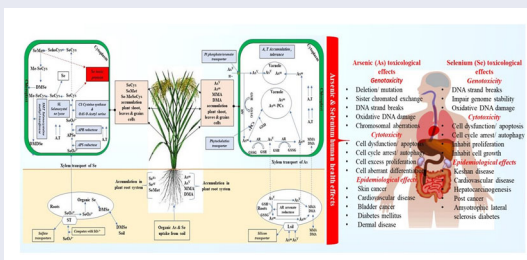
Waqar Ali^{a,b}, Hua Zhang^a, Muhammad Junaid^c, Kang Mao^a, Nan Xu^c, Chuanyu Chang^{a,b}, Atta Rasool^d, Muhammad Wajahat Aslam^{a,b}, Jamshed Ali^{a,b}, and Zhugen Yang^e

^aState Key Laboratory of Environmental Geochemistry, Institute of Geochemistry, Chinese Academy of Sciences, Guiyang, China; ^bUniversity of Chinese Academy of Sciences, Beijing, China; ^cKey Laboratory for Heavy Metal Pollution Control and Reutilization, School of Environment and Energy, Peking University Shenzhen Graduate School, Shenzhen, China; ^dDepartment of Environmental Sciences, COMSATS University, Islamabad (CUI), Vehari, Pakistan; ^eCranfield Water Science Institute, Cranfield University, Cranfield, UK

ABSTRACT

This review highlights arsenic (As) and selenium (Se) sources in the environment, their uptake in the soil-plant system, interactions between these metals and the associated toxicity in major biological compartments, which may assist in addressing the hazardous impacts associated with As and Se contamination. The interaction between As and Se is a

critical factor for a detailed systematic understanding of the transportation, environmental fate, and associated toxicological effects of these metalloids in plants, animals, and humans. Arsenic and Se induce cytotoxicity and genotoxicity through the generation of reactive oxygen species (ROS). Compared to arsenite (As^{III}), methylated arsenicals, including methylarsonous acid (MAs^{III}) and dimethylarsinous acids ($DMAs^{III}$), exhibit more cytotoxic and genotoxic potential to inhibit more potent enzymes and activate the protein AP-1, which is a critical marker of genetic stability. Methylated As^{III} and its associated metabolites are well-known potential carcinogens that induce toxicity by blocking Se metabolism pathway. The imbalance of Se compounds can lead to the generation of ROS, which can inhibit or decrease genomic stability. The As and Se nexus also affect cellular signaling through activation of transcription factors such as NF κ B and AP-1.



KEYWORDS Arsenic-selenium; complex-interactions; toxicity

CONTACT Hua Zhang  zhanghua@mail.gyig.ac.cn  State Key Laboratory of Environmental Geochemistry, Institute of Geochemistry, Chinese Academy of Sciences, Guiyang 550081, China.

© 2020 Taylor & Francis Group, LLC

1. Introduction

Previous cutting-edge studies have suggested that the understanding of mechanistic interactions between As and Se is critical to unveil their environmental fate and health-related consequences in animals and humans. Arsenic is the 20th most abundant element in the earth's crust and is a well-known human carcinogen that exists as only one isotope in nature (Ali, Aslam, et al., 2019; Ma et al., 2001). Two main species of As exist in the terrestrial environment, arsenate (As^{V}) and arsenite (As^{III}), which are dominant under oxidizing and reducing environmental conditions, respectively (Sun et al., 2014). Arsenic could present the different modes of toxicity in biological system (owning to its difference in chemical speciation). For instance, the final metabolic products of As, monomethylarsonic acid (MMA^{V}) and dimethylarsinic acid (DMA^{V}) are moderately less toxic than inorganic As, albeit the toxicity of the intermediate metabolites such as, monomethylarsonous acid (MMA^{III}) and dimethylarsinous acid (DMA^{III}) is considerably higher than inorganic As^{V} such as MMA^{V} , DMA^{V} , and As^{III} . In major biological systems (plants, animals, and humans), the toxicity behavior of different As species increases in the order of $\text{As}^{\text{V}} < \text{MMA}^{\text{V}} < \text{DMA}^{\text{V}} < \text{As}^{\text{III}} < \text{MMA}^{\text{III}} \approx \text{DMA}^{\text{III}}$ (Bastías & Beldarrain, 2016; Sun et al., 2014).

Selenium is a metalloid that was first discovered in 1817 by the Swedish chemist Jons Jacob Berzelius and exists in the earth's crust at the level of 50 to 90 $\mu\text{g}/\text{kg}$ (Shahid et al., 2018; Sneddon, 2012). Selenium has various valance states, including selenide (Se^{2-}), selenium (Se^0), thioselenate (SSeO_3^{2-}), selenite (Se^{IV}), and selenate (Se^{VI}) (Chauhan et al., 2019; Schiavon & Pilon-Smits, 2017). Similar to As, where As^{V} is less toxic than As^{III} , Se^{VI} is less toxic than Se^{IV} in both eukaryotes and prokaryotes (Sun et al., 2014). However, different studies have suggested that Se^{IV} and Se^{VI} are not only the most abundant forms of Se but also the only forms available for plant uptake (Shahid et al., 2018). Abbreviations used in the current review are listed in Table 1.

Selenium is also an essential element for microbes, animals, and humans at a certain level. For example, the Se recommended dietary allowance (RDA) limit is 55 $\mu\text{g}/\text{day}$ for adults (Sun et al., 2014; Zeng, Uthus, & Combs, 2005; Zwolak & Zaporowska, 2012). Selenium acts as a critical component in different selenoproteins, including glutathione peroxidases (GPx), a family of antioxidant enzymes in animals and humans (Savitha, 2014). Selenium occurs in numerous oxidation states that permit the production of organoselenium and selenoamino acid complexes (Tinggi, 2003). In the plant system, Se is also considered a beneficial element, acts as an antioxidant at low and acceptable doses, and protects plants from various types of abiotic stresses. However, an excessive amount of Se in the plant system behaves like a pro-oxidant and causes toxicity (Shahid et al., 2018).

Table 1. Abbreviations used in the current review.

Name	Abbreviations	Name	Abbreviations
Adenosine triphosphate	ATP	Activation protein	AP
Arsenate	As ^V	Adenosine phosphoselenate	APSe
Arsenic	As	Arsenite-glutathione complex	As (GS) ₂ -OH, As(GS) ₃
Arsenic reductase	AR	Dimethyl selenide	(CH ₃) ₂ Se (DMSe)
Arsenic triglutathione	As (GS) ₃	Dimethyl diselenide	DMDS ₂
Arsenite	As ^{III}	Ebselen	C ₁₃ H ₉ N ₃ OSe
Arsenite methyltransferase	As ^{III} MT	Glutaredoxins	Grxs
Dimethylarsenic acid	DMA	Hydrogen selenide	H ₂ Se
Dimethylarsinic	DMA ^{III}	Methylselenol	CH ₃ SeH
Dimethylarsinic acid	(CH ₃) ₂ (OH) ₂ AsO ⁻	Mitogen-Activated Protein Kinase	MAPK
Dimethylarsinic glutathione	DMA ^{III} (GS)	Phenylselenenyl chloride	C ₆ H ₅ ClSe
Dimethylarsinous	DMA ^V	Phenylseleninic acid	C ₆ H ₆ O ₂ Se
Glutathione	GSH	Phosphate transporter	Pi
Methyl group	CH ₃ ⁺	Phytochelatin transporter	PCs
Monomethyl dithioarsenic	MMDTA ^V	Reactive oxygen species	ROS
Monomethyl monothioarsenic	MMMTA ^V	S-adenosylmethionine	SAM
Monomethylarsenic acid	MMA	Selenate	Se ^{VI}
Monomethylarsonic	MMA ^{III}	Selenide	Se ²⁻
Monomethylarsonic diglutathione	MA ^{III} (GS) ₂	Selenite	Se ^{IV}
Monomethylarsonous	MMA ^V	Selenium	Se
Monomethylarsonous acid	(CH ₃)(OH) ₂ AsO ⁻	Selenocysteine	SeCys
Oxidized glutathione	GSSG	Selenomethionine	SeMet
Pentavalent dimethylarsinic acid	DMA ^V	Seleno persulfide	GSSeH
Pentavalent monomethyl arsonic acid	MMA ^V	Selenotrisulfide	RSSeSR
S-Adenosylhomocysteine	SAH	Sulfate transporter	ST
S-Adenosylmethionine	SAM	Sulfide	S ²⁻
Trimethylarsineoxide	TMAO ^{III}	Thioselenate	SSeO ₃ ²⁻
Trimethyl arsenic oxide	TMAO ^V	Phytochelatin	PCs
Damage regulated autophagy modulator	DRAM	Silicon transporter	Lsil
Thioredoxin reductase	TrxR	Thioredoxin	Trx
Trivalent monomethyl arsenous acid	DMA ^{III}	Trimethyl selenium	(CH ₃) ₃ Se

Selenite is commonly used as a feed additive in different commercial animal diets with a recognized Se dose of 0.5 mg/kg for the whole feed (Zwolak, 2019). In humans, Se intake varies across various countries. Overall, Se consumption for adults ranges from 93 to 134 µg/day in North America; the optimal Se consumption ranges from 52 to 64 µg/day in Western Europe; low levels of Se consumption range from 30 to 40 µg/day in Eastern Europe (Zwolak, 2019). This metalloid is also known as a cancer chemopreventive compound, which is indispensable for cells to function properly (Zeng et al., 2005). Several mechanisms have been reported on the chemoprotective effects of Se, such as antioxidant protection, reduction in the carcinogenic metabolic effects, enhancement of the immune surveillance system, and inhibition of the angiogenesis process and cell cycle (Lu & Jiang, 2001; Zeng, 2009).

Several mechanisms have been proposed to elucidate the interaction between As and Se. However, the biological interactions between As and Se depend on specific biochemical forms because As and Se are metalloids with similar chemical properties that are intensely alike with different biological effects (Sun et al., 2014). However, the antagonistic effects or natural

detoxification between As and Se have been confirmed in several animal species, as well as in humans (Zwolak & Zaporowska, 2012). Due to their chemical similarity, As and Se both play dual roles in cancer. Arsenic is known for its carcinogenicity; however, it has also been used in treating certain cancers. Likewise, Se is known as an anticarcinogen that also causes cancer. To date, substantial research has been done to elucidate insights into their carcinogenic mechanisms and interactions between their double roles of carcinogens and anticarcinogens (Sun et al., 2014).

Historically, Mexon first introduced and used As as a treatment in 1938 to reduce the toxicity of Se in animals (Rosen & Liu, 2009). Elevated concentrations of both As and Se in animals and humans cause the release, relocation, and removal of essential or non-essential metals *via* biliary, urinary, and expiratory pathways (Gaxiola-Robles et al., 2014). Several recent studies have elucidated the protective competence of Se from Se^{IV} in contrast to As^{III} and its renal toxicity, immunotoxicity, and/or cardiovascular injury in animals and humans (Zwolak, 2019). Mechanistic interactions between As and Se signify the protective effects of Se on As methylation efficiency, such as the elevated concentration of urinary Se mainly related to an increased percentage of DMA^V and a reduced percentage of inorganic As in the urine of As-exposed pregnant women in Chile and Taiwan (Christian, Hopenhayn, Centeno, & Todorov, 2006; Hsueh et al., 2003). However, findings from another study on As-exposed adults suggested that the plasma Se level was inversely related to the percentage of total As concentration in blood and urine and the percentage of MMA^V is related to the percentage of DMA^V in blood; moreover, plasma Se did not affect As metabolites in the urine of the studied population (Pilsner et al., 2010).

Recently, a study on unexposed preschool children in Taiwan confirmed that elevated concentrations of Se in plasma were related to a decreased percentage of MMA^V and an increased percentage of DMA^V (Su et al., 2019). However, contrary results were reported by Skröder Löveborn et al., who revealed a positive interaction between increasing erythrocyte levels of Se and increasing percentages of As and MMA^V in urine samples collected from children, implying that Se contributed to the methylation of As in children (Skröder Löveborn et al., 2016). Furthermore, Styblo and Thomas (2001) reported that Se^{IV} at a 2 μ M dose could inhibit the As^{III} methylation process and increase the cellular retention of As-induced toxicity mediated by MMA^{III}, DMA^{III}, and As^{III} in rat hepatocytes (Styblo & Thomas, 2001). To date, these contradictory results have been stated in the reviewed literature as both antagonistic and synergistic interactions, and toxicity exists between As and Se (Sun et al., 2014).

Considering all of this background information on the significance of As and Se in biological systems and most importantly their interaction (which

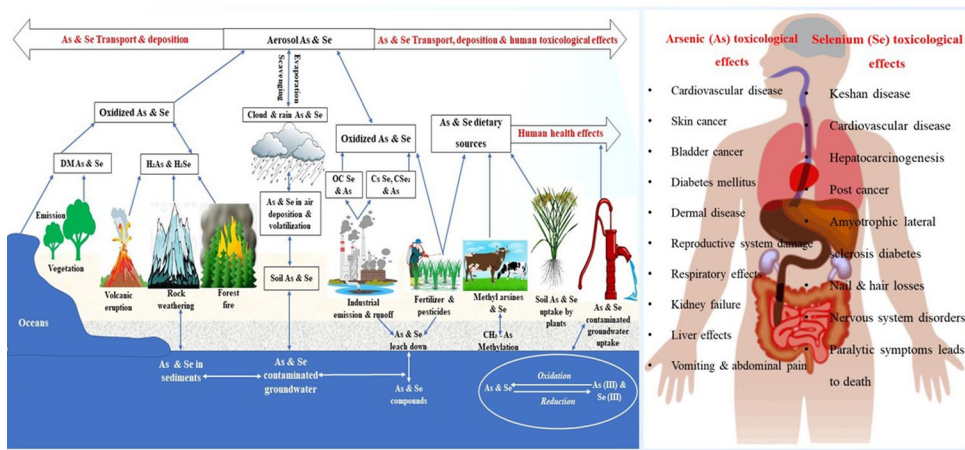


Figure 1. General overview of arsenic and selenium transport and their fate in various environmental matrices associated with human health and toxicological effects.

is currently largely scarce), this review aims to highlight the following three main objectives: 1) to explain the possible mechanisms of As and Se uptake in the soil-plant system and plant toxicity, 2) the As and Se interactions in animals and humans, and 3) the physiological significance of the metabolic process of Se to understand the toxicity and exposure routes of As.

2. Arsenic and selenium fate in the environment and their associated effects

Anthropogenic sources of As and Se include mining, smelting, metal ore processing, coal combustion, and municipal, industrial and domestic waste disposal, while natural sources comprise volcanic eruption and rock weathering (Figure 1) (Ali, Aslam, et al., 2019; Wen & Carignan, 2007; Zeng et al., 2015). In the past, As and arsenical compounds were widely used for the preparation of insecticides, pesticides, herbicides, and fungicides (Ali, Mushtaq, et al., 2019).

Arsenic naturally occurs in over 200 numerous forms of minerals, of which approximately 60% are arsenates, 20% are sulfides and sulfosalts, and 20% are oxides, arsenide, arsenite, silicates, and elemental As (Ali, Aslam, et al., 2019). Naturally, there are four processes, i.e., reductive dissolution, sulfide oxidation, alkali desorption, and geothermal activities, that are usually involved in releasing As into different environmental compartments, such as the air, soil, and groundwater (Bhattacharya, Mukherjee, Bundschuh, Zevenhoven, & Loeppert, 2007). Arsenic can also be derived from natural sources, presumably from detrital chlorite (Hering, Burris, Reisinger, & O'Day, 2008). The oxidation-reduction potential (Eh) and pH are two primary significant factors that control As speciation and solubility,

both in soil and groundwater (Frohne, Rinklebe, Diaz-Bone, & Du Laing, 2011). At neutral and slightly acidic pH values, As^{III} compounds exist as non-dissociated salts, while at $\text{pH} > 8$, they exist as anionic species (Ali, Aslam, et al., 2019).

Moreover, microbial activities influence As behavior in the soil environment and increase As availability in the soil-plant system (Khalid et al., 2017; Liu et al., 2019). Arsenic is mainly adsorbed by iron oxyhydroxides in sediment from which it is released into the soil, air, and groundwater by microbial degradation (Brammer & Ravenscroft, 2009). Microbes primarily degrade organic matter and reduce ferric iron to the soluble form of ferrous iron and, consequently, As is released into the soil system (Huang, 2014). Various microbes, such as *Bacillus arsenicoselenatis*, *Crysiogenes arsenates*, and *Geospirillum arsenophilus*, play a significant role in the redox transformation of As^{V} to As^{III} through reduction by using As^{V} as a terminal electron acceptor (Khalid et al., 2017). However, As methylation also takes place under oxidizing or reducing environmental conditions by a variety of microbes. During the As microbial methylation process, As^{V} is converted to As^{III} followed by several steps to form several organic As compounds, such as MMA^{V} , DMA^{V} , and trimethyl arsine (TMA) (Khalid et al., 2017; Rahman et al., 2014).

Arsenite is sixty times more poisonous and cancer-causing to humans than As^{V} (Hughes, Beck, Chen, Lewis, & Thomas, 2011). Arsenite can bind to tissues for an extended period through specific groups of proteins that distress ATP synthesis (Brown & Ross, 2002; Chandrakar, Pandey, & Keshavkant, 2018). Long-lasting As exposure damages the human cardiovascular, dermal, neurological, hepatic, respiratory, and reproductive systems (Ali, Mushtaq, et al., 2019).

Selenium is also a well-known toxic element, and Se and Se compounds are widely used as feed additives (Navarro-Alarcon & Cabrera-Vique, 2008), which exhibit adverse effects on the environment and food chain and have been discussed comprehensively during the recent past (Chauhan et al., 2019). Similar to As, Se can also be biologically transformed through redox methylation reactions mediated by a variety of microbes. In the soil system, microbes can reduce Se^{VI} and Se^{IV} to elemental Se directly or by changing the pH and Eh, which makes Se^{IV} comparatively more available to plants than Se. However, this transformation process can also occur in both oxidizing and reducing soil conditions (Saha, Fayiga, & Sonon, 2017). Microbes can make use of both Se^{VI} and Se^{IV} as terminal electron acceptors during respiration under reducing soil conditions (Saha et al., 2017). However, both organic and inorganic forms of Se are actively transformed into volatile methylated organic complexes such as dimethyl selenide (DMSe) and dimethyl diselenide (DMDS₂) by fungi, bacteria and plant roots (Winkel

et al., 2015). DMSe is a critical compound produced through respiration by plants and microbes (Stolz, Basu, Santini, & Oremland, 2006).

Selenium plays a vital role in the scavenging and regulation of free radicals (Hartikainen, 2005). At physiological pH, Se complexes (selenols) readily dissociate and participate in catalytic reactions (Tinggi, 2003). In the human body, excessive Se changes to selenocysteine (SeCys), which is known as the 21st proteogenic amino acid, an essential component of 25 various selenoproteins (Chauhan et al., 2019; Constantinescu-Aruxandei, Frîncu, Capră, & Oancea, 2018). Integration of SeCys instead of cysteine at the active sites of enzymes such as methionine-R-sulfoxide reductase can change their catalytic activity and electron donor specificity, which is considered to be Se toxicity in humans (Gromer, Eubel, Lee, & Jacob, 2005; Stadtman, 2005). The occurrence of SeCys in the active sites of antioxidant enzymes produces maximum catalytic activity because of the stronger nucleophilic influence of SeCys in contrast to cysteine (Cys) (Snider, Ruggles, Khan, & Hondal, 2013). This causes an alteration in SeCys biosynthesis or precise integration into Se-requiring proteins, which can lead to neurological and several other disorders (Chauhan et al., 2019).

Approximately 0.5 to 1 billion people worldwide suffer from Se deficiency (Jones et al., 2017), which makes them prone to several diseases, such as white muscle and Keshan disease (Shahid et al., 2018). Selenium deficiency occurs in humans when Se intake is $<40 \mu\text{g}/\text{d}$ (Navarro-Alarcon & Cabrera-Vique, 2008; Winkel et al., 2011), which can cause reduced bone metabolism, growth obstruction, irregularities in thyroid function, reduced fertility, a weakened immune system, and even induce cancer (Chang et al., 2019; Gupta & Gupta, 2017; Navarro-Alarcon & Cabrera-Vique, 2008). Inorganic Se is 40 times more toxic than organic Se (Vinceti, Maraldi, Bergomi, & Malagoli, 2009). However, an intake of Se that is $>400 \mu\text{g}/\text{d}$ (Winkel et al., 2011) can lead to severe toxicological effects in humans, such as skin lesions, nail and hair loss, cancer, nervous disorders, amyotrophic lateral sclerosis, diabetes, and paralytic symptoms (Chauhan et al., 2019; Fordyce, 2013).

3. Arsenic and selenium uptake, translocation, accumulation, and toxicity in plant systems

3.1. Arsenic

Arsenic uptake, translocation, accumulation, and toxicity in plants and food crops depend on environmental conditions, plant species, and the bio-availability of As species (Bhattacharya et al., 2012). Arsenate is a major As species in aerobic soil systems because As^{V} has a strong affinity to bind to iron oxide or to undergo hydrolysis; therefore, the As^{V} level ranged from

<2.3 to 53 μM in uncontaminated or moderately to highly contaminated soil solutions, respectively (Wilson, Lockwood, Ashley, & Tighe, 2010; Zhao, Ma, Meharg, & McGrath, 2009). Arsenite is predominately observed in reducing environmental conditions, such as in flooded paddy soil (Zhao et al., 2009). Thermodynamically, the reduction of As^{V} to As^{III} takes place in between redox potential, leading to the mobilization of As^{III} into the soil solution, which causes an increase in As availability to plants (Chen et al., 2017). In paddy flooded soil, the concentration of As^{III} ranges from 0.01 to 3 μM , a concentration that is much higher than that in As^{V} -contaminated soils (Zhao et al., 2009).

In plants, various protein transporters assist the uptake of As in its inorganic form, and this process usually depends on the As concentration gradient between the source and sink (Abbas et al., 2018). Arsenic uptake in plant cells depends on As species such as As^{V} and uses different phosphate (Pi) transporters that belong to the PHT1 family because phosphate is chemically similar to As^{V} (Moreno-Jiménez, Esteban, & Peñalosa, 2012). However, As^{III} uses silicon (Si) transporters due to its resemblance to Si (Bastías & Beldarrain, 2016). Arsenite is facilitated by aqua glycoprotein nodulin-like essential proteins (NIPs) (Bastías & Beldarrain, 2016). Under Si deficiency, the expression of influx Si transporters (Lsi1 and Lsi2) increases (Ma & Yamaji, 2008). The accumulation of Si in plant cells is controlled by the Lsi1 and Lsi2 transporters, which are contained at the proximal or distal flanks of epidermal and endodermal cells, which help in the transportation of As across the plant's cells and tissues (Abbas et al., 2018). However, traces of methylated As species, well known as MMA and DMA, are also found in some As-contaminated soils (Zhao et al., 2009).

Monomethylarsenic acid and DMA have mainly originated from the past use of arsenical compounds such as herbicides or insecticides or may also be synthesized by algae or soil microorganisms (Zhao et al., 2009). Monomethylarsenic acid and DMA are absorbed by aquaporins using the same uptake mechanisms as glycerol in plant cells (Bastías & Beldarrain, 2016). Once the As species mobilize from soil to plant root cells (Figure 2), As^{V} is mainly reduced by As-reductase (AR) to As^{III} , which can cause the transformation of glutathione (GSH) to its oxidized form GSSG (Abbas et al., 2018). Arsenite is transformed into trimethyl arsenic oxide (TMAO^{V}) or trimethyl arsine oxide (TMAO^{III}), and the end product of As methylation is released into the environment (Bastías & Beldarrain, 2016). The alternative route of As detoxification happens by phytochelatin (PC) synthesis due to the condensation of amino acids such as glutamate (Glu), glycine (Gly), and cysteine (Gupta & Khan, 2015). Within the vacuole, the appropriation of As^{III} -PC compounds occurs through the activation of different unknown transporters (Awasthi, Chauhan, Srivastava, & Tripathi,

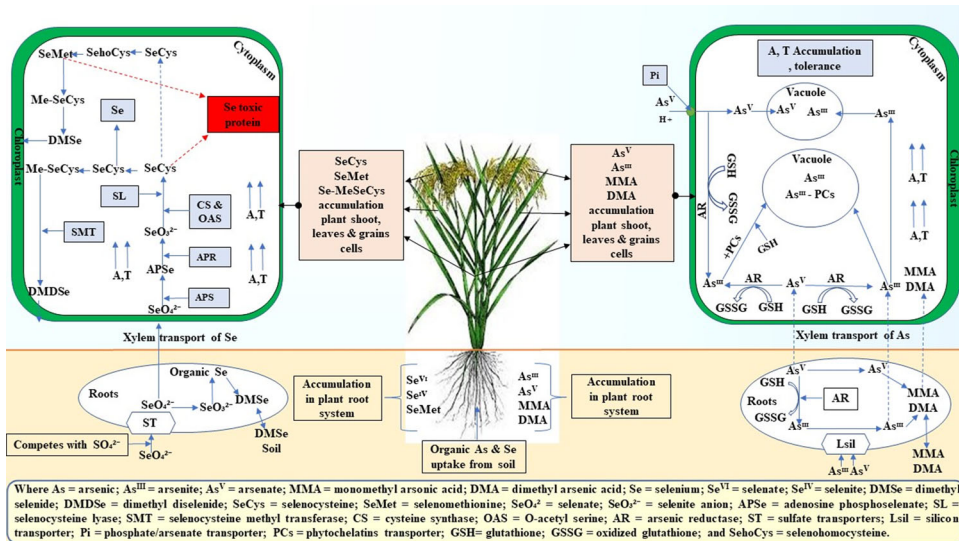


Figure 2. An overview of arsenic and selenium uptake, accumulation, metabolic reactions, and pathways in the soil-plant system.

2017). Arsenite causes more toxicity than As^V and can bind with various proteins or peptides, which contain thiol groups known as metallothionein, glutathione, and phytochelatins, making them inactive compounds that protect cell components from As-induced toxicity (Ali, Isayenkov, Zhao, & Maathuis, 2009; Bastías & Beldarrain, 2016).

Previous studies have suggested that the reduction of As occurs mainly in root cells before transport to the xylem and the remaining parts of the plants (Zhao et al., 2009). Arsenite and As^V are the predominant As species primarily found in the xylem sap of plants (Finnegan & Chen, 2012). A small concentration of total As is absorbed through the plant root, and only a minute quantity is sequestered in the leaf, shoot, and grain vacuoles because As reduction and sequestration mechanisms are similar to those of the roots (Bastías & Beldarrain, 2016). Hence, the occurrence of As^{III} and As^V in the phloem is a requirement for its distribution to other parts of the plant (Chen et al., 2017). Elevated As concentrations in the soil causes disruption of normal plant function and metabolism, leading to stunted plant growth as well as low productivity (Moreno-Jiménez et al., 2012).

Arsenic disrupts plant biochemical and metabolic pathways, such as delayed nutrient absorption, effects on the plant photosynthetic system, interruptions in plant water uptake status, interactions with different functional groups of plant enzymes, and the exchange of essential ions from ATP in plants growing in As-polluted soils (Abbas et al., 2018). Once As is absorbed by plants, the plant light-harvesting system might be affected by a decrease in chlorophyll levels and photosynthetic activity (Sharma, 2012). A

notable decrease in the chlorophyll content and pigment synthesis was described due to deficiency in the adaptive adjustment of plant photosystems I and II due to elevated As (Garg & Singla, 2011). Correspondingly, a reduction in chlorophyll synthesis was observed in different plants, such as *Trifolium pratense* L., *Zea mays*, and *Lactuca sativa* (Abbas et al., 2018).

Arsenic causes severe damage to the chloroplast membrane, which leads to disturbed functioning of essential plant photosynthetic processes, such as the rate of carbon dioxide (CO₂) fixation, and significantly reduces the functionality of PS-II (Asati, Pichhode, & Nikhil, 2016; Garg & Singla, 2011; Stoeva & Bineva, 2003). Arsenic affects photochemical proficiency and plant heat dissipation competence, which is responsible for the exchange rate of gases as well as plant fluorescence release (Chandrakar, Naithani, & Keshavkant, 2016). Arsenic also causes a reduction in both leaf and root growth, which leads to the wilting and bluish-purple coloring of leaves (Chandrakar et al., 2018). The elevated concentration of As in plant-growing soil may also inhibit the plant metabolic system, affect plant micro- and macronutrient uptake, and compete with the uptake of essential plant nutrients such as phosphate (Finnegan & Chen, 2012). Plant membranes are susceptible targets of As stress-induced toxicity that cause cellular damage and leads to reduced plant stomatal conductance, unstable and reduced nutrient uptake and disruption of the plant transpiration process (Kofroňová, Mašková, & Lipavská, 2018).

As induces molecular and biochemical effects in plant systems in two ways: 1) through the direct inactivation of essential enzymes through sulfhydryl group interactions or the replacement of compulsory ions from enzyme active sites and 2) the consequent indirect increase in ROS in a cascade of irreversible damage in plants (Chandrakar et al., 2016). Reactive oxygen species are chemically reactive and highly unbalanced molecules that contain unpaired valence electrons with short survival times (Balakhnina & Nadezhkina, 2017; Yang, Cao, & Rui, 2017). Different metabolic pathways function in different cellular compartments, such as mitochondria, chloroplasts, and peroxisomes, by continuously generating ROS as a byproduct in the typical plant metabolism process (Das & Roychoudhury, 2014). The imbalanced generation of ROS is well known to cause oxidation to nonspecific proteins, carbohydrates, and lipids, cell membrane leakage, DNA damage, and essential enzyme inactivation in plants (Hasanuzzaman, Nahar, & Fujita, 2013).

3.2. Selenium

Selenium uptake, translocation, accumulation, and toxicity depend on plant species, plant development phases, Se level, the activity of membrane

transporters, the translocation mechanisms of the plant, and soil physiological conditions (pH & salinity) (Chang et al., 2019; Gupta & Gupta, 2017). Compared with Se^{IV} , Se^{VI} is more frequently bioavailable and water-soluble in agricultural soils (Fernández-Martínez & Charlet, 2009). Selenium translocation in plant shoots, leaves, and grains depends on the rate of transpiration and the rate of xylem loading (Gupta & Gupta, 2017; Renkema et al., 2012). In soil, the occurrence of contending ions, mainly sulfate and phosphate, might be affected by Se uptake in plants (Golob et al., 2016; Gupta & Gupta, 2017). Due to chemical similarities between Se and sulfate, both elements share common metabolic pathways in plants throughout the translocation process. Selenite and Se^{VI} are available forms of Se that vigorously compete with sulfur, sulfite, thiosulfate, and sulfate in plant systems (Shahid et al., 2018).

Selenium uptake in plant systems is facilitated by transporters, whereas Se^{IV} and Se^{VI} are transported through sulfate and phosphate channels, respectively (Shahid et al., 2018). Selenate enters the plasma membrane of plant root cells by sulfate transporters (Lin et al., 2012). It is well known that the addition of sulfate to acidic soil can decrease Se uptake by plants (De Temmerman et al., 2014); however, the effects are reversed in alkaline soil (Huang, Hu, & Liu, 2007). Selenate and phosphate compete and enter into the plasma membrane of plant root cells through phosphate transporters (Winkel et al., 2015). The presence of phosphate raises the Se bioavailability most likely through the exchange of Se in sorption sites, therefore increasing Se mobility and uptake in plants (Shahid et al., 2018). Usually, younger plant leaves contain higher Se concentrations than older leaves through the seeding growth phase (Cappa et al., 2014).

Selenium naturally accumulates in plant cell vacuoles and effluxes through sulfate transporters existing in tonoplasts (Hawkesford & De Kok, 2006; Mazej, Osvald, & Stibilj, 2008). Based on the Se accumulation inside plant cells, plants are classified as non-accumulators, secondary accumulators, and hyperaccumulators (Schiavon, Pilon, Malagoli, & Pilon-Smits, 2015). Hyper-accumulator plants can accumulate more Se, >1000 mg/kg DW in plant cells. The methylated form of Se, such as SeMet and SeCys, deliberates Se tolerance in hyperaccumulator plants, which further vaporizes to DMDSe. However, secondary and non-accumulator plants can accumulate Se at concentrations ranging from 100 to 1000 and <100 mg/kg DW, respectively, showing that there are no signs of toxic effects on plants (Gupta & Gupta, 2017). After entrance into the plant cell with the help of sulfate transporters, selenium translocates into other parts of the plant, i.e., the shoots, leaves, and grain cells (Bitterli, Bañuelos, & Schulin, 2010) and is metabolized in plastids through the sulfate integration pathway to SeMet or SeCys, while the sulfur chemical analog of Se can undergo additional

methylation and evaporation into the atmosphere in a nontoxic form (Pilon-Smits & Quinn, 2010).

The first step of Se metabolism inside plant leaves or shoot cells is initiated by sulfate integrating enzymes through the conversion of Se to Se^{IV} via two enzymes, i.e., ATP sulfurylase (APS) and APS reductase (APR) (Gupta & Gupta, 2017; Shahid et al., 2018). Sulfurylase catalyzes the hydrolysis of ATP to couple ATP with Se^{VI} and form adenosine phosphoselenate (APSe), which is further reduced to Se^{IV} by the enzyme APR (Figure 2) (Pilon-Smits & Quinn, 2010; Shahid et al., 2018). In summary, Se^{IV} is changed to Se^{2-} by the enzyme sulfite reductase, and this metabolic step may also be reduced through glutaredoxins (Grxs) or GSH (Wallenberg, Olm, Hebert, Björnstedt, & Fernandes, 2010). The reduction of Se^{VI} to APSe can increase plant tolerance to Se^{IV} -induced stress (Shahid et al., 2018). In the next metabolic step, Se^{2-} is transformed into SeCys through coupling with O-acetyl serine (OAS) in the presence of the enzyme cysteine synthase (CS). The enzyme CS has a greater affinity for Se^{2-} than sulfide (S^{2-}), which depends on environmental conditions and plant species (Pilon-Smits & Quinn, 2010).

The SeCys transforms into Se in the presence of the enzyme SeCys lyase or might be methylated to Me-SeCys through selenocysteine methyltransferase (SMT) or be changed into selenomethionine (SeMet) through a sequence of enzymes (Gupta & Gupta, 2017; Shahid et al., 2018). The imbalanced incorporation of SeMet/SeCys in plant proteins can cause damage to the structure and function of the protein, which leads to Se toxicity in plants (Gupta & Gupta, 2017; Pilon-Smits & Quinn, 2010). Moreover, SeMet can further be methylated to methyl-SeMet. Me-SeCys or Me-SeMet can be volatilized into the atmosphere as nontoxic dimethyl selenide (DMSe) or dimethyl diselenide (DMDSe) in non-accumulator and hyper-accumulator plants, respectively (Pilon-Smits & Quinn, 2010; Shahid et al., 2018).

Selenium toxicity or selenosis ensues in plants by two mechanisms: 1) malformed selenoprotein-induced toxicity and 2) oxidative stress-induced Se toxicity. Malformed selenoprotein toxicity in plants occurs in the protein chain by the replacement of SeCys or SeMet with Cys or Met (Gupta & Gupta, 2017). In the plant protein chain, Cys residues play an essential role in the synthesis of protein structure and function, as well as aid in the synthesis of metal-binding sites, metal catalysis, and disulfide linkages. Hence, the replacement of Cys with SeCys causes damage to protein structure and function because SeCys has an exceptional reactivity that can be quickly deprotonated compared with Cys (Gupta & Gupta, 2017; Hondal, Marino, & Gladyshev, 2013). The replacement of Cys with SeCys leads to the dysfunction of methionine sulfoxide reductase because of the considerable

diselenide linkage and altered redox potential, which disrupts the enzyme kinetics of the plant (Châtelain et al., 2013; Hondal et al., 2013). Selenium-induced toxicity is caused by disturbance and disparity between the production and scavenging of ROS (Shahid et al., 2018). At elevated doses, Se stress causes a decrease in the level of GSH, and Se behaves as a pro-oxidant and produces ROS, which may cause oxidative stress in plants (Feng, Wei, & Tu, 2013; Hugouvieux et al., 2009).

Additionally, several nanoparticles (NPs) released into environmental compartments from different manufacturing and commercial sectors can induce toxicity in plants (Rai et al., 2018; Yang et al., 2017). Arsenic- and Se-based NPs also cause an imbalance in the generation of ROS, induce oxidative stress, and pose severe toxic effects on photosynthesis and growth in plants, which can even lead to plant death (Sarkar et al., 2015; Yang et al., 2017). However, several studies have reached consensus on the environmental behaviors, interactions, ecological effects, and toxicity of As- and Se-based NPs in plant systems, but many controversies and problems remain to be further studied.

4. Arsenic and selenium metabolic processes in animals and humans

4.1. Arsenic metabolic processes

Arsenite has an analogs structure to glycerol and is transported in cells through aqua glycerolporins, which are very small proteins that move small organic compounds similar to urea and glycerol (Liu et al., 2002). Nevertheless, As^V uses diverse pathways both in animals and human cells with similarities to physiological phosphate with the following analogs detachment constants: pKa values of As-acid: 2.26, 6.76, and 11.3 and pKa values of phosphoric acid: 2.16, 7.21, and 12.3 (Villa-Bellosta & Sorribas, 2008). Arsenite (LD₅₀ of NaAsO₂: 41 mg/kg) is considered more toxic and carcinogenic than As^V and more toxic than the organic As species dimethylarsinic acid (DMA) and monomethylarsonic acid (MMA) (Harper, Antony, & Bayse, 2014; Jain & Ali, 2000). Total As is analogs to phosphate, and the As^V oxyanion is present in solution, such as H₂AsO₄ and HAsO₄²⁻, at pH values ranging from 5 to 7; due to chemical similarity, the As^V oxyanion competes with and enters through phosphate transporters (Plant, Kinniburgh, Smedley, Fordyce, & Klinck, 2004). In humans, inorganic As, once inside the body, is heavily methylated before execution in the urine. Consumed inorganic As is methylated into MMA and DMA. MMA has more significant toxicity than inorganic As, and MMA can increase the risk of the carcinogenic potential of As (Burgess et al., 2014).

After entering an animal or human cell, As^V rapidly reduced to As^{III}. Next, As^{III} undergoes multistep-based methylation through As^{III} methyltransferase

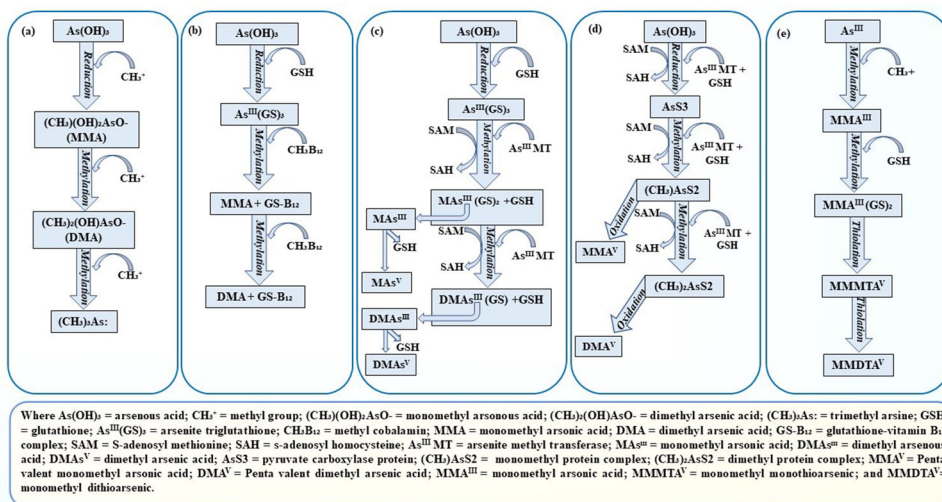


Figure 3. Arsenic metabolic pathways and thiolation in mammalian and human cells: The arsenic methylation metabolic pathway in *Scopulariopsis brevicaulis* (a), non-enzymatic arsenic methylation pathway in rat liver cells (b), arsenic metabolic pathway in rat liver cells (c), arsenic metabolic pathway in rat liver cells (d), and arsenic metabolic pathway in wild-type rat liver cells (e).

(As^{III}MT) by using an S-adenosylmethionine (SAM) methyl donor to produce several As-methylated compounds, such as MMA^{III}, DMA^{III}, MMA^V, and DMA^V (Kojima et al., 2009). Challenger in 1945 was the first to introduce arsenic-methylation in *Scopulariopsis brevicaulis*, which is the classical pathway of methylation (Figure 3a), and suggested that the As methylation process included a series of oxidation and reduction processes (Challenger, 1945). Another process suggested that As^{III} can also undergo a non-enzymatic methylation process in rat livers (Figure 3b) in the presence of methylcobalamin and GSH (Zakharyan & Aposhian, 1999). After that, Hayakawa, Kobayashi, Cui, and Hirano (2005) found that enzymes played a crucial role in As methylation and proposed a new enzymatic metabolic pathway (Figure 3c). In the As methylation enzymatic metabolic pathway, the -OH group of As(OH)₃ is substituted by glutathionyl moieties and forms the GSH conjugates As(GS)₂-OH and As-triglutathione As(GS)₃ (Hayakawa et al., 2005). After the addition of a critical substrate, As^{III}MT and arsenite-glutathione (As^{III}GS) are more methylated to monomethylarsenic-diglutathione (MMA(GS)₂) and then to dimethylarsenic-diglutathione (DMA(GS)) (Sun et al., 2014).

Another metabolic pathway of As was investigated by (Naranmandura, Suzuki, & Suzuki, 2006) *via* intravenous injection of As in rats that metabolized As in renal and hepatic regions (Figure 3d). Furthermore, As metabolites such as trivalent (inorganic) and pentavalent (organic) arsenicals were detected in As-spiked human urine samples, as well as in *in vitro* cell

lysates and cell culture medium after chronic exposure to As (Devesa et al., 2004). Recently, another insight into the As metabolic pathway was reported in wild-type rats by (Wang, Thomas, & Naranmandura, 2015), and this study identified novel As metabolites. The arsenicals (As-S bond) are structurally very similar to oxo-arsenicals (As-O bond), in which oxygen atoms bind with As atoms as a substitute for sulfur atoms. However, thioarsenate $(\text{OH})_3\text{-As}(=\text{S})$ and arsenate $(\text{OH})_3\text{-As}(=\text{O})$, which are thioarsenical-oxoarsenical, are analogs. The study further considered the origin and process that converted inorganic As into methylated oxoarsenical species and further converted oxoarsenicals into thioarsenicals (Figure 3e).

Inorganic As^{III} is absorbed in the intestinal lumen and then enzymatically changed into MMA^{III} , after which the compound is further changed into the diglutathione complex $\text{MMA}(\text{GS})_2$ that is secreted in bile. In the intestinal lumen, $\text{MMA}(\text{GS})_2$ is further converted to monomethyl-monothioarsenic (MMMTA^{V}) through microbiota, MMMTA^{V} is further absorbed across the intestinal wall, and then symmetrically dispersed and converted to another thiolate metabolite, monomethyl-dithioarsenic (MMDTA^{V}) (Wang et al., 2015).

4.2. Selenium metabolic processes

The two major species of inorganic Se, Se^{IV} , and Se^{VI} , are significant in the biological and biochemical cycles of Se; nevertheless, Se species exhibit different biochemical properties, such as their energy consumption and differences in their toxicity during uptake and metabolism (Sun et al., 2014). Sodium sulfate cotransporters are primarily responsible for transporting Se^{VI} (Bergeron, Cléménçon, Hediger, & Markovich, 2013). However, Se^{IV} is primarily absorbed into cells through passive diffusion (Skalickova et al., 2017). Different studies have verified that both organic and inorganic Se could exchange their roles in the intracellular environment through a series of reactions (Figure 4a). Organic Se metabolic processes in animals and human cells through different pathways form Se^{2-} (Shini, Sultan, & Bryden, 2015). Inorganic Se^{VI} with high redox potential entering human or animal cells first undergoes enzymatic reduction to Se^{IV} and then is rapidly reduced enzymatically to Se^{2-} by GSH (Ogra & Anan, 2009).

Selenate is intracellularly reduced to Se^{2-} through different pathways, and Se^{VI} reacts with reduced GSH to form selenodiglutathione ($\text{Se}(\text{GS})_2$). Furthermore, $\text{Se}(\text{GS})_2$ is converted to selenopersulfide (GSSeH), and GSSeH decays spontaneously or enzymatically under anaerobic conditions and is converted into hydrogen selenide (H_2Se) (Weiller, Latta, Kresse, Lucas, & Wendel, 2004). Moreover, a typical intermediate of Se^{2-} is used either for selenoprotein biosynthesis or biomethylation to methylselenol (CH_3SeH),

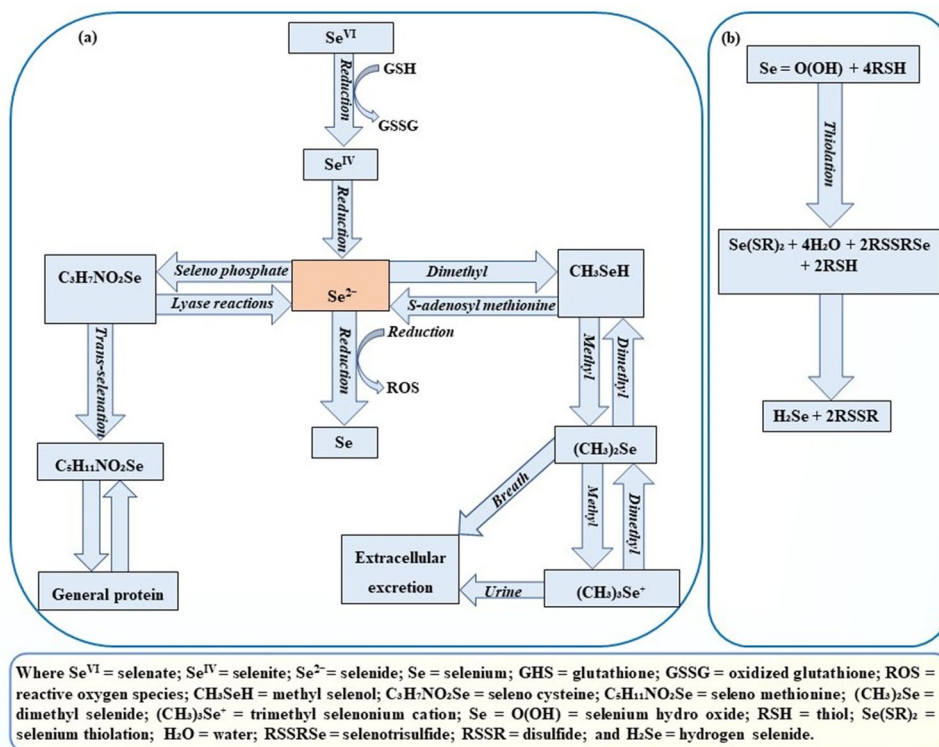


Figure 4. Selenium metabolism pathways in humans (a) and animals (rats) (b).

dimethyl selenide (CH₃)₂Se, or the trimethyl selenonium cation (CH₃)₃Se⁺. Subsequently, they can extrude from extracellular spaces with (CH₃)₂Se released through breath and (CH₃)₃Se⁺ in the urine (Gailer, 2002, 2007). Thiol reduction of Se^{IV} was defined by Harper et al. (2014), who reported that Se^{IV} reacted with four glutathiones (thiol, RSH) or with another thiol (Figure 4b) to produce selenotrisulfide (RSSeSR). RSSeSR can further reduce Se²⁻ with thiols, such as thioredoxin or GSH reductase (Björnstedt, Kumar, & Holmgren, 1992; Harper et al., 2014; Jornstedt, Kumar, & Holmgren, 1995).

Several seleno-compounds are metabolized into Se²⁻ by different metabolic pathways, such as the C-Se bond in seleno amino acids, one of the leading organic Se compounds that are cleaved and transformed into Se²⁻ by lyase reactions (Schrauzer, 2000; Suzuki, Kurasaki, & Suzuki, 2007). Selenocysteine is transformed by and forms Se²⁻ through a β -lyase reaction, and Se-Met transforms into Se²⁻ by a β -lyase reaction after a complete transselenation reaction to SeCys or *via* a γ -lyase reaction (Suzuki et al., 2007). The product of Se methyl metabolism is methyl selenide, which is further demethylated and forms Se²⁻ (Ohta & Suzuki, 2008).

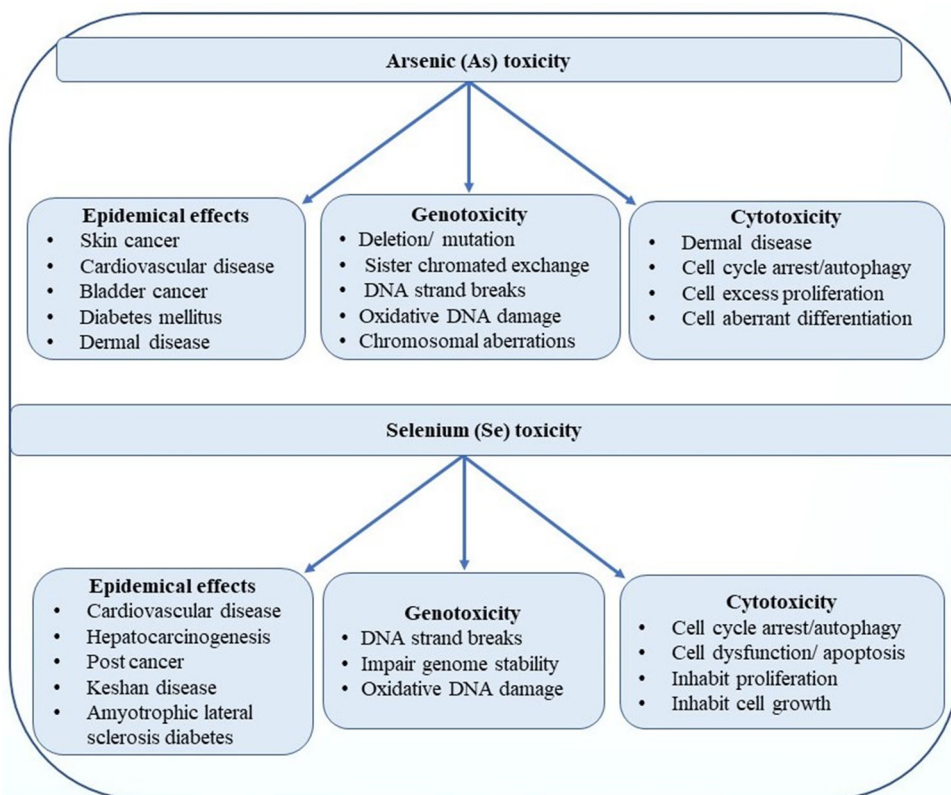


Figure 5. Arsenic and selenium epidemical effects, cytotoxicity, and genotoxicity in animals and humans.

5. Arsenic and selenium epidemiological effects, cytotoxicity, and genotoxicity in animals and humans

Arsenic is a well-known carcinogen causing liver, bladder, lung, and skin cancers (Ali, Aslam, et al., 2019). Arsenic exposure produces excessive ROS that can cause diverse types of malformations, including both lethal and non-lethal malformations (Sun et al., 2014). The acute and chronic minimal lethal doses of As in adults have been estimated to range from 100 to 300 mg/kg/day and 0.05 to 0.1 mg/kg/day, respectively (ATSDR, 2007; Ratnaik, 2003). Moreover, As exposure causes arsenicosis, Blackfoot disease, skin lesions, and peripheral vascular disease (Naujokas et al., 2013); as far as concern for Se exposure, various studies have reported that a low Se level is useful and acts as an anticarcinogen. However, a high level of Se exposure induces carcinogenic epidemical effects, cytotoxicity (Figure 5), and genotoxicity (Sun et al., 2014; Valdiglesias, Páraso, Méndez, & Laffon, 2010).

Several recent studies have suggested that As and Se can induce similar toxicity in animals and humans through diverse pathways (Sun et al.,

2014). Therefore, for this review, we focused on common mechanisms of As and Se interactions and their associated toxicity in animals and humans.

5.1. Epidemiological effects

Different studies have demonstrated that As interferes with the series of genes associated with cellular proliferation processes, DNA repair and damage, and cell cycle differentiation (Maiti, 2015). Arsenic may also alter cell signal transduction pathways, such as 53 protein signaling pathways, the MAPK pathway, and the Nrf2 cell signaling pathway (Ghosh & Sil, 2015). Reactive oxygen species activating cancer and methylated metabolites of As are known as potential carcinogens, such as the carcinogen DMA causing cancer in the urinary bladder of rats (Salnikow & Zhitkovich, 2008; Shi et al., 2004). Arsenic has caused non-carcinogenic diseases, including hypertension, diabetes mellitus, cardiovascular diseases, and dermal diseases (Shakir et al., 2016). Trivalent arsenicals As^{III} , MMA^{III} , and DMA^{III} induced diabetes by disrupting glucose metabolism, as investigated in intact pancreatic islets from mice (Douillet et al., 2013). Arsenite-induced inhibition of pyruvate and α -ketoglutarate dehydrogenases are among the leading causes of diabetes (Navas-Acien et al., 2006). Most cardiovascular diseases are closely related to hypertension, and thus far, different pathways have been investigated for As-induced hypertension that increases inflammatory activity and endothelial dysfunction and alters the vascular tone in blood vessels (Abhyankar, Jones, Guallar, & Navas-Acien, 2012; Flora, 2011). Arsenic induces ROS to inhibit cell signaling, takes part in pathogenesis, increases cytokine production, and leads to inflammation that causes further enhanced ROS generation and mutagenesis (Jomova et al., 2011).

Selenium is an essential nutrient that plays a vital role, such as that of an antioxidant in humans; however, Se deficiency in humans and animals can induce many diseases (Surai, 2006). The daily recommended dietary intake for a healthy adult is 30 to 50 $\mu\text{g}/\text{d}$ in the USA, while the Chinese Nutrition Society (CNS) and Europe have set the recommended dietary intake for a healthy adult as 50 to 250 $\mu\text{g}/\text{d}$ (Whanger, 2004). Daily intake of Se ranging from 100 to 200 $\mu\text{g}/\text{d}$ can induce genetic and cellular damage; however, excessive dosages of $\text{Se} \geq 400 \mu\text{g}/\text{d}$ can cause cancer in humans (Brigelius-Flohé, 2008; Zeng & Combs, 2008).

Long-lasting Se exposure-induced diseases include amyotrophic lateral disease, cardiovascular disease, and sclerosis. However, in humans, elevated levels of Se can cause diabetes because Se activates critical cellular metabolic enzymes that control insulin signal transduction pathways, albeit regulating various metabolic processes and pathways (pentose pathways, fatty

acid synthesis, gluconeogenesis, and glycolysis pathways) (Bleys et al., 2009; Vinceti et al., 2009).

In the 1980s, intensive research investigations failed to realize that there was any correlation between Se and cardiovascular diseases (Rayman, 2000). However, recent scientific studies and observations verified that a possible U-shaped strong correlation exists between Se level and cardiovascular disease (Joseph & Loscalzo, 2013; Rees et al., 2013). Selenium-induced neurodegenerative effects through the damage of motor neurons and activated proteins 38 to 53 induce amyotrophic lateral sclerosis (Chen, Wang, Xiong, Zou, & Liu, 2010; Vinceti et al., 2013). Different studies have suggested that oxidative stress induces Se toxicity, such as the impaired synthesis of thyroid hormones and growth hormones and the disruption of endocrine function (Letavayova, Vlčková, & Brozmanova, 2006; Maritim, Sanders, & Watkins, 2003; Valdiglesias et al., 2010). Reactive oxygen species play a significant role in the epidemiological outcomes of both As- and Se-mediated toxicity in humans as well as in mammals (Sun et al., 2014). Excessive Se produces excessive ROS, and this can affect similar pathways that induce cancer after As exposure (Klaunig & Kamendulis, 2004; Valko, Rhodes, Moncol, Izakovic, & Mazur, 2006). The imbalanced generation of ROS acts as an inner mechanism for As- and Se-associated adverse effects in mammals; however, associated adverse outcome pathways (AOPs) for cancer and cardiovascular defects have not yet been explained. Therefore, more attention should be paid to conducting studies for a mechanistic understanding of As- and Se-associated causes of cancer and epidemiological effects.

5.2. Cytotoxicity

Abnormalities within the cell are caused by toxic contaminants and is known as cytotoxicity. Several studies have reported that As and Se both induce ROS that can cause cytotoxicity within cells by different pathways (Park et al., 2012; Selvaraj, Tomblin, Armistead, & Murray, 2013). Cells exposed to high doses of As and Se exhibited elevated levels of ROS. When As is produced, ROS induce NADPH oxidase, and Se is produced when Se^{2-} reacts with thiols (Chou et al., 2004). Reactive oxygen species not only destroy protein and lipid functions but also activate mitochondrial damage by inducing oxidative stress on mitochondrial-dependent apoptotic pathways (Fleury, Mignotte, & Vayssière, 2002; Kim et al., 2007; Kim, Jeong, Yun, & Kim, 2002). Furthermore, ROS produces cytotoxicity *via* activation of the protein JNK, which is one of the relevant subgroups of the mitogen-activated protein kinases that mediates critical cellular functions such as cell apoptosis, differentiation, and proliferation (Shen & Liu, 2006), and

also stimulates JNK tumor necrosis factor (Ventura, Cogswell, Flavell, Baldwin, & Davis, 2004).

Arsenic and Se induce cytotoxicity by different pathways, and As affects tumor suppressor protein 53, causing cytotoxicity. Protein 53 plays an essential role in cellular functions through cell growth regulation, cell cycle control, repair, DNA synthesis differentiation, and apoptosis (Andrew et al., 2006). In human fibroblast cells, As induced protein 53 accumulation, which may cause cell apoptosis by facilitating Bax translocation from the cytosol toward the mitochondria and release cytochrome activating caspase-9 by Apaf-1 and apoptosomes (Kircelli, Akay, & Gazitt, 2007; Shankar & Shanker, 2014). Protein 53 induces cell cycle arrest at the G₂/M phase through transcriptional activation of protein 21, inhibiting cyclin-dependent kinase and inducing autophagy in a damage-regulated autophagy modulator (DRAM)-dependent manner (Akay, Thomas, & Gazitt, 2004; Crighton et al., 2006; Lozano & Elledge, 2000; Vogelstein, Lane, & Levine, 2000).

Selenium is a component of selenoproteins that exhibit a close relationship with redox reactions. Nevertheless, the enzyme thioredoxin reductase (TrxR), along with thioredoxin (Trx), produces an active di-thiol-di-sulfide and oxidoreductase complex, which further increases cytotoxicity (McKenzie, Arthur, & Beckett, 2002; Sun et al., 2014). The system controls cell growth by binding to cell signaling molecules, such as thioredoxin-interacting protein and apoptosis signal-regulating kinase-1, which are essential compounds responsible for cell growth and cell survival (Wallenberg et al., 2010; Yoshioka, Schreiter, & Lee, 2006). Selenium controls or modulates cell signaling pathways *via* a thiol redox mechanism and participates in cytotoxicity by reducing intracellular Cys. Arsenic and Se not only generate cytotoxicity through ROS but also affect the corresponding genes and proteins (Carlin et al., 2016; Hettick, Canas-Carrell, French, & Klein, 2015; Whanger, 2004).

5.3. Genotoxicity

Genotoxicity is defined as changes or damage to genetic information that can cause mutations in cellular information (Valdiglesias et al., 2010). Arsenic and Se induce genotoxicity, similar to cytotoxicity, by generating ROS. Higher ROS concentrations inside cells affected the cellular components of DNA resulting from the base lesions and strand breaks that induce genotoxicity. Higher levels of ROS are dangerous for gene stability, affecting DNA repair, DNA oxidation, and gene regulation (Deavall, Martin, Horner, & Roberts, 2012). However, As and Se both interact with DNA repair proteins that contain functional zinc finger motifs, and these involved essential functions are reported as DNA transcriptional factors,

DNA-protein, protein-protein and DNA-repair proteins (Hartwig, 2001; Zeng et al., 2005; Zhou et al., 2011). Selenium reacts with metallothionein and releases Zn, which damages the DNA-binding capacity and genomic stability (Blessing, Kraus, Heindl, Bal, & Hartwig, 2004; Larabee, Hocker, & Hanas, 2009; Zeng et al., 2005). Arsenic induces genotoxicity by directly impacting the DNA repair capacity resulting in the downregulated expression of ERCC1, which is an essential member of the repair and nucleotide expression excision repair pathways (Andrew et al., 2006; Andrew, Karagas, & Hamilton, 2003). Long-term exposure of As to cells can induce genotoxicity by SAM depletion in the cell, DNA hypomethylation causing genomic instability, and the global loss of DNA methylation (Bhattacharjee, Banerjee, & Giri, 2013; Ren et al., 2011). Arsenic and trivalent methylated As compounds efficiently interact with the synthetic pathways of the enzyme SAM (Tseng, 2009; Vahter, 2007).

Several researchers have confirmed that As^{III} and its metabolites also change the activity of DNA methyltransferase, resulting in the inhibition or stimulation of SAM enzymatic synthesis pathways (Hughes, 2002; Reichard & Puga, 2010; Zhong & Mass, 2001). Interestingly, As induces genotoxicity by affecting the status of protein 53, while similar mechanisms have been reported for cytotoxicity induction (Chowdhury, Chowdhury, Roychoudhury, Mandal, & Chaudhuri, 2009; Shankar & Shanker, 2014). Nevertheless, Se induced genotoxicity by generating ROS and interacting with the thiol group (Letavayova et al., 2006; Ramoutar & Brumaghim, 2007; Valko et al., 2006). Selenium can also induce genotoxicity by inhibiting the cellular DNA repair ability, directly affecting protein 53 and the ataxia-telangiectasia mutation (ATM) (Abul-Hassan, Lehnert, Guant, & Walmsley, 2004; Wei et al., 2001; Zeng & Combs, 2008; Zhou, Xiao, Li, Nur-E-Kamal, & Liu, 2003). Arsenic and Se genotoxicity-induced mechanisms have not yet been clarified; however, most studies have attributed their genotoxicity to their capability to induce oxidative stress (Sun et al., 2014).

6. Antagonistic and synergetic interactions between arsenic and selenium and the associated toxicity in animals and humans

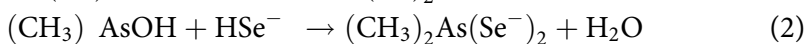
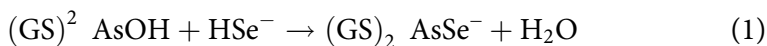
Researchers have started taking a keen interest in the interaction between As and Se after the findings reported that the chronic and acute toxicities of Se might be minimized through the administration of As^{III} and some arsenic compounds (Zeng et al., 2005). Arsenic increases the elimination of Se *via* the gastrointestinal tract when As^{III} and Se^{IV} were mutually injected at subacute doses (Zeng et al., 2005). In addition, in various experiments, it was observed that As also promoted the removal of Se from the gut (Sun et al., 2014). Likewise, As can decrease the Se level in the carcass, blood,

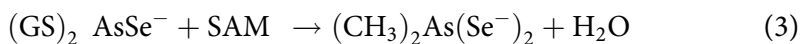
and exhaled breath; however, the administration of a massive dose of the organic arsenical sodium arsenilate can further decrease the removal of Se from the gastrointestinal contents and increase the Se level into the exhaled breath, and the combined effect causes a small decrease in the Se level retained in the carcass (Sun et al., 2014). Arsenic stimulates the excretion of Se into the gastrointestinal tract, while Se^{IV} can stimulate the excretion of As. Previous studies have demonstrated that as As increases, the level of Se excreted into rat bile reacts in the liver to form conjugates and is then excreted into the bile (Gailer, 2007).

6.1. Antagonistic

Several *in vivo* studies have suggested an antagonistic relation between As and Se and the associated toxicity effects on animals and humans. Once As and Se enter the human body, they are transported to the liver (principal detoxification organ) and rapidly reduced (Rosen & Liu, 2009). Under elevated concentrations of GSH in intracellular hepatocytes, the -OH group of $\text{As}(\text{OH})_3$ is sometimes replaced with glutathionyl moieties to form $(\text{GS})_2\text{AsOH}$, and Se^{IV} undergoes a spontaneous reaction with GSH to make HSe^- (La Porte, 2011; Rosen & Liu, 2009). In rats and mice, the concentrations of As and Se decreased during the antagonistic toxicity of As and Se (Messarah et al., 2012; Weiller et al., 2004).

The antagonistic interaction between As^{III} and Se^{IV} resulted in inhibition of gastrointestinal absorption of Se^{IV} through As^{III} (Rosen & Liu, 2009; Zwolak & Zaporowska, 2012). Immediate administration of As^{III} , along with Se^{IV} , inhibited the excretion of pulmonary $(\text{CH}_3)_2\text{Se}$ in rats and hamsters (Rosen & Liu, 2009). Arsenite also affects the distribution of Se in internal body organs and transports Se as Se^{IV} toward the liver through the bloodstream (Gailer, 2007). Acute As^{III} exposure (3–24 hours) decreased the retention of Se in rat livers (Naranmandura et al., 2006). However, chronic As^{III} exposure (2–18 months) did not decrease the Se level in rat livers (Zwolak & Zaporowska, 2012). *In vivo*, antagonistic interactions between As^{III} and Se^{IV} at the molecular level resulted in the generation of the novel As and Se compounds, such as seleno-bis (S-glutathionyl) and arsinium ions $(\text{GS})_2\text{AsSe}$, which were then excreted in the bile (Gailer, George, Pickering, et al., 2002; Gailer, Ruprecht, Reitmeir, Benker, & Schramel, 2004). This study further found that As and Se first enter the cell and then simultaneously react with hydrogen Se^{2-} to form $(\text{GS})_2\text{AsSe}$ (Gailer, George, Pickering, et al., 2002) (Eq. 1).





In the above pathway, nucleophilic HSe^- attacks the As atom and transfers its -OH group, and finally $(\text{Gs})_2\text{AsSe}^-$ and water are excreted out of the cell. A similar type of pathway was defined by (Manley et al., 2006) and specified $(\text{Gs})_2\text{AsSe}^-$ formation in erythrocytes and excretion through the blood. Moreover, Se^{IV} mediated the inhibition and reduction of methemoglobin by As^{III} in the presence of GSH, which indicated that erythrocytes are involved in facilitating this antagonistic interaction between As^{III} and Se (Zeng et al., 2005).

Arsenite suppressed the formation of H_2Se from Se^{IV} in a biological system that contained GSH reductase in bovine serum albumin (Shibata, Morita, & Fuwa, 1992). Biochemical interactions between As^{III} and Se^{IV} mostly occur in blood and liver cells (Buchet & Lauwerys, 1985; Gailer, 2007). Moreover, As and Se interaction pathways have been demonstrated by Gailer, George, Harris, et al. (2002). Arsenic and Se compounds were detected as $(\text{CH}_3)_2\text{As}(\text{Se})_2$, and it was speculated that DMA^{V} was first reduced by GSH and then converted to DMA^{III} . After that, HSe^- attacked the As atom and relocated the -OH group, yielding the compound $(\text{CH}_3)_2\text{As}(\text{Se})_2$ (Eq. 2). In another pathway (Eq. 3), the SAM provided a methyl group to transform $(\text{GS})_2\text{AsSe}^-$ into $(\text{CH}_3)_2\text{AsSe}^-$ with methyltransferase as a substrate (Figure 6a).

6.2. Synergistic

Synergistic interactions between As and Se generate Se metabolites such as trimethyl Se ions and dimethyl Se^{2-} , which increase As toxicity (Levander, 1977; Zeng et al., 2005). Methylated As^{III} caused adverse effects on Se metabolism and increased toxicity by blocking its metabolic pathways, mainly in rats (Sun et al., 2014). Furthermore, the synergetic effects and toxicity of the As and Se nexus inhibited the formation of methylated metabolites and, therefore, retained inorganic, monomethyl As and Se in tissues (Figure 6b) (Styblo & Thomas, 2001; Walton et al., 2003). Arsenic and Se undergo a similar type of metabolic change, linked through supplies such as GSH and SAM. However, GSH is one of the essential reductants in organisms during the metabolism of As and Se, as GSH provides electrons for the intended reduction reaction (Hayakawa et al., 2005; Sun et al., 2014; Yang, Kuo, Chen, & Chen, 1999). SAM is a versatile molecule in several biological reactions and is involved in the detoxification process of methyl As and Se. Once organisms are exposed to high doses of As and Se, they mutually inhibit the formation of methylated metabolites by competing with limited SAM (Styblo & Thomas, 2001; Sun et al., 2014).

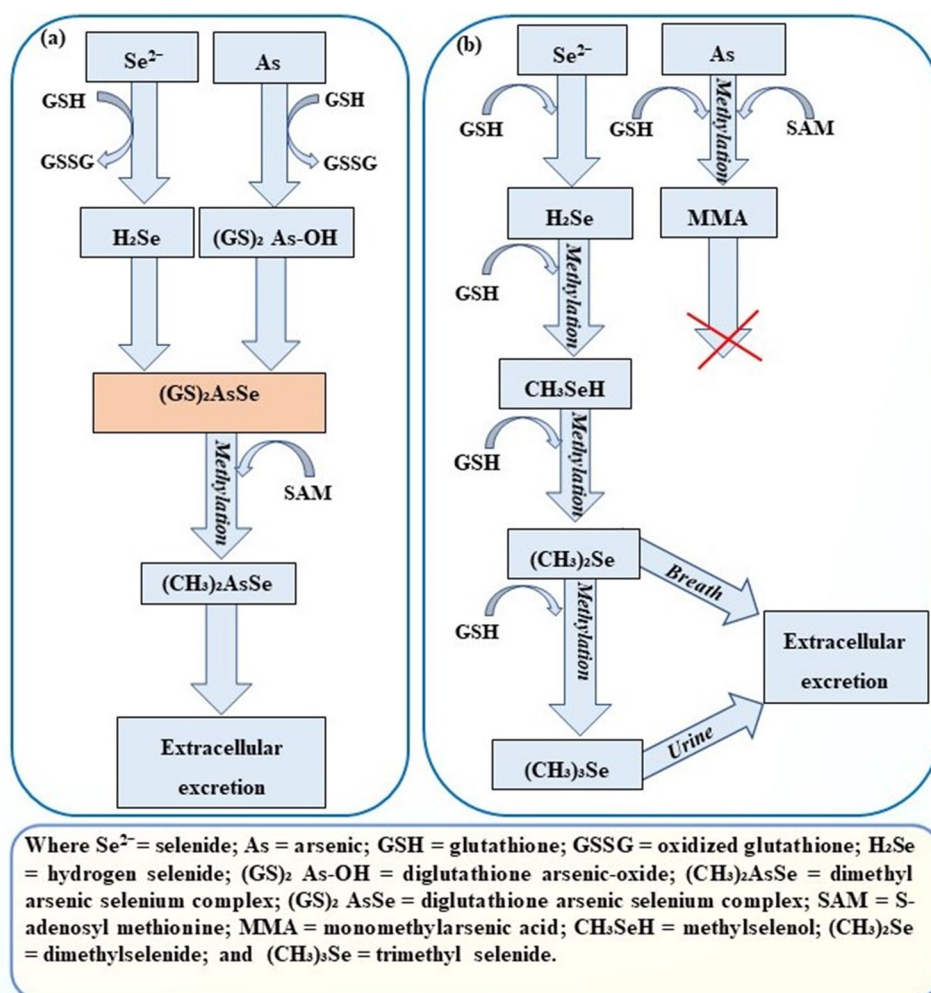


Figure 6. Antagonistic (a) and synergetic (b) interactions between arsenic and selenium and the toxicity in animals and humans.

Furthermore, a summary of studies elucidating insights into the antagonistic and synergetic supplementation interactions between As and Se and their toxicity in animal/rat and human cell culture models are described in Table 2.

7. Arsenic and selenium effects on zinc finger proteins/nucleases (ZFNs) and cellular functions

Selenium chemically and qualitatively resembles sulfur, albeit when Se combines with the zinc protein, it has more oxidoreductive potential (Zeng et al., 2005). Zinc, similar to finger structures abundant in motifs in the eukaryotic genome, performs various biological functions not only in transcription but also in various kinds of proteins that take part in maintaining genomic stability, DNA repair, and cell cycle control (Klug, 2010). It has been estimated that

Table 2. Summary of studies elucidating antagonistic and synergetic supplementation interactions between arsenic and selenium and the associated toxicity in animal/rat and human cell culture models.

Experimental duration	Arsenic & selenium form & (dose)	Biomarker & (target)	Arsenic-selenium interactions, effects in animals & humans	References
6 to 14 days	Sodium selenite (Na ₂ SeO ₃) = Na ₂ SeO ₃ = (0.025 mg/kg) BW oral drinking water	Pregnant Syrian hamster and (fetus)	<ul style="list-style-type: none"> Increases As methylation index in urine, tissues of dams in the whole fetus; the activity of glutathione peroxidase (GPx), and a viable fetus Reduced the As concentration in kidney, liver bladder, brain, the skin of pregnant animals, accumulation in the placenta, and fetus 	Zwolak (2020); Sampayo-Reyes et al. (2017)
3 weeks	Na ₂ SeO ₃ = (3 mg/kg) BW oral intubation	Wistar rat (liver)	<ul style="list-style-type: none"> Increases glutathione (GSH) level and GPx activity Reduces aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) activity in plasma compared with As-treated animals Reduces the lipid peroxidation, glutathione S-transferase activity, and cytoplasmic As-induced histological changes 	Messarah et al. (2012); Zwolak (2020)
3 weeks	Na ₂ SeO ₃ = (3 mg/kg) BW oral intubation	Sprague Dawley (SD) Rat (liver)	<ul style="list-style-type: none"> Increases liver weight and partly protects against As-induction Increases mRNA gene expression of nuclear factor erythroid 2 related factors (Nrf2), thioredoxin reductase (TrxR), and total antioxidant capacity (TAC) activity, which is decreased by As Decreases ALT and AST activity in blood serum, malondialdehyde (MDA) and nitric oxide (NO) advanced oxidation protein products, and serum interleukin-6 (IL-6) levels, which are increased by As 	Zwolak (2020); Shafik and El Batsb (2016)
20 weeks	Na ₂ SeO ₃ = (17.0 mg/L) Oral	SD Rat (liver)	<ul style="list-style-type: none"> Increases mRNA expression of GPx and superoxide dismutase (SOD) and Txnrd1 and TrxR protein expression levels, which are reduced by As Reduces the ALT and AST activities in blood and As- induced haeme oxygenase-1 (OH-1) protein expression, which are increased by As 	Zwolak (2020); Xu et al. (2013)
14 weeks	Not specified Se rich lentils Se deficient = (<0.01 mg), and Se high oral = (0.3 mg)	Wistar rat (blood, kidney & liver)	<ul style="list-style-type: none"> Increases As concentration in the urine and faces and GSH level in the blood, mitigated liver lipid peroxidation and partly recovers the antibody response, which are reduced in Se-deficient animals 	Zwolak (2020); Sah, Vandenberg, and Smits (2013)
24 hours	Selenomethionine (SeMet) = (100 μm)	Human embryonic kidney cell line (HEK-293)	<ul style="list-style-type: none"> Selenium high intake reduced the As the level in kidney Reduces As-induced cytotoxicity and reactive oxygen species (ROS) levels 	Zwolak (2020); Chittra, Figueroa, Caruso, and Merino (2013)

(continued)

Table 2. Continued.

Experimental duration	Arsenic & selenium form & (dose)	Biomarker & (target)	Arsenic-selenium interactions, effects in animals & humans	References
1 hour	Selenium nanoparticles (SeNPs) = (0.01 µg/L)	Human lymphocytes	<ul style="list-style-type: none"> Increases the phosphorylation of the protein, which is involved in ROS antitumor activity, cell growth, and detoxification 	Zwolak (2020); Prasad and Selvaraj (2014)
48 hours	Sodium arsenite (NaAsO ₂) = (2.5 µM) Na ₂ SeO ₃ = (10 µM)	Human osteosarcoma (Cells-TE85)	<ul style="list-style-type: none"> Nano selenium reduced As-induced toxicity and DNA damage Increases the level of selenite (Se^{VI}) and SeMet Partly decreases the arsenite (As^{III}) cytotoxicity Selenium compound-like organoselenium treatment blocks As species (As^{III}-dependent) accumulation of mutants in cultures after six weeks of growth 	Zwolak and Zaporowska (2012); Rossman and Uddin (2004)
Not defined	NaAsO ₂ = (6.25 µM) Na ₂ SeO ₃ = (2.5 µM)	Human hepatocellular carcinoma (Cells-HepG2)	<ul style="list-style-type: none"> Selenium species Se^{IV} reduces the lipid peroxidation (LPO) and 8-hydroxy-2deoxyguanosine (8-OHdG) levels No effects on the inhibition of 8-oxoguanine DNA glucosylase-1 expressions in cells exposed to arsenous acid (H₃AsO₃) 	Zwolak and Zaporowska (2012); Lai, Wang, Li, and Yu (2008)
24 hours	NaAsO ₂ (2 to 10 µM) ⁷⁵ Se- Se ^{IV} = (10 nM)	Human keratinocyte (Cells-HaCat)	<ul style="list-style-type: none"> Immunoblot As^{III} treatment increased the TrxR1 proteins level and reduced the GPx proteins Reduces radiolabeled TrxR1, GPx, and overall selenoprotein levels 	Zwolak and Zaporowska (2012); Ganyuc et al. (2007)
24 hours	NaAsO ₂ = (2 to 10 µM) ⁷⁵ Se- Se ^{IV} = (10 nM)	Human lung adenocarcinoma (Cells-A549)	<ul style="list-style-type: none"> Treatment of cells with As^{III} reduces radiolabeled TrxR1 and overall selenoprotein levels 	Zwolak and Zaporowska (2012); Talbot, Nelson, and Self (2008)
3 weeks	NaAsO ₂ = (5.5 mg/kg) Na ₂ SeO ₃ = (3 mg/kg) oral	Wistar rat	<ul style="list-style-type: none"> Se^{IV} increases the activity of GSH and GPx activity Reduces LPO, glutathione S-transferase, and transaminases activity, and alkaline phosphatase in the plasma of As^{III}-exposed rats 	Zwolak and Zaporowska (2012); Messarah et al. (2012)

approximately 3% of the known genes that encrypt proteins in various cellular processes include Zn finger protein domains (Laity, Lee, & Wright, 2001; Maret, 2003; Zeng et al., 2005). Selenium can replace the sulfur of Cys and change the stability of oxidation states in the course of the catalytic cycle and redox potential (Jacob, Giles, Giles, & Sies, 2003). Under reducing conditions, Se can oxidize thiols, mainly found in the cytosol (Moriarty-Craige & Jones, 2004).

At low concentrations of Se compounds and under reducing conditions, selenocystamine (diselenide) can oxidize thiol groups and release Zn ions from the metallothionein (Chen & Maret, 2001). Moreover, the low concentration of Se compounds under reducing conditions inhibits DNA regulation due to the inactivation of DNA repair proteins (Letavayova et al., 2006). The reducible Se compounds, including phenylseleninic acid ($C_6H_6O_2Se$), phenylselenyl chloride (C_6H_5ClSe), selenocysteine ($C_6H_{12}N_2O_4Se_2$), 2-nitrophenylselenocyanate ($C_3H_7N_2O_2Se$), and ebselen ($C_{13}H_9NOSe$), can also inhibit the activity of Fpg, a Zn finger protein that is involved in DNA repair (Blessing et al., 2004; Hartwig, Blessing, Schwerdtle, & Walter, 2003; Witkiewicz-Kucharczyk & Bal, 2006; Zeng et al., 2005). However, no inhibition was detected in selenomethionine methyl selenocysteine or some sulfur-containing analogs (Blessing et al., 2004; Zeng et al., 2005).

Low concentrations of Se compounds can also inhibit the Zn finger protein that binds to DNA, leading to the release of Zn from the motif of the Zn finger (Woo Youn, Fiala, & Soon Sohn, 2001). The cellular pathways are mostly dependent on Zn finger proteins, so redox responses are essential for the regulation of Zn finger proteins (Blessing et al., 2004; Zeng et al., 2005). The inequality overdose or deficiency in Se compounds inhibits or decreases genomic stability (Blessing et al., 2004; Zeng et al., 2005). Zinc finger proteins are also susceptible to intracellular targets for As^{III} at a preliminary low micromolar level of all As^{III} compounds triggered, and Zn is released from the Zn finger protein domains and develops a disease known as xeroderma pigmentosum (XPA) (Zeng et al., 2005). Based on previous findings, MMA^V and DMA^V are more reactive than As^{III} (Blessing et al., 2004; Hartwig et al., 2003; Zeng et al., 2005). During the upholding genomic stability process, Zn finger proteins are usually required in almost every intracellular reaction; therefore, the inactivation or inhibition of these proteins may enhance genomic instability (Hamilton, 2004).

Several studies have been conducted to elucidate the effects of As and Se on cellular transduction signals (Qian, Castranova, & Shi, 2003; Yang & Frenkel, 2002; Zeng, 2001). Arsenic is activated in different cellular signaling pathways, such as the mitogen-activated protein kinase (MAPK), ROS, and nuclear factor- κB (NF κB) signaling pathways (Blessing et al., 2004; Zeng, 2001). Activation protein-1 (AP-1) and NF κB are illustrative members of two diverse families of heterodimeric transcriptional complexes that

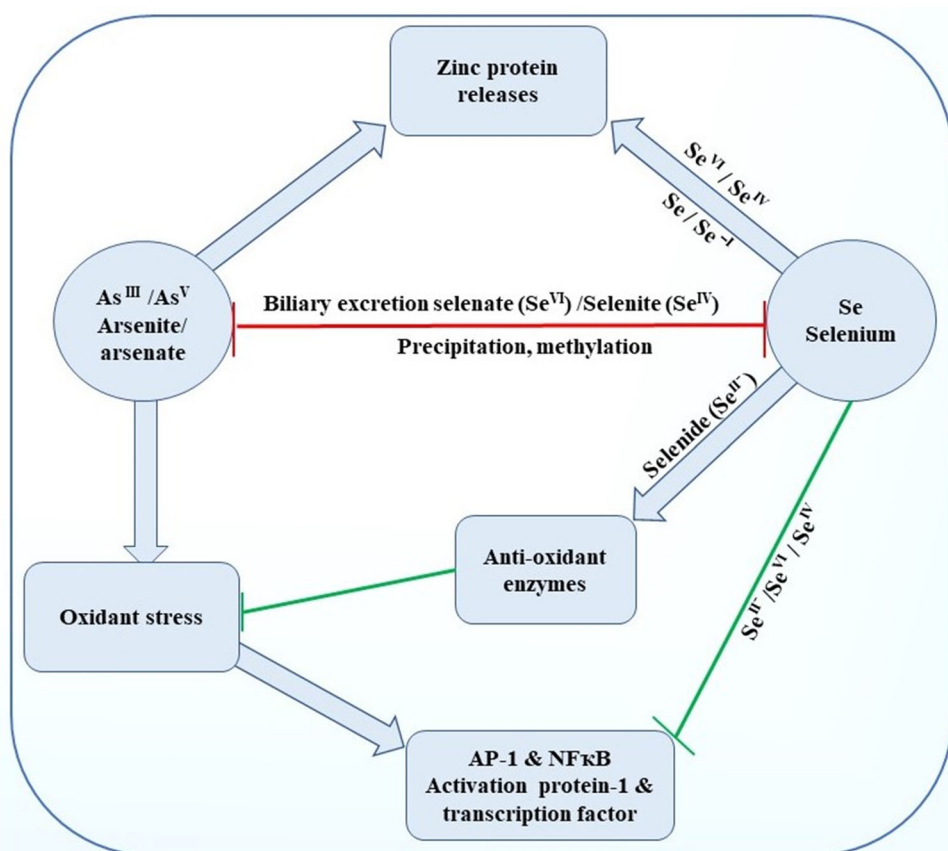


Figure 7. Arsenic and selenium effects on zinc finger protein/nuclease (ZFN) cellular function pathways. The arrows indicate induction, the single green-capped line indicates inhibition of cellular pathways, and the double capped red line indicates mutual inhibition of As/Se bioactivity by an increase in Se/As biliary excretion, the formation of As-Se precipitation and modification of As/Se methylation in the cellular pathway.

induce changes in gene expression (Zeng et al., 2005). Several studies have demonstrated that As^{III} and As^{V} induced protein expression and increased AP-1 and NF κ B DNA binding sites (Arita & Costa, 2009; Flora, 2011). However, various studies also demonstrated that Se- and Se-containing compounds reduced oxidation-related JNK AP-1 and NF κ B in the cellular activation process (Chauke, 2013; József & Filep, 2003). It has been proven globally that As^{III} is more toxic and carcinogenic than As^{V} (Ali, Aslam, et al., 2019). However, several studies have reported that methylated arsenicals such as MAs^{III} and DMAs^{III} have more potential than As^{III} on the activation of AP-1 (Drobná, Jaspers, Thomas, & Stýblo, 2003; Wang et al., 2015).

Cellular stress proteins are well known, as a C-Jun N-terminal kinase (JNK) is a member of a stress-activated protein kinase family activated through cellular stress. Arsenic activated AP-1 activity by inhibiting the JNK tyrosine phosphate protein (Figure 7), resulting in the activation of

JNK/AP-1, which was defective in the turning off of activated JNK (Cowan & Storey, 2003; Zarubin & Jiahuai, 2005). Therefore, As^{III} and As^V induced apoptosis *via* the JNK pathway (Eguchi et al., 2011). Potent antagonistic effects between As and Se at the cellular level can cause cell apoptosis as well as cell necrosis in human leukemia cells (HL-60) through incubation with Na₂SeO₃ and NaASO₂/Na₂-HASO₄ (Zeng, 2001; Zeng et al., 2005). The presence of minerals induced HL-60 cell apoptosis when the concentration of Se^{IV} (3 μM) > As^{III} (50 μM) > As^V (50 μM) was higher than that required for cell apoptosis, causing cell necrosis (Drobná et al., 2003). However, the elevated concentration of Se^{IV}, causing toxic necrotic effects and these effects, may have been suppressed or neutralized by As^{III} or As^V (Zeng, 2001).

Selenium compounds such as methylene(1,4-phenylene bis), selenocyanate (p-XSC), selenocysteine, selenomethionine, and ebselen inhibit or suppress the DNA binding activities of the transcription factors NFκB and AP-1 (József & Filep, 2003; Woo Youn et al., 2001). Arsenic activates NFκB and AP-1 inhibitors or suppresses Se, while As inhibits or suppresses the toxic necrotic effect of Se (Sun et al., 2014). These scientific insights demonstrated that Se plays an essential function as an endogenous “stop cellular signal” for As-induced cancer-causing cell signaling (Zeng et al., 2005).

8. Arsenic and selenium remediation/phytoremediation and handling of harvested biomass

Arsenic induces plant, animal, and human toxicity, whereas Se exhibits dual roles (essential and toxic), and both Se deficiency and toxicity are considered severe problems worldwide (Bastías & Beldarrain, 2016; Shahid et al., 2018). In the case of Se-deficient soils, the application of Se-amended fertilizers is a common and the best conceivable management strategy that has been adopted in different Se in soil-deficient countries (Shahid et al., 2018). Several studies have reported As- and Se-contaminated soils, especially in various regions of China and the USA (Khanam et al., 2019). With the advancement of science, technology, and research, several techniques based on diverse mechanisms or processes have been developed to remediate these metals from environmental matrices (Shahid et al., 2018; Tanmoy & Saha, 2019).

Phytoremediation is a plant-based green technology that has been widely adopted and has received cumulative consideration worldwide. Afterward, the discovery of hyperaccumulating plants was significant progress, in which plants can uptake, accumulate, and translocate the elevated concentrations of various toxic metals into their harvestable biomass (Rahman &

Hasegawa, 2011). Hyperaccumulator plants are reported as a very efficient, economical, and eco-friendly technique to remediate metals from contaminated soils (Ali, Khan, & Sajad, 2013; Rizwan et al., 2018). Phytoremediation includes several consecutive steps, such as phytoextraction, phytodegradation, rhizofiltration, phytostabilization, and phytovolatilization. Both aquatic and terrestrial plants have been confirmed to remediate metal-contaminated waters and soils, respectively (Rahman & Hasegawa, 2011).

In an As contamination case, the use of hyperaccumulator plants such as the fern *Pteris vittata* has been suggested (Bastías & Beldarrain, 2016). However, the significant limitation of this method is that the plants absorb As without using it and transfer it back into the food chain system (Singh, Singh, Parihar, Singh, & Prasad, 2015). Fungi can also offset As toxicity by transforming the organic form with reduced toxicity (Bastías & Beldarrain, 2016). The basic behaviors of *Glomus geosporum* (Gg), *G. versiforme* (Gv), and *G. mosseae* (Gm) are considered to decrease As absorption mainly by rice plants; it was reported that these species, taken distinctly or diverse, might be used because the concentration of As decreases in all conditions (Chan, Li, Wu, Wu, & Wong, 2013).

Similar to As, nearly 30 different kinds of plant species of the Fabaceae, Brassicaceae, and Asteraceae families have been reported to hyperaccumulate and tolerate high concentrations of Se from the soil system (Shahid et al., 2018; Winkel et al., 2015). Several studies have reported that the use of genetically modified plants efficiently increases Se uptake, accumulation, tolerance, and volatilization (Pilon-Smits & LeDuc, 2009; Shahid et al., 2018). Different remediation technologies have suggested that the application of hybrid plants, which are genetically modified with remediation characteristics, are efficiently used to remediate specific or miscellaneous metals from polluted soil (Shahid et al., 2017). Some studies, particularly in urban agricultural soil systems, purposed the wise use of plants by adopting various crop rotation systems (Shahid et al., 2018; Xiong et al., 2016). Genetically modified plants increase Se uptake and accumulation by plants, which has been significantly reviewed earlier in some studies (Pilon-Smits & LeDuc, 2009; Terry, Zayed, De Souza, & Tarun, 2000).

Phytoremediation of metals, such as As and Se, from contaminated soil, is likely to decrease the concentrations of metals in the soil system and reduce environmental risks (Wu et al., 2015; Ye, Khan, McGrath, & Zhao, 2011). Metals are sequestered in plant aboveground biomass and are classified as hazardous waste, leading to wide-ranging ecological risks (Rizwan et al., 2017, 2018). Hence, appropriate handling of biomass, either recycled or disposed of, is crucial to avoid secondary contamination and prevent potential risks (Rizwan et al., 2018). Depending on the defined regulations and existing metal concentrations in plants, the contaminated biomass needs to be

placed into a landfill or have the metals reclaimed by smelting, pyrolysis of biomass, and extraction (Da Conceição Gomes, Hauser-Davis, de Souza, & Vitória, 2016). If plants are first incinerated (i.e., combustion & gasification), the subsequent ash must be disposed of in hazardous waste landfills, although the ash volume is approximately <10% of the total volume that might be created if the polluted soil itself is excavated for treatment, which is still beneficial in this regard (Da Conceição Gomes et al., 2016).

Combustion technology for biomass disposal is generally used for energy production at both the domestic and industrial levels, but the burning of metal-polluted biomass in conventional firing systems is not appropriate because it may pose a severe environmental risk (Rizwan et al., 2018). Pyrolyzed metal-contaminated biomass underwent the phytoremediation process afterward. Pyrolysis stabilizes potentially toxic metals, and the pyrolyzed material could adsorb the dye, such as methylene blue. Several researchers have suggested that biomass obtained from contaminated sites might be further utilized for the adsorption of dyes after pyrolysis. Overall, the biomass of plants after harvesting obtained from As- and Se-polluted soil might be treated to avoid secondary pollution and energy. In addition, the substance obtained from this process can be further utilized.

9. Conclusion and future research perspectives

The current review highlighted the critical biogeochemical mechanisms of As and Se in the soil-plant system and focused on insights into the interaction between As and Se and their mechanisms of inducing toxicity in animals and humans.

The reduction of As^{V} to As^{III} can occur in-between redox potential, which leads to the mobilization of As^{III} into the soil and increases its availability to plants. Arsenic uptake in plant cells depends on As species, such as As^{V} , which uses phosphate as a transporter since phosphate is chemically similar to As^{V} , whereas As^{III} uses Si transporters. The molecular and biochemical effects of As in plant systems occur in two ways: 1) the direct inactivation of essential enzymes, either through sulfhydryl group interactions or replacement of compulsory ions from the enzyme active sites, and 2) the consequential, indirect increase of ROS in a cascade of irretrievable damage.

Se^{IV} and Se^{VI} are transported through phosphate and sulfate channels, respectively. Selenosis takes place in plants by two mechanisms: 1) malformed selenoprotein induced plant toxicity and 2) ROS induced Se toxicity. Malformed selenoprotein toxicity in plants occurs in the protein chain by replacement of Cys or Met with that of SeCys or SeMet.

Arsenic and Se induce cytotoxicity and genotoxicity in animals and humans through ROS generation, which ultimately affects DNA repair and

gene regulation. Under reducible conditions, a low Se concentration inhibits the DNA regulation process because it inactivates DNA repair proteins. Arsenite and Se^{IV} did not wholly transfer through aquaglyceroporins, albeit both are very toxic due to their metabolic processes associated with GSH and SAM. Likewise, low levels of Se compounds can constrain the Zn finger protein that binds to and releases Zn from the motif of the zinc finger.

Inhibition of Se^{IV} by As^{III} during gastrointestinal absorption results from the antagonistic interaction between As^{III} and Se^{IV} . Immediate As^{III} contamination inhibits the excretion of pulmonary $(\text{CH}_3)_2\text{Se}$ in animals/rats and hamsters. At low concentrations, Se forms complexes with As such as $((\text{GS}_3)_2\text{AsSe})$ due to insufficient Se interaction with $\text{As}^{\text{III}}\text{MT}$. The elevated concentration of As in the forms of MMA^{V} and DMA^{V} can form incomplete complexes $((\text{GS}_3)_2\text{AsSe})$ and retain more As and MMA in a biological system, which can cause severe toxicity to animals and humans.

Although a large number of efforts have been made to understand the interaction mechanisms between As and Se and the associated toxicity in plants, animals, and humans, further research should be carried out to save crop production and reduce animal and human toxicity. This should include the following research perspectives:

- Pilot studies are required to investigate As and Se detoxification mechanisms in the soil-plant system, animals, and humans.
- The long-term stability of toxicity and insights into the interactions between As and Se in the soil-plant system, animals, and humans still need to be further studied.
- Insights into the interaction mechanisms between As and Se in aquatic ecosystems can cause extended ecological risks and genotoxicity for aquatic life; therefore, further investigations are warranted.
- The scientific community should pay more attention to insights into the mechanisms involved in As and Se interactions in various biological matrices and the associated outcomes to further normalize the rational use and potential intake of these elements.

Acknowledgment

The authors would like to thank seven anonymous reviewers for their constructive comments that significantly improved the quality of the manuscript.

Conflict of interest

The authors have no conflict of interest.

Funding

This work is supported by National Key Research and Development Program of China (No. 2019 YFC1803600, and No. 2017YFD0800302), the National Science Foundation of China-Project of Karst Science Research Center (U1612442), and Science and Technology program of Guizhou Province [Grant No. (2019)5618/2019(2963)/(2019)4428], and ZY thanks UK NERC Fellowship grant (NE/R013349/2) and Royal Academy of Engineering seed grant (FoDSF\1819\1\8).

References

- Abbas, G., Murtaza, B., Bibi, I., Shahid, M., Niazi, N., Khan, M., ... Hussain, M. (2018). Arsenic uptake, toxicity, detoxification, and speciation in plants: Physiological, biochemical, and molecular aspects. *International Journal of Environmental Research and Public Health*, *15*, 59. doi:10.3390/ijerph15010059
- Abhyankar, L. N., Jones, M. R., Guallar, E., & Navas-Acien, A. (2012). Arsenic exposure and hypertension: A systematic review. *Environmental Health Perspectives*, *120*(4), 494–500. doi:10.1289/ehp.1103988
- Abul-Hassan, K. S., Lehnert, B. E., Guant, L., & Walmsley, R. (2004). Abnormal DNA repair in selenium-treated human cells. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, *565*(1), 45–51. doi:10.1016/j.mrgentox.2004.09.004
- Agency for Toxic Substances and Disease Registry (ATSDR). (2007). *Toxicological profile for arsenic*. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.
- Akay, C., Thomas, C., III, & Gazitt, Y. (2004). Arsenic trioxide and paclitaxel induce apoptosis by different mechanism. *Cell Cycle*, *3*(3), 322–332. doi:10.4161/cc.3.3.657
- Ali, H., Khan, E., & Sajad, M. A. (2013). Phytoremediation of heavy metals—Concepts and applications. *Chemosphere*, *91*(7), 869–881. doi:10.1016/j.chemosphere.2013.01.075
- Ali, W., Aslam, M. W., Feng, C., Junaid, M., Ali, K., Li, S., ... Zhang, H. (2019). Unraveling prevalence and public health risks of arsenic, uranium and co-occurring trace metals in groundwater along riverine ecosystem in Sindh and Punjab, Pakistan. *Environmental Geochemistry and Health*, *41*(5), 2223–2238. doi:10.1007/s10653-019-00278-7
- Ali, W., Isayenkov, S. V., Zhao, F.-J., & Maathuis, F. J. (2009). Arsenite transport in plants. *Cellular and Molecular Life Sciences*, *66*(14), 2329–2339. doi:10.1007/s00018-009-0021-7
- Ali, W., Mushtaq, N., Javed, T., Zhang, H., Ali, K., Rasool, A., & Farooqi, A. (2019). Vertical mixing with return irrigation water the cause of arsenic enrichment in groundwater of district Larkana Sindh, Pakistan. *Environmental Pollution*, *245*, 77–88. doi:10.1016/j.envpol.2018.10.103
- Andrew, A. S., Burgess, J. L., Meza, M. M., Demidenko, E., Waugh, M. G., Hamilton, J. W., & Karagas, M. R. (2006). Arsenic exposure is associated with decreased DNA repair in vitro and in individuals exposed to drinking water arsenic. *Environmental Health Perspectives*, *114*(8), 1193–1198. doi:10.1289/ehp.9008
- Andrew, A. S., Karagas, M. R., & Hamilton, J. W. (2003). Decreased DNA repair gene expression among individuals exposed to arsenic in United States drinking water. *International Journal of Cancer*, *104*(3), 263–268. doi:10.1002/ijc.10968
- Arita, A., & Costa, M. (2009). Epigenetics in metal carcinogenesis: Nickel, arsenic, chromium and cadmium. *Metallomics*, *1*(3), 222–228. doi:10.1039/b903049b
- Asati, A., Pichhode, M., & Nikhil, K. (2016). Effect of heavy metals on plants: An overview. *International Journal of Applied Engineering and Management*, *5*, 2319–4847.

- Awasthi, S., Chauhan, R., Srivastava, S., & Tripathi, R. D. (2017). The journey of arsenic from soil to grain in rice. *Frontiers in Plant Science*, 8, 1007. doi:10.3389/fpls.2017.01007
- Balakhnina, T., & Nadezhkina, E. (2017). Effect of selenium on growth and antioxidant capacity of *Triticum aestivum* L. during development of lead-induced oxidative stress. *Russian Journal of Plant Physiology*, 64(2), 215–223. doi:10.1134/S1021443717010022
- Bastias, J. M., & Beldarrain, T. (2016). Arsenic translocation in rice cultivation and its implication for human health. *Chilean Journal of Agricultural Research*, 76(1), 114–122. doi:10.4067/S0718-58392016000100016
- Bergeron, M., Cléménçon, B., Hediger, M., & Markovich, D. (2013). SLC13 family of Na⁺-coupled di- and tri-carboxylate/sulfate transporters. *Molecular Aspects of Medicine*, 34(2–3), 299–312. doi:10.1016/j.mam.2012.12.001
- Bhattacharjee, P., Banerjee, M., & Giri, A. K. (2013). Role of genomic instability in arsenic-induced carcinogenicity. A review. *Environment International*, 53, 29–40. doi:10.1016/j.envint.2012.12.004
- Bhattacharya, P., Mukherjee, A. B., Bundschuh, J., Zevenhoven, R., & Loeppert, R. H. (2007). *Arsenic in soil and groundwater environment: Biogeochemical interactions, health effects and remediation*. Oxford: Elsevier.
- Bhattacharya, S., Gupta, K., Debnath, S., Ghosh, U. C., Chattopadhyay, D., & Mukhopadhyay, A. (2012). Arsenic bioaccumulation in rice and edible plants and subsequent transmission through food chain in Bengal basin: A review of the perspectives for environmental health. *Toxicological & Environmental Chemistry*, 94, 429–441. doi:10.1080/02772248.2012.657200
- Bitterli, C., Bañuelos, G., & Schulin, R. (2010). Use of transfer factors to characterize uptake of selenium by plants. *Journal of Geochemical Exploration*, 107(2), 206–216. doi:10.1016/j.jexplo.2010.09.009
- Björnstedt, M., Kumar, S., & Holmgren, A. (1992). Selenodiglutathione is a highly efficient oxidant of reduced thioredoxin and a substrate for mammalian thioredoxin reductase. *Journal of Biological Chemistry*, 267, 8030–8034. doi:10.1074/jbc.M206452200
- Blessing, H., Kraus, S., Heindl, P., Bal, W., & Hartwig, A. (2004). Interaction of selenium compounds with zinc finger proteins involved in DNA repair. *European Journal of Biochemistry*, 271(15), 3190–3199. doi:10.1111/j.1432-1033.2004.04251.x
- Bleys, J., Navas-Acien, A., Laclaustra, M., Pastor-Barriuso, R., Menke, A., Ordoñas, J., ... Guallar, E. (2009). Serum selenium and peripheral arterial disease: Results from the national health and nutrition examination survey, 2003–2004. *American Journal of Epidemiology*, 169(8), 996–1003. doi:10.1093/aje/kwn414
- Brammer, H., & Ravenscroft, P. (2009). Arsenic in groundwater: A threat to sustainable agriculture in South and South-east Asia. *Environment International*, 35(3), 647–654. doi:10.1016/j.envint.2008.10.004
- Brigelius-Flohé, R. (2008). Selenium compounds and selenoproteins in cancer. *Chemistry & Biodiversity*, 5, 389–395.
- Brown, K. G., & Ross, G. L. (2002). Arsenic, drinking water, and health: A position paper of the American Council on Science and Health. *Regulatory Toxicology and Pharmacology*, 36(2), 162–174. doi:10.1006/rtph.2002.1573
- Buchet, J. P., & Lauwerys, R. (1985). Study of inorganic arsenic methylation by rat liver in vitro: Relevance for the interpretation of observations in man. *Archives of Toxicology*, 57(2), 125–129. doi:10.1007/BF00343122
- Burgess, J. L., Kurzius-Spencer, M., Poplin, G. S., Littau, S. R., Kopplin, M. J., Stürup, S., ... Lantz, R. C. (2014). Environmental arsenic exposure, selenium and sputum alpha-1

- antitrypsin. *Journal of Exposure Science & Environmental Epidemiology*, 24, 150. doi:10.1038/jes.2013.35
- Cappa, J. J., Cappa, P. J., El Mehdawi, A. F., McAleer, J. M., Simmons, M. P., & Pilon-Smits, E. A. (2014). Characterization of selenium and sulfur accumulation across the genus *Stanleya* (Brassicaceae): A field survey and common-garden experiment. *American Journal of Botany*, 101(5), 830–839. doi:10.3732/ajb.1400041
- Carlin, D. J., Naujokas, M. F., Bradham, K. D., Cowden, J., Heacock, M., Henry, H. F., ... Tokar, E. J. (2016). Arsenic and environmental health: State of the science and future research opportunities. *Environmental Health Perspectives*, 124(7), 890–899. doi:10.1289/ehp.1510209
- Challenger, F. (1945). Biological methylation. *Chemical Reviews*, 36(3), 315–361. doi:10.1021/cr60115a003
- Chan, W., Li, H., Wu, F., Wu, S., & Wong, M. H. (2013). Arsenic uptake in upland rice inoculated with a combination or single arbuscular mycorrhizal fungi. *Journal of Hazardous Materials*, 262, 1116–1122. doi:10.1016/j.jhazmat.2012.08.020
- Chandrakar, V., Naithani, S. C., & Keshavkant, S. (2016). Arsenic-induced metabolic disturbances and their mitigation mechanisms in crop plants: A review. *Biologia*, 71(4), 367–377. doi:10.1515/biolog-2016-0052
- Chandrakar, V., Pandey, N., & Keshavkant, S. (2018). Plant responses to arsenic toxicity: Morphology and physiology. In M. Hasanuzzaman, K. Nahar, & M. Fujita (Eds.), *Mechanisms of arsenic toxicity and tolerance in plants* (pp. 27–48). Singapore: Springer.
- Chang, C., Yin, R., Wang, X., Shao, S., Chen, C., & Zhang, H. (2019). Selenium translocation in the soil-rice system in the Enshi seleniferous area, Central China. *Science of the Total Environment*, 669, 83–90. doi:10.1016/j.scitotenv.2019.02.451
- Châtelain, E., Satour, P., Laugier, E., Vu, B. L., Payet, N., Rey, P., & Montrichard, F. (2013). Evidence for participation of the methionine sulfoxide reductase repair system in plant seed longevity. *Proceedings of the National Academy of Sciences*, 110(9), 3633–3638. doi:10.1073/pnas.1220589110
- Chauhan, R., Awasthi, S., Srivastava, S., Dwivedi, S., Pilon-Smits, E. A., Dhankher, O. P., & Tripathi, R. D. (2019). Understanding selenium metabolism in plants and its role as a beneficial element. *Critical Reviews in Environmental Science and Technology*, 49(21), 1937–1958. doi:10.1080/10643389.2019.1598240
- Chauke, T. L. (2013). *Evaluating the efficacy, safety and possible mechanism of action of potassium humate with selenium*. Pretoria: University of Pretoria.
- Chen, Q., Wang, Z., Xiong, Y., Zou, X., & Liu, Z. (2010). Comparative study of p38 MAPK signal transduction pathway of peripheral blood mononuclear cells from patients with coal-combustion-type fluorosis with and without high hair selenium levels. *International Journal of Hygiene and Environmental Health*, 213(5), 381–386. doi:10.1016/j.ijheh.2010.06.002
- Chen, Y., Han, Y.-H., Cao, Y., Zhu, Y.-G., Rathinasabapathi, B., & Ma, L. Q. (2017). Arsenic transport in rice and biological solutions to reduce arsenic risk from rice. *Frontiers in Plant Science*, 8, 268. doi:10.3389/fpls.2017.00268
- Chen, Y., & Maret, W. (2001). Catalytic oxidation of zinc/sulfur coordination sites in proteins by selenium compounds. *Antioxidants & Redox Signaling*, 3(4), 651–656. doi:10.1089/15230860152542998
- Chitta, K. R., Figueroa, J. A. L., Caruso, J. A., & Merino, E. J. (2013). Selenium mediated arsenic toxicity modifies cytotoxicity, reactive oxygen species and phosphorylated proteins. *Metallomics*, 5(6), 673–685. doi:10.1039/c3mt20213e

- Chou, W.-C., Jie, C., Kenedy, A. A., Jones, R. J., Trush, M. A., & Dang, C. V. (2004). Role of NADPH oxidase in arsenic-induced reactive oxygen species formation and cytotoxicity in myeloid leukemia cells. *Proceedings of the National Academy of Sciences*, *101*(13), 4578–4583. doi:[10.1073/pnas.0306687101](https://doi.org/10.1073/pnas.0306687101)
- Chowdhury, R., Chowdhury, S., Roychoudhury, P., Mandal, C., & Chaudhuri, K. (2009). Arsenic induced apoptosis in malignant melanoma cells is enhanced by menadione through ROS generation, p38 signaling and p53 activation. *Apoptosis*, *14*(1), 108–123. doi:[10.1007/s10495-008-0284-8](https://doi.org/10.1007/s10495-008-0284-8)
- Christian, W. J., Hopenhayn, C., Centeno, J. A., & Todorov, T. (2006). Distribution of urinary selenium and arsenic among pregnant women exposed to arsenic in drinking water. *Environmental Research*, *100*, 115–122. doi:[10.1016/j.envres.2005.03.009](https://doi.org/10.1016/j.envres.2005.03.009)
- Constantinescu-Aruxandei, D., Frîncu, R., Capră, L., & Oancea, F. (2018). Selenium analysis and speciation in dietary supplements based on next-generation selenium ingredients. *Nutrients*, *10*(10), 1466. doi:[10.3390/nu10101466](https://doi.org/10.3390/nu10101466)
- Cowan, K. J., & Storey, K. B. (2003). Mitogen-activated protein kinases: New signaling pathways functioning in cellular responses to environmental stress. *Journal of Experimental Biology*, *206*(7), 1107–1115. doi:[10.1242/jeb.00220](https://doi.org/10.1242/jeb.00220)
- Crighton, D., Wilkinson, S., O'Prey, J., Syed, N., Smith, P., Harrison, P. R., ... Ryan, K. M. (2006). DRAM, a p53-induced modulator of autophagy, is critical for apoptosis. *Cell*, *126*(1), 121–134. doi:[10.1016/j.cell.2006.05.034](https://doi.org/10.1016/j.cell.2006.05.034)
- Da Conceição Gomes, M. A., Hauser-Davis, R. A., de Souza, A. N., & Vitória, A. P. (2016). Metal phytoremediation: General strategies, genetically modified plants and applications in metal nanoparticle contamination. *Ecotoxicology and Environmental Safety*, *134*, 133–147. doi:[10.1016/j.ecoenv.2016.08.024](https://doi.org/10.1016/j.ecoenv.2016.08.024)
- Das, K., & Roychoudhury, A. (2014). Reactive oxygen species (ROS) and response of anti-oxidants as ROS-scavengers during environmental stress in plants. *Frontiers in Environmental Science*, *2*, 53. doi:[10.3389/fenvs.2014.00053](https://doi.org/10.3389/fenvs.2014.00053)
- De Temmerman, L., Waegeneers, N., Thiry, C., Du Laing, G., Tack, F., & Ruttens, A. (2014). Selenium content of Belgian cultivated soils and its uptake by field crops and vegetables. *Science of the Total Environment*, *468*, 77–82. doi:[10.1016/j.scitotenv.2013.08.016](https://doi.org/10.1016/j.scitotenv.2013.08.016)
- Deavall, D. G., Martin, E. A., Horner, J. M., & Roberts, R. (2012). Drug-induced oxidative stress and toxicity. *Journal of Toxicology*, *2012*, 1–13. doi:[10.1155/2012/645460](https://doi.org/10.1155/2012/645460)
- Devesa, V., Del Razo, L. M., Adair, B., Drobná, Z., Waters, S. B., Hughes, M. F., ... Thomas, D. J. (2004). Comprehensive analysis of arsenic metabolites by pH-specific hydride generation atomic absorption spectrometry. *Journal of Analytical Atomic Spectrometry*, *19*(11), 1460–1467. doi:[10.1039/B407388F](https://doi.org/10.1039/B407388F)
- Douillet, C., Currier, J., Saunders, J., Bodnar, W. M., Matoušek, T., & Stýblo, M. (2013). Methylated trivalent arsenicals are potent inhibitors of glucose stimulated insulin secretion by murine pancreatic islets. *Toxicology and Applied Pharmacology*, *267*(1), 11–15. doi:[10.1016/j.taap.2012.12.007](https://doi.org/10.1016/j.taap.2012.12.007)
- Drobná, Z., Jaspers, I., Thomas, D. J., & Stýblo, M. (2003). Differential activation of AP-1 in human bladder epithelial cells by inorganic and methylated arsenicals. *The FASEB Journal*, *17*(1), 67–69. doi:[10.1096/fj.02-0287fje](https://doi.org/10.1096/fj.02-0287fje)
- Eguchi, R., Fujimori, Y., Takeda, H., Tabata, C., Ohta, T., Kuribayashi, K., ... Nakano, T. (2011). Arsenic trioxide induces apoptosis through JNK and ERK in human mesothelioma cells. *Journal of Cellular Physiology*, *226*(3), 762–768. doi:[10.1002/jcp.22397](https://doi.org/10.1002/jcp.22397)
- Feng, R., Wei, C., & Tu, S. (2013). The roles of selenium in protecting plants against abiotic stresses. *Environmental and Experimental Botany*, *87*, 58–68. doi:[10.1016/j.envexpbot.2012.09.002](https://doi.org/10.1016/j.envexpbot.2012.09.002)

- Fernández-Martínez, A., & Charlet, L. (2009). Selenium environmental cycling and bioavailability: A structural chemist point of view. *Reviews in Environmental Science and Bio/Technology*, 8(1), 81–110. doi:10.1007/s11157-009-9145-3
- Finnegan, P., & Chen, W. (2012). Arsenic toxicity: The effects on plant metabolism. *Frontiers in Physiology*, 3, 182. doi:10.3389/fphys.2012.00182
- Fleury, C., Mignotte, B., & Vayssière, J.-L. (2002). Mitochondrial reactive oxygen species in cell death signaling. *Biochimie*, 84(2–3), 131–141. doi:10.1016/S0300-9084(02)01369-X
- Flora, S. J. (2011). Arsenic-induced oxidative stress and its reversibility. *Free Radical Biology and Medicine*, 51(2), 257–281. doi:10.1016/j.freeradbiomed.2011.04.008
- Fordyce, F. M. (2013). Selenium deficiency and toxicity in the environment. In O. Selinus (Ed.), *Essentials of medical geology* (pp. 375–416). Berlin, Heidelberg: Springer.
- Frohne, T., Rinklebe, J., Diaz-Bone, R. A., & Du Laing, G. (2011). Controlled variation of redox conditions in a floodplain soil: Impact on metal mobilization and biomethylation of arsenic and antimony. *Geoderma*, 160(3–4), 414–424. doi:10.1016/j.geoderma.2010.10.012
- Gailer, J. (2002). Review: Reactive selenium metabolites as targets of toxic metals/metalloids in mammals: A molecular toxicological perspective. *Applied Organometallic Chemistry*, 16(12), 701–707. doi:10.1002/aoc.376
- Gailer, J. (2007). Arsenic–selenium and mercury–selenium bonds in biology. *Coordination Chemistry Reviews*, 251(1–2), 234–254. doi:10.1016/j.ccr.2006.07.018
- Gailer, J., George, G. N., Harris, H. H., Pickering, I. J., Prince, R. C., Somogyi, A., ... Denton, M. B. (2002). Synthesis, purification, and structural characterization of the dimethyldiselenoarsinate anion. *Inorganic Chemistry*, 41(21), 5426–5432. doi:10.1021/ic0113146
- Gailer, J., George, G. N., Pickering, I. J., Prince, R. C., Younis, H. S., & Winzerling, J. (2002). Biliary excretion of [(GS) 2AsSe]-after intravenous injection of rabbits with arsenite and selenate. *Chemical Research in Toxicology*, 15(11), 1466–1471. doi:10.1021/tx025538s
- Gailer, J., Ruprecht, L., Reitmeir, P., Benker, B., & Schramel, P. (2004). Mobilization of exogenous and endogenous selenium to bile after the intravenous administration of environmentally relevant doses of arsenite to rabbits. *Applied Organometallic Chemistry*, 18(12), 670–675. doi:10.1002/aoc.655
- Ganyc, D., Talbot, S., Konate, F., Jackson, S., Schanen, B., Cullen, W., & Self, W. T. (2007). Impact of trivalent arsenicals on selenoprotein synthesis. *Environmental Health Perspectives*, 115(3), 346–353. doi:10.1289/ehp.9440
- Garg, N., & Singla, P. (2011). Arsenic toxicity in crop plants: Physiological effects and tolerance mechanisms. *Environmental Chemistry Letters*, 9(3), 303–321. doi:10.1007/s10311-011-0313-7
- Gaxiola-Robles, R., Labrada-Martagón, V., Celis de la Rosa, A. D J., Acosta-Vargas, B., Méndez-Rodríguez, L. C., & Zenteno-Savín, T. (2014). Interaction between mercury (Hg), arsenic (As) and selenium (Se) affects the activity of glutathione S-transferase in breast milk; possible relationship with fish and shellfish intake. *Nutricion Hospitalaria*, 30(2), 436–446. doi:10.3305/nh.2014.30.2.7441
- Ghosh, J., & Sil, P. C. (2015). Mechanism for arsenic-induced toxic effects. In S. J. S. Flora (Ed.), *Handbook of arsenic toxicology* (pp. 203–231). London: Elsevier.
- Golob, A., Gadžo, D., Stibilj, V., Djikić, M., Gavrić, T., Kreft, I., & Germ, M. (2016). Sulphur interferes with selenium accumulation in Tartary buckwheat plants. *Plant Physiology and Biochemistry*, 108, 32–36. doi:10.1016/j.plaphy.2016.07.001
- Gromer, S., Eubel, J., Lee, B., & Jacob, J. (2005). Human selenoproteins at a glance. *Cellular and Molecular Life Sciences CMLS*, 62(21), 2414–2437. doi:10.1007/s00018-005-5143-y

- Gupta, M., & Gupta, S. (2017). An overview of selenium uptake, metabolism, and toxicity in plants. *Frontiers in Plant Science*, 7, 2074. doi:10.3389/fpls.2016.02074
- Gupta, M., & Khan, E. (2015). Mechanism of arsenic toxicity and tolerance in plants: Role of silicon and signalling molecules. In B. Tripathi & M. Müller (Eds.), *Stress responses in plants* (pp. 143–157). Cham: Springer.
- Hamilton, S. J. (2004). Review of selenium toxicity in the aquatic food chain. *Science of the Total Environment*, 326(1–3), 1–31. doi:10.1016/j.scitotenv.2004.01.019
- Harper, L. K., Antony, S., & Bayse, C. A. (2014). Thiol reduction of arsenite and selenite: DFT modeling of the pathways to an As–Se bond. *Chemical Research in Toxicology*, 27(12), 2119–2127. doi:10.1021/tx500384h
- Hartikainen, H. (2005). Biogeochemistry of selenium and its impact on food chain quality and human health. *Journal of Trace Elements in Medicine and Biology*, 18(4), 309–318. doi:10.1016/j.jtemb.2005.02.009
- Hartwig, A. (2001). Zinc finger proteins as potential targets for toxic metal ions: Differential effects on structure and function. *Antioxidants & Redox Signaling*, 3(4), 625–634. doi:10.1089/15230860152542970
- Hartwig, A., Blessing, H., Schwerdtle, T., & Walter, I. (2003). Modulation of DNA repair processes by arsenic and selenium compounds. *Toxicology*, 193(1–2), 161–169. doi:10.1016/j.tox.2003.08.004
- Hasanuzzaman, M., Nahar, K., & Fujita, M. (2013). Extreme temperature responses, oxidative stress and antioxidant defense in plants. In K. Vahdati (Ed.), *Abiotic stress - Plant responses and applications in agriculture* (pp. 169–205). London: InTech.
- Hawkesford, M. J., & De Kok, L. J. (2006). Managing sulphur metabolism in plants. *Plant, Cell & Environment*, 29(3), 382–395. doi:10.1111/j.1365-3040.2005.01470.x
- Hayakawa, T., Kobayashi, Y., Cui, X., & Hirano, S. (2005). A new metabolic pathway of arsenite: Arsenic–glutathione complexes are substrates for human arsenic methyltransferase Cyt19. *Archives of Toxicology*, 79(4), 183–191. doi:10.1007/s00204-004-0620-x
- Hering, J. G., Burris, D., Reisinger, H., & O'Day, P. (2008). Environmental fate and exposure assessment for Arsenic in Groundwater. SERDP Project ER-1374.
- Hettick, B. E., Canas-Carrell, J. E., French, A. D., & Klein, D. M. (2015). Arsenic: A review of the element's toxicity, plant interactions, and potential methods of remediation. *Journal of Agricultural and Food Chemistry*, 63(32), 7097–7107. doi:10.1021/acs.jafc.5b02487
- Hondal, R. J., Marino, S. M., & Gladyshev, V. N. (2013). Selenocysteine in thiol/disulfide-like exchange reactions. *Antioxidants & Redox Signaling*, 18, 1675–1689. doi:10.1089/ars.2012.5013
- Hsueh, Y.-M., Ko, Y.-F., Huang, Y.-K., Chen, H.-W., Chiou, H.-Y., Huang, Y.-L., ... Chen, C.-J. (2003). Determinants of inorganic arsenic methylation capability among residents of the Lanyang Basin, Taiwan: Arsenic and selenium exposure and alcohol consumption. *Toxicology Letters*, 137(1–2), 49–63. doi:10.1016/S0378-4274(02)00380-6
- Huang, J.-H. (2014). Impact of microorganisms on arsenic biogeochemistry: A review. *Water, Air, & Soil Pollution*, 225, 1848. doi:10.1007/s11270-013-1848-y
- Huang, Y.-Z., Hu, Y., & Liu, Y.-X. (2007). Interactions between sulfur and selenium uptake by corn in solution culture. *Journal of Plant Nutrition*, 31(1), 43–54. doi:10.1080/01904160701741826
- Hughes, M. F. (2002). Arsenic toxicity and potential mechanisms of action. *Toxicology Letters*, 133(1), 1–16. doi:10.1016/S0378-4274(02)00084-X
- Hughes, M. F., Beck, B. D., Chen, Y., Lewis, A. S., & Thomas, D. J. (2011). Arsenic exposure and toxicology: A historical perspective. *Toxicological Sciences*, 123(2), 305–332. doi:10.1093/toxsci/kfr184

- Hugouvieux, V., Dutilleul, C., Jourdain, A., Reynaud, F., Lopez, V., & Bourguignon, J. (2009). Arabidopsis putative selenium-binding protein1 expression is tightly linked to cellular sulfur demand and can reduce sensitivity to stresses requiring glutathione for tolerance. *Plant Physiology*, *151*(2), 768–781. doi:[10.1104/pp.109.144808](https://doi.org/10.1104/pp.109.144808)
- Jacob, C., Giles, G. I., Giles, N. M., & Sies, H. (2003). Sulfur and selenium: The role of oxidation state in protein structure and function. *Angewandte Chemie International Edition*, *42*(39), 4742–4758. doi:[10.1002/anie.200300573](https://doi.org/10.1002/anie.200300573)
- Jain, C., & Ali, I. (2000). Arsenic: Occurrence, toxicity and speciation techniques. *Water Research*, *34*(17), 4304–4312. doi:[10.1016/S0043-1354\(00\)00182-2](https://doi.org/10.1016/S0043-1354(00)00182-2)
- Jomova, K., Jenisova, Z., Feszterova, M., Baros, S., Liska, J., Hudecova, D., ... Valko, M. (2011). Arsenic: Toxicity, oxidative stress and human disease. *Journal of Applied Toxicology*, *31*, 95–107. doi:[10.1002/jat.1649](https://doi.org/10.1002/jat.1649)
- Jones, G. D., Droz, B., Greve, P., Gottschalk, P., Poffet, D., McGrath, S. P., ... Winkel, L. H. (2017). Selenium deficiency risk predicted to increase under future climate change. *Proceedings of the National Academy of Sciences*, *114*(11), 2848–2853. doi:[10.1073/pnas.1611576114](https://doi.org/10.1073/pnas.1611576114)
- Jornstedt, M. B., Kumar, S., & Holmgren, A. (1995). Selenite and selenodiglutathione: Reactions with thioredoxin systems. *Methods in Enzymology*, *252*(22), 209–219.
- Joseph, J., & Loscalzo, J. (2013). Selenistasis: Epistatic effects of selenium on cardiovascular phenotype. *Nutrients*, *5*(2), 340–358. doi:[10.3390/nu5020340](https://doi.org/10.3390/nu5020340)
- József, L., & Filep, J. G. (2003). Selenium-containing compounds attenuate peroxynitrite-mediated NF- κ B and AP-1 activation and interleukin-8 gene and protein expression in human leukocytes. *Free Radical Biology and Medicine*, *35*(9), 1018–1027. doi:[10.1016/S0891-5849\(03\)00439-8](https://doi.org/10.1016/S0891-5849(03)00439-8)
- Khalid, S., Shahid, M., Niazi, N. K., Rafiq, M., Bakhat, H. F., Imran, M., ... Dumat, C. (2017). Arsenic behaviour in soil-plant system: Biogeochemical reactions and chemical speciation influences. In N. A. Anjum, S. S. Gill, & N. Tuteja (Eds.), *Enhancing cleanup of environmental pollutants* (pp. 97–140). Cham: Springer.
- Khanam, R., Kumar, A., Nayak, A., Shahid, M., Tripathi, R., Vijayakumar, S., ... Panneerselvam, P. (2019). Metal (loid) s (As, Hg, Se, Pb and Cd) in paddy soil: Bioavailability and potential risk to human health. *Science of the Total Environment*, *134330*. doi:[10.1016/j.scitotenv.2019.134330](https://doi.org/10.1016/j.scitotenv.2019.134330)
- Kim, E. H., Sohn, S., Kwon, H. J., Kim, S. U., Kim, M.-J., Lee, S.-J., & Choi, K. S. (2007). Sodium selenite induces superoxide-mediated mitochondrial damage and subsequent autophagic cell death in malignant glioma cells. *Cancer Research*, *67*(13), 6314–6324. doi:[10.1158/0008-5472.CAN-06-4217](https://doi.org/10.1158/0008-5472.CAN-06-4217)
- Kim, T.-S., Jeong, D.-W., Yun, B. Y., & Kim, I. Y. (2002). Dysfunction of rat liver mitochondria by selenite: Induction of mitochondrial permeability transition through thiol-oxidation. *Biochemical and Biophysical Research Communications*, *294*(5), 1130–1137. doi:[10.1016/S0006-291X\(02\)00612-5](https://doi.org/10.1016/S0006-291X(02)00612-5)
- Kircelli, F., Akay, C., & Gazitt, Y. (2007). Arsenic trioxide induces p53-dependent apoptotic signals in myeloma cells with SiRNA-silenced p53: MAP kinase pathway is preferentially activated in cells expressing inactivated p53. *International Journal of Oncology*, *30*, 993–1001. doi:[10.3892/ijo.30.4.993](https://doi.org/10.3892/ijo.30.4.993)
- Klaunig, J. E., & Kamendulis, L. M. (2004). The role of oxidative stress in carcinogenesis. *Annual Review of Pharmacology and Toxicology*, *44*(1), 239–267. doi:[10.1146/annurev.pharmtox.44.101802.121851](https://doi.org/10.1146/annurev.pharmtox.44.101802.121851)

- Klug, A. (2010). The discovery of zinc fingers and their applications in gene regulation and genome manipulation. *Annual Review of Biochemistry*, 79(1), 213–231. doi:10.1146/annurev-biochem-010909-095056
- Kofroňová, M., Mašková, P., & Lipavská, H. (2018). Two facets of world arsenic problem solution: Crop poisoning restriction and enforcement of phytoremediation. *Planta*, 248(1), 19–35. doi:10.1007/s00425-018-2906-x
- Kojima, C., Ramirez, D. C., Tokar, E. J., Himeno, S., Drobná, Z., Stýblo, M., ... Waalkes, M. P. (2009). Requirement of arsenic biomethylation for oxidative DNA damage. *Journal of the National Cancer Institute*,
- La Porte, P. F. (2011). *Selenium in the detoxification of arsenic: Mechanisms and clinical efficacy*. Chicago: The University of Chicago.
- Lai, R., Wang, Y., Li, X., & Yu, R. (2008). Effect of selenium and arsenic on oxidative stress, DNA oxidative damage and repair in HepG2 cells. *Wei sheng yan jiu = Journal of Hygiene Research*, 37(6), 645–648.
- Laity, J. H., Lee, B. M., & Wright, P. E. (2001). Zinc finger proteins: New insights into structural and functional diversity. *Current Opinion in Structural Biology*, 11(1), 39–46. doi:10.1016/S0959-440X(00)00167-6
- Larabee, J. L., Hocker, J. R., & Hanas, J. S. (2009). Mechanisms of inhibition of zinc-finger transcription factors by selenium compounds ebselen and selenite. *Journal of Inorganic Biochemistry*, 103(3), 419–426. doi:10.1016/j.jinorgbio.2008.12.007
- Letavayova, L., Vlčková, V., & Brozmanova, J. (2006). Selenium: From cancer prevention to DNA damage. *Toxicology*, 227, 1–14. doi:10.1016/j.tox.2006.07.017
- Levander, O. A. (1977). Metabolic interrelationships between arsenic and selenium. *Environmental Health Perspectives*, 19, 159–164. doi:10.1289/ehp.7719159
- Lin, L., Zhou, W., Dai, H., Cao, F., Zhang, G., & Wu, F. (2012). Selenium reduces cadmium uptake and mitigates cadmium toxicity in rice. *Journal of Hazardous Materials*, 235, 343–351. doi:10.1016/j.jhazmat.2012.08.012
- Liu, J., Yin, M., Zhang, W., Tsang, D. C., Wei, X., Zhou, Y., ... Sun, Y. (2019). Response of microbial communities and interactions to thallium in contaminated sediments near a pyrite mining area. *Environmental Pollution*, 248, 916–928. doi:10.1016/j.envpol.2019.02.089
- Liu, Z., Shen, J., Carbrey, J. M., Mukhopadhyay, R., Agre, P., & Rosen, B. P. (2002). Arsenite transport by mammalian aquaglyceroporins AQP7 and AQP9. *Proceedings of the National Academy of Sciences*, 99(9), 6053–6058. doi:10.1073/pnas.092131899
- Lozano, G., & Elledge, S. J. (2000). Cancer: P 53 sends nucleotides to repair DNA. *Nature*, 404(6773), 24–25. doi:10.1038/35003670
- Lu, J., & Jiang, C. (2001). Antiangiogenic activity of selenium in cancer chemoprevention: Metabolite-specific effects. *Nutrition and Cancer*, 40(1), 64–73. doi:10.1207/S15327914NC401_12
- Ma, J. F., & Yamaji, N. (2008). Functions and transport of silicon in plants. *Cellular and Molecular Life Sciences*, 65(19), 3049–3057. doi:10.1007/s00018-008-7580-x
- Ma, L. Q., Komar, K. M., Tu, C., Zhang, W., Cai, Y., & Kennelley, E. D. (2001). A fern that hyperaccumulates arsenic. *Nature*, 409(6820), 579–579. doi:10.1038/35054664
- Maiti, S. (2015). Arsenic-induced mutagenesis and carcinogenesis: A possible mechanism. In S. J. S. Flora (Ed.), *Handbook of arsenic toxicology* (pp. 233–279). London: Elsevier.
- Manley, S. A., George, G. N., Pickering, I. J., Glass, R. S., Prenner, E. J., Yamdagni, R., ... Gailer, J. (2006). The seleno bis (S-glutathionyl) arsinium ion is assembled in erythrocyte lysate. *Chemical Research in Toxicology*, 19(4), 601–607. doi:10.1021/tx0503505

- Maret, W. (2003). Cellular zinc and redox states converge in the metallothionein/thionein pair. *The Journal of Nutrition*, 133(5), 1460S–1462S. doi:10.1093/jn/133.5.1460S
- Maritim, A., Sanders, A., & Watkins, rJ. (2003). Diabetes, oxidative stress, and antioxidants: A review. *Journal of Biochemical and Molecular Toxicology*, 17(1), 24–38. doi:10.1002/jbt.10058
- Mazej, D., Osvald, J., & Stibilj, V. (2008). Selenium species in leaves of chicory, dandelion, lamb's lettuce and parsley. *Food Chemistry*, 107(1), 75–83. doi:10.1016/j.foodchem.2007.07.036
- McKenzie, R. C., Arthur, J. R., & Beckett, G. J. (2002). Selenium and the regulation of cell signaling, growth, and survival: Molecular and mechanistic aspects. *Antioxidants & Redox Signaling*, 4(2), 339–351. doi:10.1089/152308602753666398
- Messarrah, M., Klibet, F., Boumendjel, A., Abdennour, C., Bouzerna, N., Boulakoud, M. S., & El Feki, A. (2012). Hepatoprotective role and antioxidant capacity of selenium on arsenic-induced liver injury in rats. *Experimental and Toxicologic Pathology*, 64(3), 167–174. doi:10.1016/j.etp.2010.08.002
- Moreno-Jiménez, E., Esteban, E., & Peñalosa, J. M. (2012). The fate of arsenic in soil-plant systems. In D. M. Whitacre (Ed.), *Reviews of environmental contamination and toxicology* (pp. 1–37). New York: Springer.
- Moriarty-Craige, S. E., & Jones, D. P. (2004). Extracellular thiols and thiol/disulfide redox in metabolism. *Annual Review of Nutrition*, 24(1), 481–509. doi:10.1146/annurev.nutr.24.012003.132208
- Naranmandura, H., Suzuki, N., & Suzuki, K. T. (2006). Trivalent arsenicals are bound to proteins during reductive methylation. *Chemical Research in Toxicology*, 19(8), 1010–1018. doi:10.1021/tx060053f
- Naujokas, M. F., Anderson, B., Ahsan, H., Aposhian, H. V., Graziano, J. H., Thompson, C., & Suk, W. A. (2013). The broad scope of health effects from chronic arsenic exposure: Update on a worldwide public health problem. *Environmental Health Perspectives*, 121(3), 295–302. doi:10.1289/ehp.1205875
- Navarro-Alarcon, M., & Cabrera-Vique, C. (2008). Selenium in food and the human body: A review. *Science of the Total Environment*, 400(1–3), 115–141. doi:10.1016/j.scitotenv.2008.06.024
- Navas-Acien, A., Silbergeld, E. K., Streeter, R. A., Clark, J. M., Burke, T. A., & Guallar, E. (2006). Arsenic exposure and type 2 diabetes: A systematic review of the experimental and epidemiologic evidence. *Environmental Health Perspectives*, 114(5), 641–648. doi:10.1289/ehp.8551
- Ogra, Y., & Anan, Y. (2009). Selenometabolomics: Identification of selenometabolites and specification of their biological significance by complementary use of elemental and molecular mass spectrometry. *Journal of Analytical Atomic Spectrometry*, 24(11), 1477–1488. doi:10.1039/b910235c
- Ohta, Y., & Suzuki, K. T. (2008). Methylation and demethylation of intermediates selenide and methylselenol in the metabolism of selenium. *Toxicology and Applied Pharmacology*, 226(2), 169–177. doi:10.1016/j.taap.2007.09.011
- Park, S.-H., Kim, J.-H., Chi, G. Y., Kim, G.-Y., Chang, Y.-C., Moon, S.-K., ... Choi, Y. H. (2012). Induction of apoptosis and autophagy by sodium selenite in A549 human lung carcinoma cells through generation of reactive oxygen species. *Toxicology Letters*, 212(3), 252–261. doi:10.1016/j.toxlet.2012.06.007
- Pilon-Smits, E. A., & LeDuc, D. L. (2009). Phytoremediation of selenium using transgenic plants. *Current Opinion in Biotechnology*, 20(2), 207–212. doi:10.1016/j.copbio.2009.02.001

- Pilon-Smits, E. A., & Quinn, C. F. (2010). Selenium metabolism in plants. In R. Hell & R.-R. Mendel (Eds.), *Cell biology of metals and nutrients* (pp. 225–241). Berlin, Heidelberg: Springer.
- Pilsner, J. R., Hall, M. N., Liu, X., Ahsan, H., Ilievski, V., Slavkovich, V., ... Gamble, M. V. (2010). Associations of plasma selenium with arsenic and genomic methylation of leukocyte DNA in Bangladesh. *Environmental Health Perspectives*, 119(1), 113–118. doi: [10.1289/ehp.1001973](https://doi.org/10.1289/ehp.1001973)
- Plant, J., Kinniburgh, D., Smedley, P., Fordyce, F., & Klinck, B. (2004). Arsenic and selenium.
- Prasad, K. S., & Selvaraj, K. (2014). Biogenic synthesis of selenium nanoparticles and their effect on As (III)-induced toxicity on human lymphocytes. *Biological Trace Element Research*, 157(3), 275–283. doi:[10.1007/s12011-014-9891-0](https://doi.org/10.1007/s12011-014-9891-0)
- Qian, Y., Castranova, V., & Shi, X. (2003). New perspectives in arsenic-induced cell signal transduction. *Journal of Inorganic Biochemistry*, 96(2–3), 271–278. doi:[10.1016/S0162-0134\(03\)00235-6](https://doi.org/10.1016/S0162-0134(03)00235-6)
- Rahman, M. A., & Hasegawa, H. (2011). Aquatic arsenic: Phytoremediation using floating macrophytes. *Chemosphere*, 83(5), 633–646. doi:[10.1016/j.chemosphere.2011.02.045](https://doi.org/10.1016/j.chemosphere.2011.02.045)
- Rahman, M. A., Hogan, B., Duncan, E., Doyle, C., Krassoi, R., Rahman, M. M., ... Hassler, C. (2014). Toxicity of arsenic species to three freshwater organisms and biotransformation of inorganic arsenic by freshwater phytoplankton (*Chlorella* sp. CE-35). *Ecotoxicology and Environmental Safety*, 106, 126–135. doi:[10.1016/j.ecoenv.2014.03.004](https://doi.org/10.1016/j.ecoenv.2014.03.004)
- Rai, P. K., Kumar, V., Lee, S., Raza, N., Kim, K.-H., Ok, Y. S., & Tsang, D. C. (2018). Nanoparticle-plant interaction: Implications in energy, environment, and agriculture. *Environment International*, 119, 1–19. doi:[10.1016/j.envint.2018.06.012](https://doi.org/10.1016/j.envint.2018.06.012)
- Ramoutar, R. R., & Brumaghim, J. L. (2007). Effects of inorganic selenium compounds on oxidative DNA damage. *Journal of Inorganic Biochemistry*, 101(7), 1028–1035. doi:[10.1016/j.jinorgbio.2007.03.016](https://doi.org/10.1016/j.jinorgbio.2007.03.016)
- Ratnaike, R. N. (2003). Acute and chronic arsenic toxicity. *Postgraduate Medical Journal*, 79(933), 391–396. doi:[10.1136/pmj.79.933.391](https://doi.org/10.1136/pmj.79.933.391)
- Rayman, M. P. (2000). The importance of selenium to human health. *The Lancet*, 356(9225), 233–241. doi:[10.1016/S0140-6736\(00\)02490-9](https://doi.org/10.1016/S0140-6736(00)02490-9)
- Rees, K., Hartley, L., Day, C., Flowers, N., Clarke, A., & Stranges, S. (2013). Selenium supplementation for the primary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews*, (1), CD009671.
- Reichard, J. F., & Puga, A. (2010). Effects of arsenic exposure on DNA methylation and epigenetic gene regulation. *Epigenomics*, 2(1):87–104.
- Ren, X., McHale, C. M., Skibola, C. F., Smith, A. H., Smith, M. T., & Zhang, L. (2011). An emerging role for epigenetic dysregulation in arsenic toxicity and carcinogenesis. *Environmental Health Perspectives*, 119(1), 11–19. doi:[10.1289/ehp.1002114](https://doi.org/10.1289/ehp.1002114)
- Renkema, H., Koopmans, A., Kersbergen, L., Kikkert, J., Hale, B., & Berkelaar, E. (2012). The effect of transpiration on selenium uptake and mobility in durum wheat and spring canola. *Plant and Soil*, 354(1–2), 239–250. doi:[10.1007/s11104-011-1069-3](https://doi.org/10.1007/s11104-011-1069-3)
- Rizwan, M., Ali, S., Adrees, M., Ibrahim, M., Tsang, D. C., Zia-Ur-Rehman, M., ... Ok, Y. S. (2017). A critical review on effects, tolerance mechanisms and management of cadmium in vegetables. *Chemosphere*, 182, 90–105. doi:[10.1016/j.chemosphere.2017.05.013](https://doi.org/10.1016/j.chemosphere.2017.05.013)
- Rizwan, M., Ali, S., Ur Rehman, M. Z., Rinklebe, J., Tsang, D. C., Bashir, A., ... Ok, Y. S. (2018). Cadmium phytoremediation potential of Brassica crop species: A review. *Science of the Total Environment*, 631, 1175–1191. doi:[10.1016/j.scitotenv.2018.03.104](https://doi.org/10.1016/j.scitotenv.2018.03.104)

- Rosen, B. P., & Liu, Z. (2009). Transport pathways for arsenic and selenium: A minireview. *Environment International*, 35(3), 512–515. doi:10.1016/j.envint.2008.07.023
- Rossman, T. G., & Uddin, A. N. (2004). Selenium prevents spontaneous and arsenite-induced mutagenesis. In *International congress series* (pp. 173–179). New York: Elsevier. doi:10.1016/j.ics.2004.09.038
- Sah, S., Vandenberg, A., & Smits, J. (2013). Treating chronic arsenic toxicity with high selenium lentil diets. *Toxicology and Applied Pharmacology*, 272(1), 256–262. doi:10.1016/j.taap.2013.06.008
- Saha, U., Fayiga, A., & Sonon, L. (2017). Selenium in the soil-plant environment: A review. *International Journal of Applied Agricultural Sciences*, 3(1), 1–18. doi:10.11648/j.ijaas.20170301.11
- Salnikow, K., & Zhitkovich, A. (2008). Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: Nickel, arsenic, and chromium. *Chemical Research in Toxicology*, 21(1), 28–44. doi:10.1021/tx700198a
- Sampayo-Reyes, A., Taméz-Guerra, R. S., de León, M. B., Vargas-Villarreal, J., Lozano-Garza, H. G., Rodríguez-Padilla, C., ... Hernández, A. (2017). Tocopherol and selenium modulate the transplacental effects induced by sodium arsenite in hamsters. *Reproductive Toxicology*, 74, 204–211. doi:10.1016/j.reprotox.2017.10.003
- Sarkar, B., Bhattacharjee, S., Daware, A., Tribedi, P., Krishnani, K., & Minhas, P. (2015). Selenium nanoparticles for stress-resilient fish and livestock. *Nanoscale Research Letters*, 10(1), 371. doi:10.1186/s11671-015-1073-2
- Savitha, P. (2014). Role of selenium. *Journal of Pharmaceutical Sciences and Research*, 6, 56.
- Schiavon, M., Pilon, M., Malagoli, M., & Pilon-Smits, E. A. (2015). Exploring the importance of sulfate transporters and ATP sulphurylases for selenium hyperaccumulation—A comparison of *Stanleya pinnata* and *Brassica juncea* (Brassicaceae). *Frontiers in Plant Science*, 6, 2. doi:10.3389/fpls.2015.00002
- Schiavon, M., & Pilon-Smits, E. A. (2017). Selenium biofortification and phytoremediation phytotechnologies: A review. *Journal of Environmental Quality*, 46(1), 10–19. doi:10.2134/jeq2016.09.0342
- Schrauzer, G. N. (2000). Selenomethionine: A review of its nutritional significance, metabolism and toxicity. *The Journal of Nutrition*, 130(7), 1653–1656. doi:10.1093/jn/130.7.1653
- Selvaraj, V., Tomblin, J., Armistead, M. Y., & Murray, E. (2013). Selenium (sodium selenite) causes cytotoxicity and apoptotic mediated cell death in PLHC-1 fish cell line through DNA and mitochondrial membrane potential damage. *Ecotoxicology and Environmental Safety*, 87, 80–88. doi:10.1016/j.ecoenv.2012.09.028
- Shafik, N. M., & El Batsh, M. M. (2016). Protective effects of combined selenium and *Punica granatum* treatment on some inflammatory and oxidative stress markers in arsenic-induced hepatotoxicity in rats. *Biological Trace Element Research*, 169(1), 121–128. doi:10.1007/s12011-015-0397-1
- Shahid, M., Dumat, C., Khalid, S., Schreck, E., Xiong, T., & Niazi, N. K. (2017). Foliar heavy metal uptake, toxicity and detoxification in plants: A comparison of foliar and root metal uptake. *Journal of Hazardous Materials*, 325, 36–58. doi:10.1016/j.jhazmat.2016.11.063
- Shahid, M., Niazi, N. K., Khalid, S., Murtaza, B., Bibi, I., & Rashid, M. I. (2018). A critical review of selenium biogeochemical behavior in soil-plant system with an inference to human health. *Environmental Pollution*, 234, 915–934. doi:10.1016/j.envpol.2017.12.019
- Shakir, S. K., Azizullah, A., Murad, W., Daud, M. K., Nabeela, F., Rahman, H., ... Häder, D.-P. (2016). Toxic metal pollution in Pakistan and its possible risks to public health. In

- D. M. Whitacre (Ed.), *Reviews of environmental contamination and toxicology* (pp. 1–60). New York: Springer.
- Shankar, S., & Shanker, U. (2014). Arsenic contamination of groundwater: A review of sources, prevalence, health risks, and strategies for mitigation. *The Scientific World Journal*, 2014doi:10.1155/2014/304524
- Sharma, I. (2012). Arsenic induced oxidative stress in plants. *Biologia*, 67(3), 447–453. doi: 10.2478/s11756-012-0024-y
- Shen, H.-M., & Liu, Z.-G. (2006). JNK signaling pathway is a key modulator in cell death mediated by reactive oxygen and nitrogen species. *Free Radical Biology and Medicine*, 40(6), 928–939. doi:10.1016/j.freeradbiomed.2005.10.056
- Shi, H., Hudson, L. G., Ding, W., Wang, S., Cooper, K. L., Liu, S., ... Liu, K. J. (2004). Arsenite causes DNA damage in keratinocytes via generation of hydroxyl radicals. *Chemical Research in Toxicology*, 17(7), 871–878. doi:10.1021/tx049939e
- Shibata, Y., Morita, M., & Fuwa, K. (1992). Selenium and arsenic in biology: Their chemical forms and biological functions. *Advances in Biophysics*, 28, 31–80. doi:10.1016/0065-227X(92)90022-J
- Shini, S., Sultan, A., & Bryden, W. (2015). Selenium biochemistry and bioavailability: Implications for animal agriculture. *Agriculture*, 5(4), 1277–1288. doi:10.3390/agriculture5041277
- Singh, R., Singh, S., Parihar, P., Singh, V. P., & Prasad, S. M. (2015). Arsenic contamination, consequences and remediation techniques: A review. *Ecotoxicology and Environmental Safety*, 112, 247–270. doi:10.1016/j.ecoenv.2014.10.009
- Skalickova, S., Milosavljevic, V., Cihalova, K., Horoky, P., Richtera, L., & Adam, V. (2017). Selenium nanoparticles as a nutritional supplement. *Nutrition*, 33, 83–90. doi:10.1016/j.nut.2016.05.001
- Skröder Löveborn, H., Kippler, M., Lu, Y., Ahmed, S., Kuehnelt, D., Raqib, R., & Vahter, M. (2016). Arsenic metabolism in children differs from that in adults. *Toxicological Sciences*, 152(1), 29–39. doi:10.1093/toxsci/kfw060
- Sneddon, A. (2012). Selenium nutrition and its impact on health. *Journal of Food & Health Innovation Service*, 6, 104–108.
- Snider, G. W., Ruggles, E., Khan, N., & Hondal, R. J. (2013). Selenocysteine confers resistance to inactivation by oxidation in thioredoxin reductase: Comparison of selenium and sulfur enzymes. *Biochemistry*, 52(32), 5472–5481. doi:10.1021/bi400462j
- Stadtman, T. C. (2005). Selenoproteins—Tracing the role of a trace element in protein function. *PLoS Biology*, 3(12), e421. doi:10.1371/journal.pbio.0030421
- Stoeva, N., & Bineva, T. (2003). Oxidative changes and photosynthesis in oat plants grown in As-contaminated soil. *Bulgarian Journal of Plant Physiology*, 29, 87–95.
- Stolz, J. F., Basu, P., Santini, J. M., & Oremland, R. S. (2006). Arsenic and selenium in microbial metabolism. *Annual Review of Microbiology*, 60(1), 107–130. doi:10.1146/annurev.micro.60.080805.142053
- Styblo, M., & Thomas, D. J. (2001). Selenium modifies the metabolism and toxicity of arsenic in primary rat hepatocytes. *Toxicology and Applied Pharmacology*, 172(1), 52–61. doi:10.1006/taap.2001.9134
- Su, C.-T., Hsieh, R.-L., Chung, C.-J., Huang, P.-T., Lin, Y.-C., Ao, P.-L., ... Lin, M.-I. (2019). Plasma selenium influences arsenic methylation capacity and developmental delays in preschool children in Taiwan. *Environmental Research*, 171, 52–59. doi:10.1016/j.envres.2019.01.003
- Sun, H.-J., Rathinasabapathi, B., Wu, B., Luo, J., Pu, L.-P., & Ma, L. Q. (2014). Arsenic and selenium toxicity and their interactive effects in humans. *Environment International*, 69, 148–158. doi:10.1016/j.envint.2014.04.019

- Surai, P. F. (2006). *Selenium in nutrition and health*. Nottingham: Nottingham University Press.
- Suzuki, K. T., Kurasaki, K., & Suzuki, N. (2007). Selenocysteine β -lyase and methylselenol demethylase in the metabolism of Se-methylated selenocompounds into selenide. *Biochimica et Biophysica Acta (BBA) - General Subjects*, 1770(7), 1053–1061. doi:10.1016/j.bbagen.2007.03.007
- Talbot, S., Nelson, R., & Self, W. (2008). Arsenic trioxide and auranofin inhibit selenoprotein synthesis: Implications for chemotherapy for acute promyelocytic leukaemia. *British Journal of Pharmacology*, 154(5), 940–948. doi:10.1038/bjp.2008.161
- Tanmoy, P., & Saha, N. C. (2019). Environmental arsenic and selenium contamination and approaches towards its bioremediation through the exploration of microbial adaptations: A review. *Pedosphere*, 29, 554–568. doi:10.1016/S1002-0160(19)60829-5
- Terry, N., Zayed, A., De Souza, M., & Tarun, A. (2000). Selenium in higher plants. *Annual Review of Plant Physiology and Plant Molecular Biology*, 51(1), 401–432. doi:10.1146/annurev.arplant.51.1.401
- Tinggi, U. (2003). Essentiality and toxicity of selenium and its status in Australia: A review. *Toxicology Letters*, 137(1–2), 103–110. doi:10.1016/S0378-4274(02)00384-3
- Tseng, C.-H. (2009). A review on environmental factors regulating arsenic methylation in humans. *Toxicology and Applied Pharmacology*, 235(3), 338–350. doi:10.1016/j.taap.2008.12.016
- Vahter, M. E. (2007). Interactions between arsenic-induced toxicity and nutrition in early life. *The Journal of Nutrition*, 137(12), 2798–2804. doi:10.1093/jn/137.12.2798
- Valdiglesias, V., Pásaro, E., Méndez, J., & Laffon, B. (2010). In vitro evaluation of selenium genotoxic, cytotoxic, and protective effects: A review. *Archives of Toxicology*, 84(5), 337–351. doi:10.1007/s00204-009-0505-0
- Valko, M., Rhodes, C., Moncol, J., Izakovic, M., & Mazur, M. (2006). Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chemico-Biological Interactions*, 160(1), 1–40. doi:10.1016/j.cbi.2005.12.009
- Ventura, J.-J., Cogswell, P., Flavell, R. A., Baldwin, A. S., & Davis, R. J. (2004). JNK potentiates TNF-stimulated necrosis by increasing the production of cytotoxic reactive oxygen species. *Genes & Development*, 18, 2905–2915. doi:10.1101/gad.1223004
- Villa-Bellosta, R., & Sorribas, V. (2008). Role of rat sodium/phosphate cotransporters in the cell membrane transport of arsenate. *Toxicology and Applied Pharmacology*, 232(1), 125–134. doi:10.1016/j.taap.2008.05.026
- Vinceti, M., Maraldi, T., Bergomi, M., & Malagoli, C. (2009). Risk of chronic low-dose selenium overexposure in humans: Insights from epidemiology and biochemistry. *Reviews on Environmental Health*, 24(3), 231–248. doi:10.1515/REVEH.2009.24.3.231
- Vinceti, M., Solovyev, N., Mandrioli, J., Crespi, C. M., Bonvicini, F., Arcolin, E., ... Michalke, B. (2013). Cerebrospinal fluid of newly diagnosed amyotrophic lateral sclerosis patients exhibits abnormal levels of selenium species including elevated selenite. *NeuroToxicology*, 38, 25–32. doi:10.1016/j.neuro.2013.05.016
- Vogelstein, B., Lane, D., & Levine, A. J. (2000). Surfing the p53 network. *Nature*, 408(6810), 307–310. doi:10.1038/35042675
- Wallenberg, M., Olm, E., Hebert, C., Björnstedt, M., & Fernandes, A. P. (2010). Selenium compounds are substrates for glutaredoxins: A novel pathway for selenium metabolism and a potential mechanism for selenium-mediated cytotoxicity. *Biochemical Journal*, 429(1), 85–93. doi:10.1042/BJ20100368
- Walton, F. S., Waters, S. B., Jolley, S. L., LeCluyse, E. L., Thomas, D. J., & Styblo, M. (2003). Selenium compounds modulate the activity of recombinant rat AsIII-

- methyltransferase and the methylation of arsenite by rat and human hepatocytes. *Chemical Research in Toxicology*, 16(3), 261–265. doi:10.1021/tx025649r
- Wang, Q. Q., Thomas, D. J., & Naranmandura, H. (2015). Importance of being thiomethylated: formation, fate, and effects of methylated thioarsenicals. *Chemical Research in Toxicology*, 28(3), 281–289. doi:10.1021/tx500464t
- Wei, Y., Cao, X., Ou, Y., Lu, J., Xing, C., & Zheng, R. (2001). SeO₂ induces apoptosis with down-regulation of Bcl-2 and up-regulation of P53 expression in both immortal human hepatic cell line and hepatoma cell line. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, 490(2), 113–121. doi:10.1016/S1383-5718(00)00149-2
- Weiller, M., Latta, M., Kresse, M., Lucas, R., & Wendel, A. (2004). Toxicity of nutritionally available selenium compounds in primary and transformed hepatocytes. *Toxicology*, 201(1–3), 21–30. doi:10.1016/j.tox.2004.03.026
- Wen, H., & Carignan, J. (2007). Reviews on atmospheric selenium: Emissions, speciation and fate. *Atmospheric Environment*, 41(34), 7151–7165. doi:10.1016/j.atmosenv.2007.07.035
- Whanger, P. (2004). Selenium and its relationship to cancer: An update. *British Journal of Nutrition*, 91(1), 11–28. doi:10.1079/BJN20031015
- Wilson, S. C., Lockwood, P. V., Ashley, P. M., & Tighe, M. (2010). The chemistry and behaviour of antimony in the soil environment with comparisons to arsenic: A critical review. *Environmental Pollution*, 158(5), 1169–1181. doi:10.1016/j.envpol.2009.10.045
- Winkel, L. H., Johnson, C. A., Lenz, M., Grundl, T., Leupin, O. X., Amini, M., & Charlet, L. (2011). *Environmental selenium research: From microscopic processes to global understanding*. Washington, DC: ACS Publications.
- Winkel, L. H., Vriens, B., Jones, G. D., Schneider, L. S., Pilon-Smits, E., & Bañuelos, G. S. (2015). Selenium cycling across soil-plant-atmosphere interfaces: A critical review. *Nutrients*, 7(6), 4199–4239. doi:10.3390/nu7064199
- Witkiewicz-Kucharczyk, A., & Bal, W. (2006). Damage of zinc fingers in DNA repair proteins, a novel molecular mechanism in carcinogenesis. *Toxicology Letters*, 162, 29–42. doi:10.1016/j.toxlet.2005.10.018
- Woo Youn, B., Fiala, E. S., & Soon Sohn, O. (2001). Mechanisms of organoselenium compounds in chemoprevention: Effects on transcription factor-DNA binding. *Nutrition and Cancer*, 40(1), 28–33. doi:10.1207/S15327914NC401_7
- Wu, Z., Bañuelos, G. S., Lin, Z.-Q., Liu, Y., Yuan, L., Yin, X., & Li, M. (2015). Biofortification and phytoremediation of selenium in China. *Frontiers in Plant Science*, 6, 136. doi:10.3389/fpls.2015.00136
- Xiong, T., Austruy, A., Pierart, A., Shahid, M., Schreck, E., Mombo, S., & Dumat, C. (2016). Kinetic study of phytotoxicity induced by foliar lead uptake for vegetables exposed to fine particles and implications for sustainable urban agriculture. *Journal of Environmental Sciences*, 46, 16–27. doi:10.1016/j.jes.2015.08.029
- Xu, Z., Wang, Z., Li, J.-J., Chen, C., Zhang, P.-C., Dong, L., ... Wang, Z.-L. (2013). Protective effects of selenium on oxidative damage and oxidative stress related gene expression in rat liver under chronic poisoning of arsenic. *Food and Chemical Toxicology*, 58, 1–7. doi:10.1016/j.fct.2013.03.048
- Yang, C., & Frenkel, K. (2002). Arsenic-mediated cellular signal transduction, transcription factor activation, and aberrant gene expression: Implications in carcinogenesis. *Journal of Environmental Pathology, Toxicology and Oncology*, 21. doi:10.1615/JEnvironPatholToxicolOncol.v21.i4.20
- Yang, C., Kuo, M., Chen, J., & Chen, Y. (1999). Arsenic trioxide sensitivity is associated with low level of glutathione in cancer cells. *British Journal of Cancer*, 81(5), 796–799. doi:10.1038/sj.bjc.6690766

- Yang, J., Cao, W., & Rui, Y. (2017). Interactions between nanoparticles and plants: Phytotoxicity and defense mechanisms. *Journal of Plant Interactions*, 12(1), 158–169. doi: [10.1080/17429145.2017.1310944](https://doi.org/10.1080/17429145.2017.1310944)
- Ye, W.-L., Khan, M. A., McGrath, S. P., & Zhao, F.-J. (2011). Phytoremediation of arsenic contaminated paddy soils with *Pteris vittata* markedly reduces arsenic uptake by rice. *Environmental Pollution*, 159(12), 3739–3743. doi: [10.1016/j.envpol.2011.07.024](https://doi.org/10.1016/j.envpol.2011.07.024)
- Yoshioka, J., Schreiter, E. R., & Lee, R. T. (2006). Role of thioredoxin in cell growth through interactions with signaling molecules. *Antioxidants & Redox Signaling*, 8, 2143–2151. doi: [10.1089/ars.2006.8.2143](https://doi.org/10.1089/ars.2006.8.2143)
- Zakharyan, R. A., & Aposhian, H. V. (1999). Arsenite methylation by methylvitamin B 12 and glutathione does not require an enzyme. *Toxicology and Applied Pharmacology*, 154(3), 287–291. doi: [10.1006/taap.1998.8587](https://doi.org/10.1006/taap.1998.8587)
- Zarubin, T., & Jiahuai, H. (2005). Activation and signaling of the p38 MAP kinase pathway. *Cell Research*, 15(1), 11–18. doi: [10.1038/sj.cr.7290257](https://doi.org/10.1038/sj.cr.7290257)
- Zeng, G., Wu, H., Liang, J., Guo, S., Huang, L., Xu, P., ... He, Y. (2015). Efficiency of biochar and compost (or composting) combined amendments for reducing Cd, Cu, Zn and Pb bioavailability, mobility and ecological risk in wetland soil. *RSC Advances*, 5(44), 34541–34548. doi: [10.1039/C5RA04834F](https://doi.org/10.1039/C5RA04834F)
- Zeng, H. (2001). Arsenic suppresses necrosis induced by selenite in human leukemia HL-60 cells. *Biological Trace Element Research*, 83(1), 01–15. doi: [10.1385/BTER:83:1:01](https://doi.org/10.1385/BTER:83:1:01)
- Zeng, H. (2009). Selenium as an essential micronutrient: Roles in cell cycle and apoptosis. *Molecules*, 14(3), 1263–1278. doi: [10.3390/molecules14031263](https://doi.org/10.3390/molecules14031263)
- Zeng, H., & Combs, G. F. (2008). Selenium as an anticancer nutrient: Roles in cell proliferation and tumor cell invasion. *The Journal of Nutritional Biochemistry*, 19(1), 1–7. doi: [10.1016/j.jnutbio.2007.02.005](https://doi.org/10.1016/j.jnutbio.2007.02.005)
- Zeng, H., Uthus, E. O., & Combs, G. F., Jr. (2005). Mechanistic aspects of the interaction between selenium and arsenic. *Journal of Inorganic Biochemistry*, 99(6), 1269–1274. doi: [10.1016/j.jinorgbio.2005.03.006](https://doi.org/10.1016/j.jinorgbio.2005.03.006)
- Zhao, F. J., Ma, J. F., Meharg, A., & McGrath, S. (2009). Arsenic uptake and metabolism in plants. *New Phytologist*, 181(4), 777–794. doi: [10.1111/j.1469-8137.2008.02716.x](https://doi.org/10.1111/j.1469-8137.2008.02716.x)
- Zhong, C. X., & Mass, M. J. (2001). Both hypomethylation and hypermethylation of DNA associated with arsenite exposure in cultures of human cells identified by methylation-sensitive arbitrarily-primed PCR. *Toxicology Letters*, 122(3), 223–234. doi: [10.1016/S0378-4274\(01\)00365-4](https://doi.org/10.1016/S0378-4274(01)00365-4)
- Zhou, N., Xiao, H., Li, T.-K., Nur-E-Kamal, A., & Liu, L. F. (2003). DNA damage-mediated apoptosis induced by selenium compounds. *Journal of Biological Chemistry*, 278(32), 29532–29537. doi: [10.1074/jbc.M301877200](https://doi.org/10.1074/jbc.M301877200)
- Zhou, X., Sun, X., Cooper, K. L., Wang, F., Liu, K. J., & Hudson, L. G. (2011). Arsenite interacts selectively with zinc finger proteins containing C3H1 or C4 motifs. *Journal of Biological Chemistry*, 286(26), 22855–22863. doi: [10.1074/jbc.M111.232926](https://doi.org/10.1074/jbc.M111.232926)
- Zwolak, I. (2019). The role of selenium in arsenic and cadmium toxicity: An updated review of scientific literature. *Biological Trace Element Research*, (1), 20. doi: [10.1007/s12011-019-01691-w](https://doi.org/10.1007/s12011-019-01691-w)
- Zwolak, I. (2020). The role of selenium in arsenic and cadmium toxicity: An updated review of scientific literature. *Biological Trace Element Research*, 193(1), 44–63. doi: [10.1007/s12011-019-01691-w](https://doi.org/10.1007/s12011-019-01691-w)
- Zwolak, I., & Zaporowska, H. (2012). Selenium interactions and toxicity: A review. *Cell Biology and Toxicology*, 28(1), 31–46. doi: [10.1007/s10565-011-9203-9](https://doi.org/10.1007/s10565-011-9203-9)