Comparative Study of the Biochemical Response Behavior of Some Highly Toxic Minerals on Selenosis in Rats

LOAI ALJERF*, MIKE WILLIAMS2, ATEM BETHEL AJONG3, UKAOGO PRINCE ONYDINMA4, FAROUK DEHMCHI5, VIET TY PHAM6, SUHASINI BHATNAGAR7, NASSER BELBOUKHARI8

1Key Laboratory of Organic Industries, Department of Chemistry, Faculty of Sciences, Damascus University, Damascus, Syria
27101M, USEPA, William Jefferson Clinton Building North (WJC North) 1200 Pennsylvania Avenue N.W. Washington, DC 20004, USA
3Kekem District Hospital, Kekem, West Region, Cameroon; Department of Biochemistry, University of Dschang, Dschang, West Region, Cameroon
4Analytical/Environmental Unit, Department of Pure and Industrial Chemistry, Abia State University, Uturu, Nigeria
5Chemistry Department, Badji Mokhtar University, Annaba, Algeria
6Faculty of Chemistry, Hue University of Education, 34 Le Loi Str., Hue city, Vietnam
7Swaroop Enterprises and Biotech Pvt. Ltd., Noida UP, India
8Bioactive Molecules & Chiral Separation Laboratory, University of TM Bechar, Bechar 08000, Algeria

Abstract: Many researchers have studied the metabolism of toxics including selenium (Se) in biological medium in rats and defined some correlations between selenium and other minerals as arsenic (As), cadmium (Cd), mercury (Hg), and thallium (Tl). An investigation of the potential influences of As, Hg, Tl and Pb on Se metabolism, which can suggest new drugs to cope the poisonousness of Se. The current study also has looked into the potential use of As(III)/As(V) toxic in the treatment of essential mineral Se in the animals (as rats) based on sequestration of these toxic elements into biologically inert complexes, reflecting the enormous interest in this subject. The acute studies have been initially achieved by shaping the pulmonary and biliary excretions of the volatile Se in neonatal masculine Holtzman rats which were injected with selenite subcutaneously in the hind flank, then the volatile Se was trapped in 8N HNO3 and the radioselenate detected in a scintillation counter. The chronic cases were carried out with the nursing of rats with a purified diet of water-soluble vitamin mix, fat-soluble vitamin mix, saccharides, oil, and salts. One week after the basic diet, the rats taken Se have received diets containing 10 ppm of the element as sodium selenite (Na2SeO3) or selenate (Na2SeO4) added in the salts. The calorimeter was used to analyze Se in the frozen tissue specimens. As, Hg, and Tl were repressed the volatized Se excreted from the lungs. As has assisted the biliary excretion of Se and inhibited the chronic selenosis. Tl has increased the retention of Se in the liver and kidney, but, had no chronic effect on the amount of Se deposited in all the studied tissues. Similarly, Hg has increased the retention of Se but in the spleen and carcass of rats indicating to the high Se concentration in blood. Hg and Tl have inhibited the Se in urine. No effects of the doses rich in As, Hg, and Tl on the Se excretion in fecal. Even though, we suggest As as a possible medication to chronic selenosis.

Keywords: Biological medium, New drug, Poisonousness of Se, Biliary excretion, Tissue, Carcass, Cancer cell

1. Introduction

Recently, many countries have posed several legislations [1] and slated very specific strategies [2] in pharmaceutical industry that serve health challenge [3]. However, these created new modifying rules and regulations should control the added ingredients to the drugs including minerals and radioactive materials but in innocuous quantities [1,2]. These supplemented constituents to the pharmaceutical products should be analyzed in reliable analytical procedures [4] which must satisfy the international pharmacological standards [2]. But the problem is that these principles of the aforementioned

* email: loai789.aljerf@damascusuniversity.edu.sy
legislations are sometimes affected by the uncertainties of the toxicology of some metals and metalloids. For instance, a high concentration of organic arsenic (As) compounds is found in many kinds of seafood. These are nontoxic arsinebathine (finfish and shellfish) and potentially toxic arsenosugars (seaweed) and arsenolipid (fish oils) [5]. As a consequence, we believe that, the health risk posed by seafood-derived As still needs evaluation due to the lack of data on its toxicity and chronic exposure in humans and other mammals. Although, four organoaarsenic drugs, namely roxarsone, carbasone, arsanilic acid, and nitarsone, were used for many years as veterinary feed additives to prevent certain diseases in poultry, in 2014 and 2015, the U.S. Food and Drug Administration formally withdrew the approval for the use of these animal drug products.

What is more, As and selenium (Se) are unusual metalloids as they both induce and cure cancer. They both cause carcinogenesis, pathology, cytotoxicity, and genotoxicity in humans, with reactive oxygen species playing an important role [6]. The fulfillment of Se functions in animals mainly depends on the expression of selenoproteins. This small (25 selenoproteins in humans) but pivotal group of proteins includes among others glutathione peroxidases (GPxs) and thioredoxin reductase (TrxR) participating in redox state regulation and antioxidant defense, idothyronine deiodinases (DIOs) required for thyroid hormone synthesis and metabolism, GPx4 playing specific roles in spermatogenesis, and selenoprotein S involved in immune responses. While As induces adverse effects by decreasing DNA methylation and affecting protein 53 expression, Se induces adverse effects by modifying thioredoxin reductase [7]. They can react with glutathione and S-adenosylmethionine by forming an As–Se complex, which can be secreted extracellularly. Since then, Se deficiency has been linked directly or indirectly with a large variety of animal and human disorders. Dietary Se prevents liver necrosis in vitamin E-deficient. Nevertheless, there still exist contradictory reports as both synergistic and antagonistic toxicity between As and Se. Consequently, the relation between As and Se has attracted increasing attention.

Among such trials, Hamid et al. [8] has stimulated much research concerning the metabolism of toxic elements as selenium. This element is mostly existed in biological medium as selenite (SeO$_3$$^-$) and selenate (SeO$_4$$^{2-}$). Selenite is called as gypsum flower, desert rose, satin spar, and satin spar are four assortments of mineral crystals of gypsum. Those four kinds of gypsum can be assembled together and termed selenite [9]. The selenite anion is a Se oxoanion of a formula SeO$_3$$^2$$. A selenite is a compound of this ion. Under weak acidic conditions, hydrogen selenite ion, HSeO$_3$$^−$, is formed; however, in higher acid cases, selenous acid H$_2$SeO$_3$, occurs. It is more required in minute quantities for the proper growth, development, and physiology of an organism [10]. SeO$_3$$^{2-}$ exacerbates hepatic insulin resistance in mouse model of type II diabetes through oxidative stress-mediated JNK pathway [11]. In A549 cancer cells, the discerning increment of SOD1 content is accompanied with SeO$_3$$^{2-}$ generation of superoxide radical anions and this boosts apoptosis and Se-Cu linkage [10]. On the other hand, selenate is a sturdy dibasic acid with molecular formula (H$_2$SeO$_4$), so it is an acid form of inorganic salts of dihydrogen selenium tetraoxide. It is toxic by dust ingestion, inhalation or skin contact. Selenate is naturally occurring or synthetic substances that inhibit or retard oxidation reactions. They counteract the damaging effects of oxidation in animal tissues [9].

By hand, several metabolic interrelationships among minerals and Se are instituted [12,13]. As represses Se toxicity [14,15] and diminishes Se retention in mice’ livers [16]. This advantageous trait of As is owing to the augmented clearance of Se from liver into bile [17].

Cd inhibits Se detoxification and forms volatile methylated Se compounds, so results in increasing Se retained in liver [18-20]. Nonetheless, Cd in rats which causes testis injury can be protected by Se [20-22].

Endemic human selenosis was described very thoroughly by studies of Se-excessive regions of China located in Western Hubei Province and Southern Shaaixi Province, where high Se content in soils, water, and corn was identified [23]. The dietary intake of Se in the regions affected by selenosis estimated in the 1970s was 3.2–6.8 mg/day [23]. Due to the lower dependence on locally grown food, no human cases of selenosis have been reported in those areas since 1987 [23]. During the last years, cases of selenosis in humans induced by environmental exposure to Se were reported in the state of
Punjab, India, where the disease was caused by excessive Se content in locally grown grains [24]. Acute Se poisoning resulting in a massive alopecia was also described in a 55-year-old woman who ingested paradise nuts (Lecythis ollaria) [25]. Moreover, as reported by some epidemiologic studies, even low-level but chronic overexposure to Se, for example from drinking water, may be associated with adverse health effects in humans such as an increased risk of amyotrophic lateral sclerosis and cancer [26].

Novel studies show that Se can protect against Hg and Tl toxification [27-30]. The aim of the current study was to compare the influences of As, Hg, Tl, and Pb on Se metabolism. It was concluded that As, Hg, and Tl all repressed the pulmonary excreted amount of Se volatilized compounds, but that As alone was capable to improve the excretion of Se in bile. As was also the only cooperating tested element that reduced the chronic Se poisoning effects.

2. Materials and methods

Acute studies. Nursling male of Holtzman rats (in small bowels, one contained significantly lower concentrations of adenosine-3′,5′-cyclic monophosphate than all the others) (Photo 1) was nourished a stock diet [30] for 2-3 weeks and their pulmonary excretions of exhausted Se compounds were assessed. The animals were shot subcutaneously in one hind flank with the appropriate test element in physiological saline and then 10 min later in the opposite hind flank with 2mg Se per kg as sodium selenite (Na2SeO3) containing approximately 1 microcurie (µCi) of H275SeO3 (Preliminary observation: a formation of dimethylselenide (CH3)2Se and dimethyldiselenide (CH3)2Se2 in the breath of the rats). For capturing the exhausted Se, the animals were left 12 h in all-glass metabolism cages furnished with sintered-glass scrubbers containing 8N HNO3. The rats were sacrificed, and the tissues were isolated for direct measurement of radioactivity in a well-type scintillation counter (Perkin Elmer Tri-Carb). Data are expressed as percentage of the dose of labeled selenium injected.

![Photo 1. Newborn Holtzman rat males](image)

In newborn Holtzman male rats nursed a routine diet, Se excretion from the bile has been investigated. The bile ducts have been cannulated as described in many works [31-33]. In one flank, about 0.5 µCi of radioactive Se in physiological saline was subcutaneously injected, and the participating element was given in the opposite flank. Dose and timing schedules are registered in Tables 1-3. Where required, radioselenate was made by a repetitive digestion of radioselenite with conc. HNO3 [34,35]. Bile was collected for 1 h and the radioactivity was detected in a well-type scintillation counter. Data are expressed as percentage of the dose of labeled selenium injected.

Chronic studies

Neonatal masculine Holtzman rats were nourished a purified diet which included the following components in g/kg: sucrose (C12H22O11), 710; casein (C38H57N9O9), 200; corn oil (calories and total fat were 122 and 21%, respectively) 50; salts [36], 35; water-soluble vitamin mix, 2; fat-soluble vitamin mix, 2; and choline chloride (CH3)3NCH2CH2OH]Cl, 1. The water-soluble vitamin mix contained, in mg/g: myo-inositol (C6H12O6), 100; nicotinic acid (vitamin B3 (VB3), C6H5NO2), 11; calcium pantothenate (Ca salt of water-soluble VB5, C18H22CaN2O10), 6; riboflavin (VB2, C17H20N2O6), 2;
properties of Tl and Hg on Se in urine were recorded. Similar to the Experiment A conditions, trials of using Hg, Tl, or Pb were failed to initiate Se excretion from the bile. Similar selenium excreted over 20% of the dose of selenium in the same time interval. Under similar tentative conditions, trials of using Hg, Tl, or Pb were failed to initiate Se excretion from the bile.

The rats fed selenium received diets containing 10 ppm of the element as Na₂SeO₃ or Na₂SeO₄ added in the salts. So that, the tested elements were participated by means of their soluble salts at a level of 10 ppm in the potable water to examine their impacts on Se metabolism and toxification. The weights were logged twice each 7 days. The living rats were sacrificed and checked for gross pathological lesions.

3. Results and discussions

3.1. Acute studies

30% of the dosage was exhaled as Se volatilized shape in 12 h of injecting the control animals with 2 mg Se/kg as SeO₃²⁻ and saline (Table 1). The quantity of the volatilized Se was diminished to 5.4% of dosage when the rats were administered 4 mg As/kg as arsenite (AsO₃³⁻). Even the animals needed higher dosages, but we registered a pulmonary Se excretion inhibition when Hg or Tl was administered. High dosages of Pb (48 mg/kg) did not show any effect on the Se circulation or volatilization. However, the noticeable reduction of the Se volatilized shape during As and Hg treatment was followed with high levels of Se in the kidney and carcass. Treatment with Tl had retained higher amounts of Se in the kidney and liver. Possibly due to the Se increasing concentrations in the gastrointestinal innards, high quantities of Se in the carcass were enrolled when As has been taken [41]. In addition, probably due to the extremely high concentration of Se in blood, the retention of this element in carcass has been noticed during Hg intake. This is not just the interesting notice with Hg administration in rats, nevertheless, we also observed a large amount of Se retained in spleen.

Table 1. Effect of AsO₃³⁻ and the collaborated chemical elements on SeO₃⁻² metabolism by rats

| Chemical form and dosage of test elements⁵ (mg/kg) | Proportion of the dose of selenium (%)³ |   |   |   |   |   |   |
|-----------------------------------------------|----------------------------------------|---|---|---|---|---|---|
|                                               | Volatile compounds                     | Liver | Kidney | Carcass⁵ | Spleen | Blood, mL | Feces | Urine |
| None                                          | 30.6±3.72                             | 11.3±0.02 | 1.90±0.11 | 20.2±1.07 | 0.20±0.05 | 0.80±0.16 | 1.10±0.54 | 14.7±2.38 |
| NaAsCl₂-4                                    | 5.40±0.74                             | 8.65±0.01 | 5.02±0.29 | 42.8±1.70 | 0.10±0.05 | 0.40±0.02 | 0.40±0.32 | 16.0±0.97 |
| HgCl₂-12                                     | 8.70±2.11                             | 15.8±0.84 | 4.23±0.27 | 37.4±0.60 | 1.80±0.11 | 1.70±0.20 | 0.50±0.20 | 7.80±1.60 |
| TlAc-12                                      | 5.90±1.27                             | 37.5±6.20 | 9.83±0.52 | 17.9±1.20 | 0.30±0.00 | 0.42±0.00 | 0.90±0.21 | 6.33±0.50 |
| Pb(AsO₃)⁻·48                                 | 32.6±2.40                             | 13.7±2.65 | 2.17±0.36 | 21.3±1.40 | 0.34±0.10 | 1.15±0.40 | 0.92±0.50 | 13.9±0.60 |

³ Distribution of radioactivity 12 hours after subcutaneous injection of 2 mg of Se per kilogram body weight containing approximately 1 µCi ³²Se as H₂³²SeO₄; mean of four animals ± standard error; weight range of animals 119-189 g.
⁴ Before injecting with Se by 10 min., the rat has been injected with saline solution or the test element subcutaneously.
⁵ Includes gastrointestinal contents.

No treatment of the groups in any of these short-interim testing was affected Se fecal excretion, but the depressing properties of Tl and Hg on Se in urine were recorded. Similar to the Experiment A presented in Table 2, in another study [31], As has promoted Se bile excretion. Animals receiving only selenium excreted about 1 % of the dose in the bile in 1 h whereas animals receiving both arsenic and selenium excreted over 20% of the dose of selenium in the same time interval. Under similar tentative conditions, trials of using Hg, Tl, or Pb were failed to initiate Se excretion from the bile.
Yet, As may possess diverse impacts on Se metabolism depending on the time interval between injections, valance state, and dose of the elements [42,43]. Similar reports to the current experiments had demonstrated an antagonism effect of Se against Tl and Hg [42-45]. Even though, according to the Experiments B & C in Table 2 and under the prespecified conditions, Tl and Hg have not exhibited any effect on Se excretion from the bile. Likewise, that was also right once Tl was experienced along with Se introduction as selenate (SeO$_4^{2-}$) in lieu of SeO$_3^{2-}$.

### 3.2. Chronic studies

Conferring to Experiment A in Table 3, As was the one tested element that shielded rats against chronic selenosis [46] as ruled by 3-unlike measures: reduced liver damage, reduced Se retention in diverse tissues, and high mass gains. Under parallel conditions, compared to the rats which did not fed Se, these animals that received Se + As have exercised no substantial growth-promoting effect even they showed growing mass gain (the mass gain of control and As treated animals was 235±9.80 and 249±15.5 g, respectively, P > 0.3). This cluster of rats which supplemented Se + As exhibited quite pretty normal distribution of radioactivity 1 hour after subcutaneous injection of stated dose of selenium containing approximately 0.5 µCi $^{75}$Se as H$_2$SeO$_4$ or H$_2$SeO$_3$; weight range of animals 344-403 g; mean of three or four animals ± standard error.

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### Table 2. Effect of AsO$_2^-$ and heavy metals (i.e. Hg, Tl, Pb) on Se excretion in bile

| Selenium form and dosage (mg element/kg) | Test element | Proportion of the dose of selenium (%)$^d$ | Bile | Liver |
|----------------------------------------|--------------|------------------------------------------|------|-------|
| NaSeO$_3$-0.5                          | None         | 1.18±0.20                                | 28.6±1.01 |
| NaSeO$_3$-0.5                          | NaAsO$_2$-1  | 21.2±4.47                                | 10.6±1.73 |
| NaSeO$_3$-0.5                          | HgCl$_2$-1   | 1.50±0.32                                | 28.8±1.51 |
| NaSeO$_3$-0.5                          | TlAc-1       | 0.90±0.25                                | 29.3±2.96 |
| NaSeO$_3$-0.5                          | Pb(Ac)$_2$-1 | 1.08±0.11                                | 28.9±0.74 |
| NaSeO$_3$-0.5                          | None         | 0.90±0.13                                | 22.0±2.57 |
| NaSeO$_3$-0.5                          | NaAsO$_2$-1  | 3.90±3.69                                | 8.10±1.32 |
| NaSeO$_3$-0.5                          | TlAc-1       | 0.90±0.21                                | 19.7±2.08 |

$^d$ Distribution of radioactivity 1 hour after subcutaneous injection of stated dose of selenium containing approximately 0.5 µCl $^{75}$Se as H$_2$SeO$_4$ or H$_2$SeO$_3$; weight range of animals 344-403 g; mean of three or four animals ± standard error.

$^e$ Se injection followed by 10 min. the saline or the specified test element injection subcutaneously.

$^f$ Se injection after 1 hour of injection subcutaneously with the saline or the specified dose of Hg.

$^g$ Se injection after 2 hrs. of injection subcutaneously with the saline or the specified dose of Tl.
compounds retained in livers of SeO$_4^{2-}$-fed rats. However, more notably, Tl resulted an increase in the content of Se observed in kidney.

### Table 3. Effect of AsO$_2^-$ and heavy metals in chronic selenosis

| Salt in drinking water | Weight gain (g) | Survival | Gross liver damage | Se content (µg/g wet weight) |
|------------------------|-----------------|----------|--------------------|-----------------------------|
|                        |                 |          |                    | Liver | Kidney                  |
| None                   | 68.9±8.91       | 9/10     | Severe             | 7.64±2.10 | 36.8±2.76 |
| NaAsO$_2$              | 116±16.3        | 8/10     | Mild               | 2.72±0.20 | 11.5±2.30 |
| HgCl$_2$               | 105±34.3        | 4/7      | Severe             | 6.60±0.90 | 24.3±4.82 |
| TlAc                   | 70.0±8.25       | 6/7      | Moderately severe  | 7.48±0.60 | 33.3±6.30 |

Experiment A

| Salt in drinking water | Weight gain (g) | Survival | Gross liver damage | Se content (µg/g wet weight) |
|------------------------|-----------------|----------|--------------------|-----------------------------|
|                        |                 |          |                    | Liver | Kidney                  |
| None                   | 75.0±8.50       | 6/7      | Severe             | 22.1±5.80 | 42.5±6.61 |
| TlAc                   | 72.0±11.9       | 6/7      | Moderately severe  | 14.3±1.70 | 104.4±5.30 |

Experiment B

h Add at level of 10 ppm of the test element.

i After 7 weeks on a diet containing 10 ppm Se as SeO$_3^{-2}$; mean±standard error.

j After 7 weeks on a diet containing 10 ppm Se as SeO$_4^{-2}$.

### 3.3. Metabolic detoxification activity

The studied metals as Arsenic are taken up by plants as they grow - this means they make their way into our food, even that it does not build up in the body [6]. Both inorganic and organic forms of Arsenic leave human body in urine. Most of the inorganic arsenic will be gone within several days, although some will remain in body for several months or even longer. If exposed to organic arsenic, most of it will leave the body within several days. Methyl groups bind to arsenic and help remove it from the body. Arsenic appears to have toxic effects on neurotransmitters involved in cell-to-cell signaling within the brain. We expect from our experience, that in humans, arsenic-induced regional increases in levels of dopamine, serotonin, and their metabolites and also induced a decrease in norepinephrine levels in discrete brain regions, the event which needs more investigations by next researchers.

Due to the complexity of human internal environment, the process of how As interferes with Se metabolism is susceptible to multi-factors (nutritional status, health status and dietary habits), which may result in different effect [6]. This makes the synergistic effects between As and Se toxicity in humans under question. We hypothesize that there are two types of interactions between As and Se. At low concentration, Se can decrease As toxicity via excretion of As–Se compound [(GS3)$_2$AsSe$^{-}$], but at high concentration, excessive Se can enhance As toxicity by reacting with S–adenosylmethionine and glutathione, and modifying the structure and activity of arsenite methyltransferase.

The current findings establish an exceptional aptitude of As to develop the excretion of Se bile and lessen Se toxification. The chronically selenized animals taken As showed a reduction in the Se retained in livers, makes it look as if appear that the valuable factor of As in chronic selenium poisoning is probably related to the increased Se excretion into the bile of As-handled rats. The later action of As performance on biliary Se is left over for further deep investigations to explain this important mechanism.

Ostensibly, Se pulmonary excretive reduction per se did not entail adequate conditions for enhancing Se excretion in bile, probably for a reason that As, Tl, and Hg can impede the biosynthesis of Se volatile compounds. However, As is the sole among the other tested elements that has enthused the excretion of Se in bile. Likewise, the augmented quantity of Se in the bile of As-handled animals has not seemed to be associated to a wide-ranging infiltration of As on the active thiol functional groups of structural
proteins or enzymes [47-50] attributing to the only fact that Pb, Tl, and Hg all attack and strongly react with thiol groups (sulphydryl, –SH) as well [51] and might be expected to mimic the effect of arsenic where this the lone factor involved.

The probability of constructing specific selenoarsenic conjugates as purifying agents excreted into the bile is being deliberated beforehand [14]. Nevertheless, the present biochemical fractionation investigations that propose an incidence of numerous diverse forms of biliary Se, lean towards rejecting this supposition.

Here, we think, the arsenic activity have interfered in the adjustment of the expression of oxidative stress-related genes, which controlled the extent of Se that improved the activities of antioxidant enzymes, and in turn protected liver cells from As-induced oxidative damage. Besides, the balance between As and Se concentrations have maintained the body’s capability of As methylation which involves the reductive thioredoxin (Trx) system. In fact, the As–Se conjugate, namely a seleno-bis(S-glutathionyl) arsinium ion [(GS)₂AsSe]⁻ is nontoxic which has been identified in the bile of experimental rabbits and rats [52,53] and the precise mechanism of [(GS)₂AsSe]⁻ generation has been thoroughly described in review articles by Gailer [54] and Sun et al. [55]. Accordingly, hydrogen selenide (HSe⁻ produced from selenite in the presence of GSH) reacts inside erythrocytes and probably hepatocytes with (GS)₂As-OH (produced in the reaction of arsenite and GSH), forming a nontoxic complex selenobis(S-glutathionyl) arsinium ion [(GS)₂AsSe]⁻. Once formed, the [(GS)₂AsSe]⁻ species are removed out of the cells followed by rapid excretion via the liver and bile into the intestinal tract [56]. The complex [(GS)₂AsSe]⁻ is proposed to play a role of a detoxification product which protects the mammalian organism from arsenic toxicity.

4. Conclusions

The metabolism of Se is reliant on the valency state and the dose amount of the elements, in addition to the interval period among shoots. From the results of this research, we refer clearly to the antagonism property including biliary excretion of Se against Hg and Tl. As compounds have successfully proved themselves as a medication of liver damage, which can be suggested as supplemented ingredients in releasing Se from various tissues. Not even that, Se, regardless of its form (as selenite, selenomethionine, nanoSe, or Se from lentils), can reduce As toxicity in the liver, kidney, spleen, brain, or heart in animal models. Se antagonizes the toxicity of As mainly through sequestration of this element into biologically inert complexes and/or through the action of Se-dependent antioxidant enzymes. An increase in the As methylation efficiency is proposed as a possible mechanism by which Se can reduce As toxicity. It is expected that Se may diminish As toxicity by activation of the nuclear factor erythroid 2-related factor (Nrf2) pathway. The well-known antioxidant selenoenzymes such as GPx and TrxR also mediate Se-dependent detoxification of As and Cd, but they probably play a secondary role. Therefore, the interactive benefits of taking arsenic in selenosis are more profitable than its endemic risks.

More studies are needed to investigate the mechanism of the valuable arsenic performance in treating biliary selenium. Further, this paper suggests studying possible signs of As toxic effects, which may be a challenge for its future use in the therapy of Se poisoning in humans and provide future directions to address this issue.

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