Review

Arsenic: A Review on a Great Health Issue Worldwide

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Abstract: Arsenic intoxication represents a worldwide health problem and occurs mainly through drinking water. Arsenic, a metalloid and naturally occurring element, is one of the most abundant elements in the earth's crust, whose toxicity depends on the reduction state. The trivalent arsenicals are more toxic than the pentavalent arsenicals. In the trivalent state, inorganic and organic arsenic may react with thiol groups in proteins inhibiting their activity, whereas inorganic arsenic in the pentavalent state may replace phosphate ions in several reactions. Arsenic induces various epigenetic changes in mammalian cells, both in vivo and in vitro, often leading to the development of various types of cancers, including skin, lung, liver, urinary tract, prostate, and hematopoietic cancers. Potential mechanisms of arsenic toxicity in cancer include genotoxicity, altered DNA methylation and cell proliferation, co-carcinogenesis, tumor promotion, and oxidative stress. On the other hand, the FDA-certified drug arsenic trioxide provides solutions for various diseases, including several types of cancers. Detoxification from arsenic includes chelation therapy. Recently, investigations of the capability of some plants, such as *Eucalyptus camadulensis* L., *Terminalia arjuna* L. and *Salix tetrasperma* L., to remove arsenic from polluted soil and water have been studied. Moreover, nanophytoremediation is a green technology including the nanoscale materials used for absorption and degradation of organic and inorganic pollutants, such as arsenic compounds. This brief review represents an overview of arsenic uses, toxicity, epigenetics, and detoxification therapies.

Keywords: cancer; chelating agents; mitochondrial dysfunction; toxic element; epigenetic modifications; phytoremediation

1. Introduction

Arsenic is a ubiquitous element in nature and ranks twentieth among the elements in abundance in the earth's crust, fourteenth in seawater, and twelfth in the human body [1]. Arsenic is a metalloid and exists in various allotropic forms such as elemental, sulfide, and carbonate forms. Its common valence states are −3, 0, +3, and +5. Arsenic is mobilized through a combination of natural processes, including weathering reactions, biological processes, volcanic emissions, and anthropogenic activities. Most problems related to arsenic are the result of its mobilization under natural conditions. However, an important additional impact was due to anthropogenic sources, such as mining activity, combustion of fossil fuels, use of arsenical pesticides, herbicides and crop desiccants, and the use of arsenic as an additive to livestock feed, specifically for poultry [2,3]. Although the use of arsenical pesticides and herbicides has decreased significantly in the past decades, its use as wood preservative is still common. Heat treatments of chromate copper arsenate (CCA)-treated wood may still cause release behavior of arsenic [4]. Ingestion, inhalation, and skin absorption are some of the critical routes for arsenic entering human body. Both pentavalent and trivalent arsenic compounds are extensively and rapidly absorbed from the gastrointestinal tract. Several health problems are related to arsenic exposure, ranging

from the development of cancer, inducing epigenetic changes, to skin diseases [5]. Since it is not a mutagen, the mechanism by which it causes changes in gene expression and disease pathogenesis has not been clearly defined [6]; however, its anti-cancer activities against various human neoplastic diseases have been extensively studied. On the other hand, arsenic trioxide is one of the first-line chemotherapeutic drugs for acute promyelocytic leukemia [7]. Natural sources of human exposure to arsenic are represented by volcanic ash, weathering of minerals and ores. Arsenic is present in the smelter dust from copper, gold, and lead smelters, and is recovered principally from copper refinement dust, and mineralized groundwater. Inhalation of atmospheric gases and dusts represents an additional way of exposure. Arsenic trioxide is used in the industries of pesticides, treated wood products, herbicides, and insecticides. It may be also found in food, water, soil, and air. Arsenic is generally absorbed by all plants, and is concentrated especially in leafy vegetables, rice, apple and grape juice, and seafood. The United States Environmental Protection Agency states that all forms of arsenic are a serious risk to human health. Arsenic has been classified as a Group-A carcinogen. Several studies documented the tissue-specific accumulation of arsenic in the hepatopancreas, cephalothorax, viscera, inhalant and exhalant siphon, digestive glands and mantle in shellfish, mollusks, and crustaceans [8–11]. Anthropogenic and submarine volcanic activities (IARC, International Agency for Research on Cancer 2012) increase the risk by shellfish ingestion of inorganic forms of arsenic (As^{3+} and As^{5+}) and organic form of arsenic (methylarsonic and dimethylarsonic acids, and arsenobetaine) [12]. Seafood often contains high concentrations of arsenic (approximately 10–100 mg/kg dry weight). In seaweeds, arsenic occurs predominantly as ribose derivatives known as arsenosugars. Although it is clear that arsenosugars are not acutely toxic, there is a chance of arsenosugars to show slight chronic toxicity [13]. Fish and shellfish contain higher arsenic concentrations than other food [11] and terrestrial animals in the form of arsenobetaine [14]. Arsenobetaine is neither metabolized nor accumulated in human beings; thus, it may be considered non-toxic [15,16]. Although arsenobetaine is the prevalent arsenic compound present in shellfish, many researchers presented risk results to human health with the shellfish consumption [17–19]. Several removal technologies have been used for removing arsenic [20]. Several technologies have been used for removing arsenic from the water and environment using, including adsorption technique [21], porous ceramic (Fe/TiPC) beads with photocatalytic performances [22], nanofiltration membranes [23], coagulation with ferric chloride and chitosan [24], and new materials such as graphite oxides and carbon nanotubes [20]. Trivalent arsenic is more difficult to remove than pentavalent arsenic. Therefore, the former has to be oxidized prior to its removal [25]. Phytoremediation, a technique that makes use of plants to remove pollutants from the environment, has been widely used for the removal of arsenic [26]. Appropriate plants such as *Brassica juncea*, *Hydrilla verticilata*, *Pteris vittata* L., *Vallisneria natans*, can be used for phytoremediation [27,28]. Furthermore, the use of nanotechnologies with bioremediation has created new perspectives in the renewal of remediation methods [29]. In this review we highlight the most interesting topics related to toxicity of arsenic and its uses, along with epigenetics and the most used detoxification methods.

2. Chemical Forms and Properties of Arsenic

Arsenic (As, atomic number 33) is a metalloid found either in many minerals in combination with sulfur and other metals, or as a pure element [30]. Arsenic exists in three allotropes: gray, yellow, and black arsenic; the gray form is the most common and important to industry. Gray arsenic is brittle and has a relatively low Mohs hardness of 3.5; its density is 5.73 g/cm^3 (Table 1). The most volatile, least dense, and the most toxic form is represented by yellow arsenic, which is soft and waxy, with a density of 1.97 g/cm^3; it is rapidly transformed into gray arsenic by light. Black arsenic, glassy and brittle, can be formed by cooling vapor at about 150–220 °C and by crystallizing arsenic in the presence of mercury vapors. The most common oxidation numbers of As are −3, +3, and +5, in which the element is able to form inorganic and organic compounds, both in the environment and

within the human body. Arsenic does not melt at atmospheric pressure, but sublimes from solid to vapor at 615 °C.

Table 1. Physicochemical properties of arsenic.

Atomic number	33
Atomic weight	74.92 u
Electronic configuration	[Ar] $3d^{10}4s^24p^3$
Melting point	817 °C
Boiling point (sublimation) *	615 °C
Density at 20 °C	5.73 g/cm^3
Covalent radius	119 ± 4 pm
Van der Waals radius	185 pm
Heat of fusion (grey)	24.44 KJ/mol
Heat of vaporization	34.76 KJ/mol
Pauling electronegativity number	2.18
First ionization energy	947.0 KJ/mol
Second ionization energy	1798.0 KJ/mol
Third ionization energy	2735.0 KJ/mol
Standard potential	-0.3 V (As^{3+}/As)
Allotropes	Grey, Yellow, Black

* At normal pressure, arsenic has no melting point; arsenic sublimes into a gas. This table is an elaboration based on data retrieved from ref. [31].

Arsenic is stable in dry air but forms a golden-bronze tarnish when exposed to humidity, which turns to a black surface layer black upon prolonged exposure. After heating in air, arsenic oxidizes to arsenic trioxide (As_2O_3), producing fumes with odor resembling garlic, and arsenic pentoxide (As_2O_5). It is possible to prepare arsenic acid (H_3AsO_4) with concentrated nitric acid, arsenous acid (H_3AsO_3) with dilute nitric acid, and arsenic trioxide with concentrated sulfuric acid; however, arsenic does not react with water, alkalis, or non-oxidizing acids. Arsenic easily forms covalent molecules with several nonmetals and may react with metals to form arsenides. Arsenic comprises about 1.5 ppm (0.00015%) of the earth's crust and is the 53rd most abundant element. Typical background concentrations of arsenic do not exceed 100 mg/kg in soil [32], and 10 μg/L in freshwater [33,34]. The maximum tolerance limit for arsenic in drinking and public water is 10 μg/L [35]. Concerning soils, the maximum acceptable limit for agricultural soil is 20.0 mg/kg recommended by the European Union [36]. In the crust, arsenic exists together with copper (domeykite Cu_3As; enargite Cu_3AsS_4), iron (arsenopyrite AsFeS), cobalt (cobaltite CoAsS), nickel (nickeline NiS), and silver (proustite Ag_3AsS_3). In soil and water, in the presence of oxygen, As^{5+} is oxidized to As^{5+}, while in low oxygen environment in deep well water and deep sea and ocean it is present as reduced As^{3+} [37].

3. Uses of Arsenic

Since ancient time, arsenic was used in different and multiple applications until it was banned by the governments of Western States for the danger to which humans, animals and environment are subjected. Arsenic is used in medicine, militarily, in alloys, and in preservation of wood. During the Bronze Age, bronze was often produced with small addition of arsenic, which makes the alloy harder [38]. Two arsenic pigments were used since their discovery: Paris green (copper acetate triarsenite) and Scheele green (copper arsenite) (Table 2). These chemicals were first used as pigments and then as insecticides. In 1945, Paris green was sprayed by airplane in Italy to control malaria. Despite of its high toxicity, Scheele green was also used as a food dye for sweets such as blancmange. Other two arsenic compounds were used starting in the 1890 [39]. Calcium arsenate and lead arsenate were used as herbicides, pesticides, and germicides until the use of DDT (para-dichlorodiphenyltrichloroetane) in 1942. In the past centuries, many arsenic compounds were used as medicines, such as arsphenamine (also known as Salvarsan) and Neosalvarsan, indicated for syphilis, but both of them have been now superseded by antibiotics like penicillin. Human trypanosomiasis, also known as sleeping sickness, is

induced by microscopic protozoal parasites of the species *Trypanosoma brucei* transmitted by infected tsetse flies and endemic in sub-Saharan African. Without treatment with arsenicals such as melarsoprol, the disease is considered fatal even if this drug is very toxic [40]. In 2008, [74]As (a positron emitter) was also used with success to locating tumors. This isotope produces clearer PET (positron emission tomography) scan images than [124]I. The iodine accumulates into thyroid gland producing signal noise [41]. An additional use of arsenic is in alloys of lead in car batteries and in ammunitions. It also represents a common n-type dopant in semiconductor devices, and is a component of III-V semiconductors gallium arsenide, indium arsenide, and aluminum arsenide [42]. Several organoarsenic compounds were developed as chemical warfare agents during World War I, such as vesicants including lewisite (2-chlorovinyldichloroarsine) and vomiting agents such as adamsite (diphenylaminechlorarsine). During the Vietnam War, the United States used a mixture of cacodylic acid (dimethylarsenic acid, DMA) and sodium cacodylate as one of the six Rainbow herbicides (specifically, Agent Blue, along with the other five: Agent Orange, Agent Green, Agent Pink, Agent Purple and Agent White) and defoliants to deprive North Vietnamese soldiers of a food source, such as crops and upland rice [43]. Arsenic was employed for treatment of wood as chromate copper arsenate (CCA) until 2003. It is utilized to impregnate timbers for outdoor use to protect them from attack by termites, fungi, and microbes. CCA lumber is still utilized in several countries as a structural and outdoor building material. Despite the ban of the use of these treated lumbers in many countries, arsenic can leach out of the wood into the soil. Moreover, burning CCA timber and wood ash could cause serious poisoning in humans (lethal dose 20 g of ash). In 2018, Subastri and collaborators (2018) [44] synthesized arsenic nanoparticles starting from arsenic trioxide to study the mechanism of interaction with DNA and the effect of cytotoxicity on breast cancer cell lines (MDA-MB-231 and MCF-7). The bond to nanoparticles did not act on the structural integrity of the DNA while the cytotoxicity was confirmed. The authors can confirm that their nanoparticles might be successfully utilized against breast cancer and other types of solid tumors.
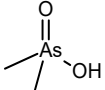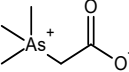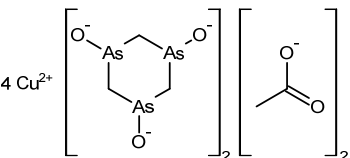
Table 2. Arsenic-containing compounds.
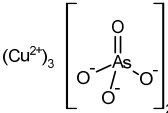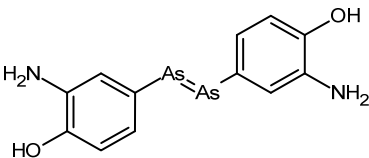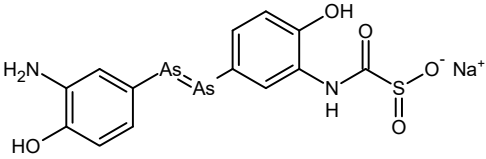
Structure	Compound
	Methylarsonic acid (MMA)
	Cacodylic acid or DMA (dimethyl arsinic acid)
	Arsenobetaine (trimethyl arseniumyl acetate)
	Paris green (copper acetate triarsenite)
	Scheele green (copper arsenite)

Table 2. *Cont.*

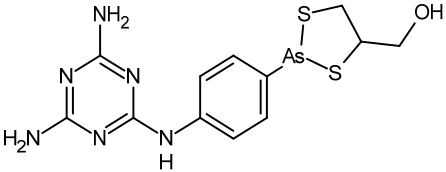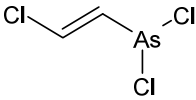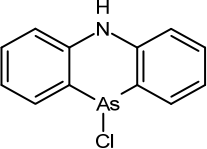| Structure	Compound
	Arsphenamine (also known as Salvarsan)
	Neosalvarsan
	Melarsoprol
	Lewisite (2-chloro vinyl dichloro arsine)
	Adamsite (diphenylaminechlorarsine).

4. Arsenic Sources and Exposure

Arsenic is a natural element found in freshwater and foods; it is also found in ocean, lakes, rivers, soil, and air. In humans, the main sources of arsenic exposure can be divided in natural and anthropogenic sources. The most important contribution of arsenic in nature is attributed to geological formation, including the deposition of this element in sedimentary rocks, volcanic rocks and soil in the form of sulfide in over 200 mineral species containing a mixture of many different metals. Arsenic levels in the crust fluctuate between 1.5 and 5 mg/kg [45]. Other significant sources of inorganic arsenic are geothermal activity and geothermal water, coal and volcanic activity. In addition to volcanic activity, leaching of arsenic from soil to groundwater through natural erosion releases this metal into the air, water, and soil [46]. Arsenic contamination in groundwater has been found in about 100 countries (including China, USA and India) with more than 200 million people worldwide due to anthropogenic activities through mining and petroleum extraction. Burning of petroleum and As-rich coal, use of pesticides, herbicides, insecticides containing arsenic, phosphate fertilizers contaminated with arsenic, act as major anthropogenic sources of arsenic. Human activities may trigger and contribute to the arsenic contamination such as the use of arsenic-contaminated irrigation water for agriculture, mining and smelting activities, fossil fuel combustion, and wood preservatives [47]. Some of the major sources of arsenic exposure in humans are represented by drinking water, arsenic-contaminated foods and agricultural products (rice, wheat, potato, and vegetables) [48,49].

5. Metabolic Pathways and Toxicity of Arsenic

In living organisms, arsenic is present in both inorganic and organic form and in trivalent and pentavalent oxidation states. The inorganic As (III; arsenite) is more toxic than As (V; arsenate) and inorganic arsenicals are more toxic than organic arsenicals. Arsenous

acid enters the cells of kidney, testis, and liver through aquaglyceroporins and glucose transporters (GLUT1, GLUT4), while arsenic acid crosses the cellular membranes via phosphate transporters, given the extreme similarity between arsenate (AsO_4^{3-}) and phosphate (PO_4^{3-}) anions. Inorganic arsenic metabolites are exported through the multidrug resistance proteins (MRP1, MRP2, or MRP4). The metabolic pathway of arsenic is depicted in Figure 1. Inorganic arsenic (V, in the form of arsenic acid) is reduced to arsenic (III, in the form of arsenous acid) in the presence of the enzyme arsenate reductase mediated by glutathione. Furthermore, the enzyme arsenic methyltransferase, in the presence of S-adenosyl methionine (SAM) as methyl-donor, allows oxidative methylation reaction of the arsenous acid (As III) to form monomethylarsenic acid (MMA-V) and dimethylarsenic acid (DMA-V) through the reduction of pentavalent arsenic acids to trivalent arsenic acids, ultimately producing dimethylarsenuos acid (DMA-III) [50]. Inorganic and organic arsenic compounds are bound tightly to thiol groups (-SH) and vicinal dithiols, as for example the dihydrolipoic acid. As (III) reacts with the sulfhydryl groups of enzymes and proteins. The affinity between As (III) and sulfhydryl groups is responsible for its accumulation in keratin rich-tissue such as skin, hair, and nails [51]. Furthermore, organic arsenic compounds also show high affinity to selenol groups (-SeH) present in thioredoxin reductase and glutathione peroxidase enzymes. Inorganic arsenic and its metabolites are eliminated through the urine and feces; however, high quantities of these compounds are accumulated in different tissues, such as lung, heart, and brain. Arsenic metabolites easily cross the blood–brain barrier accumulating in different regions of the brain, such as the striatum, hypothalamus, and hippocampus [52]. Arsenosugars and arsenobetaine, present in algae and seafood, are excreted in urine. Arsenic level in urine is an excellent marker of arsenic intoxication and has been used to identify the exposure in the population living close arsenic sources [53].
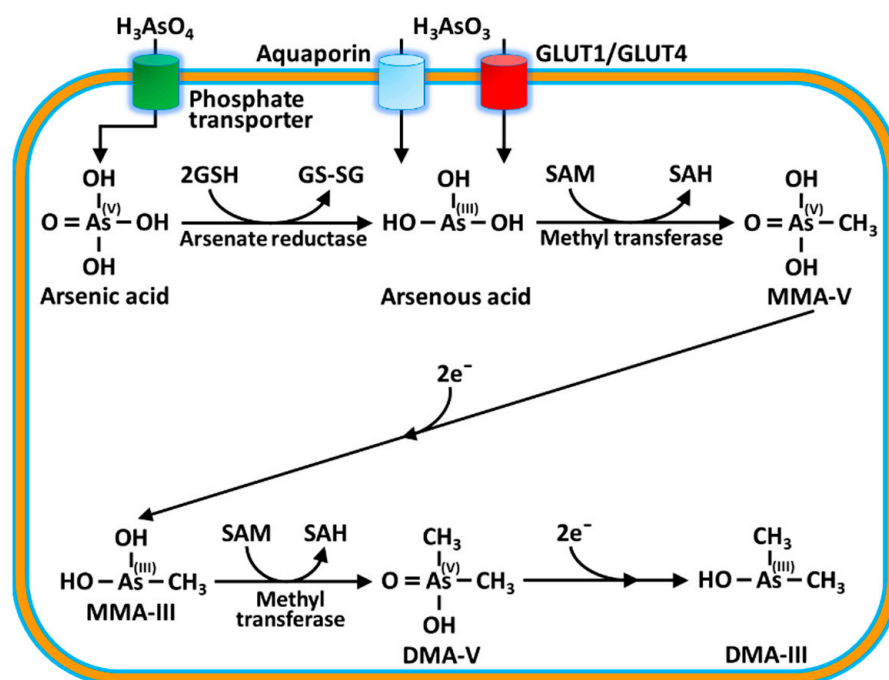
Figure 1. Metabolic pathways of arsenic. As (V) is reduced to As (III) by GSH (as electron donor) in the presence of arsenate reductase; As(III) undergoes sequential methylation with SAM (methyl donor) in the presence of methyl transferase and reduction with GSH to generate MMA(V), MMA(III), DMA(V) and DMA(III). GSH: reduced glutathione; GS-SG: oxidized glutathione; SAM: S-adenosyl methionine; SAH: S-adenosyl homocysteine; MMA(V): monomethyl arsenic acid; MMA(III): mono methyl arsenous acid; DMA(V): dimethyl arsenic acid; DMA(III): dimethyl arsenous acid). This figure is an elaboration based on information retrieved from ref. [54,55].

The main and most abundant urinary metabolite found in human urine is DMA-V (60–80%). Tseng and coauthors (2005) [56] demonstrated that the urinary arsenic concentration at level higher than 50 μg/g creatinine can be associated to the development of different diseases.

6. Effects of Arsenic in Mitochondrial Dysfunction

Mitochondria are cellular organelles responsible for the oxidation-reduction reaction of the food of our diet for the production of ATP, owing to the electron transport chain and oxidative phosphorylation. The mitochondrial reactions take place in the presence of oxygen with the production of free radicals and oxidative stress. Under physiological conditions, normal levels of reactive oxygen species (ROS) are maintained by enzymatic and non-enzymatic antioxidant mechanisms, whereas in conditions of damaged or aged mitochondria, ROS formation increases [57]. The exposure to the xenobiotic arsenic causes disruption of mitochondrial function, inhibition of mitochondrial utilization, leading to disturbed membrane potential, and decreased ATP levels. Arsenic inhibits mitochondrial complex I (NADH ubiquinone oxidoreductase), complex II (succinate dehydrogenase), and complex IV (cytochrome c oxidase), followed by increased ROS production, lipid peroxidation, protein, and DNA damage [58]. During arsenic poisoning, glycolysis produces pyruvate without net ATP production, as arsenate ions compete with phosphate ions due to their structural similarities. Normally, the enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) oxidizes, in the presence of inorganic phosphate, glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate, that in turn is converted to 3-phosphoglycerate in the presence of phosphoglycerate kinase, releasing one molecule of ATP. It must be pointed out that this enzyme can also catalyze the reaction between arsenate and glyceraldehyde-3-phosphate to form 1-arseno-3-phosphoglycerate that hydrolyzes to arsenate and 3-phosphoglycerate without forming any ATP molecule. Arsenate actually competes with the inorganic phosphate for the GAPDH. This event happens cyclically. In fact, released arsenate reacts again to glyceraldehyde-3-phosphate resulting in the loss of ATP production. Therefore, at mitochondrial level, arsenate uncouples the oxidative phosphorylation. In the presence of arsenate in lieu of ATP, ADP-arsenate is produced. ADP-arsenate is not stable as ATP and hydrolyzes causing depletion of ATP. Arsenic inhibits also two important metabolic enzymatic complexes. The first complex is pyruvate dehydrogenase (glycolytic pathway) (Figure 2), and the second one is ketoglutarate dehydrogenase (Krebs tricarboxylic acids cycle). The enzymes and the co-enzymes of oxidative decarboxylation of pyruvate and ketoglutarate are the same, concerning the reactions mechanism: pyruvate/ketoglutarate decarboxylase, dihydrolipoyl transacetylase/dihydrolipoyl transsuccinylase, dihydrolipoyl dehydrogenase, thiamine pyrophosphate (TPP), lipoic acid, CoASH (Co-enzyme A), FAD, and NAD^+. Arsenic affects the conversion of lipoic acid to acetyl-CoA and succinyl-CoA interfering with –SH groups of reduced dihydrolipoamide. Arsenic forms a covalent adduct with dihydrolipoic acid inhibiting the regeneration of lipoic acid. Arsenic halts the formation of acetyl-CoA and succinyl-CoA, as well as the TCA cycle and ultimately respiration is ceased without ATP synthesis. Ketoglutarate dehydrogenase complex closely resembles the pyruvate dehydrogenase complex in both structure, function, and mechanism.
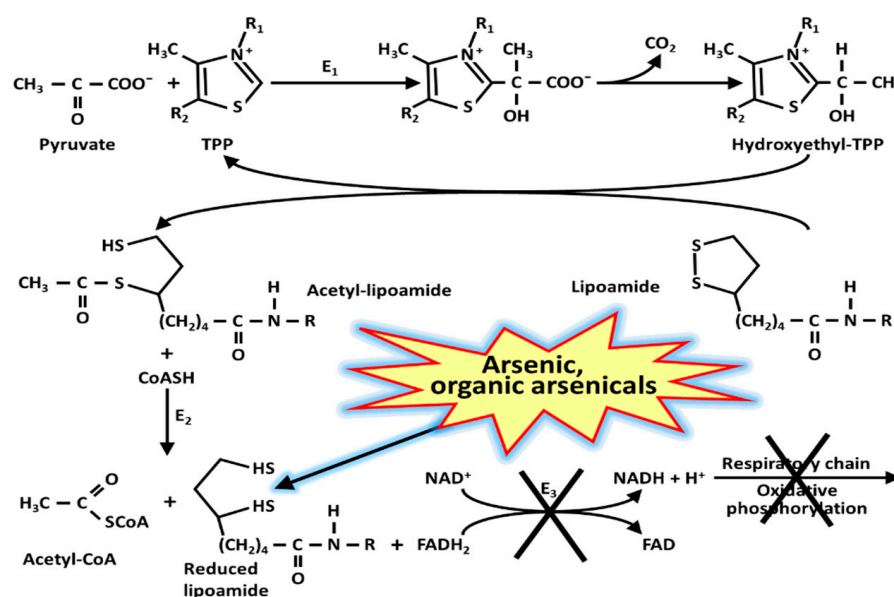
Figure 2. Effect of arsenic on pyruvate dehydrogenase complex. Arsenic and organic arsenicals form an adduct with the two –SH groups of dihydrolipoamide that alter the function of dihydrolipoyl dehydrogenase affecting the respiratory chain and the oxidative phosphorylation (E_1: pyruvate decarboxylase; E_2: dihydrolipoyl transacetylase; E_3: dihydrolipoyl dehydrogenase. TPP: thiamine pyro phosphate; FAD: flavin adenine dinucleotide; $FADH_2$: reduced FAD; NAD^+: nicotinamide adenine dinucleotide; NADH: reduced NAD^+; CoASH: Coenzyme A). This figure is an elaboration based on information retrieved from ref. [54,55].

7. Arsenic Epigenetic Modifications

Exposure to heavy metals (Cd, Cr, Hg, Fe, Ni, Pb, and Tl) and metalloids (like As) is correlated with a risk of skin, lung, liver, urinary tract, prostate, and hematopoietic cancers [59–62]. Chromosomal instability and epigenetic modifications may also play important roles in the arsenic carcinogenicity. Epigenetics refer to inherited changes in gene expression not involving a change in the nucleotide sequence of DNA. Epigenetics may be conditioned by different environmental factors and their dysregulation is involved in many diseases [63]. Eukaryotic DNA is packaged in the form of chromatin with the nucleosomes as a basic repeating unit. Each nucleosome consists of 147 DNA base pairs wrapped around histones H2A, H2B, H3, and H4 that aggregate each other forming the histone octamer. The N-terminal end of these histones may undergo a variety of post-translational modifications promoted by specific enzymes with acetylation and deacetylation, methylation and demethylation, phosphorylation, citrullination, sumoylation, biotinylation, and ubiquitination processes. These covalent reactions influence the chromatin structure facilitating gene transcription [64,65] or its inhibition [66]. Histone acetylation modification is regulated by two classes of enzymes: histone acetyl-transferase and histone deacetylase. In this modification reaction, in the presence of acetyl coenzyme A, an acetyl group is transferred on lysine amino acid residue which loses its ability to bind the DNA phosphate groups. Jo et al. (2009) [67] showed that exposure to MMA(III) and As(III) in human bladder cells reduced histone 4 lysine 16 (H4K16) acetylation suggesting that chronic arsenic exposure could contribute to bladder cancer. Lysine or arginine on N-terminal end of H3 and H4 may undergo a methyl reversible modification. Zhou et al. (2008, 2009) [68,69] published that arsenite (As III) can act on histone modification modulating the methylation of H3. These authors showed that human lung carcinoma A549 cells exposed to As(III) increased H3K9 demethylation (H3K9me2) and decreased H3K27 trimethylation (H3K27me3). In addition, microRNAs (miRNAs) act on epigenetic mechanisms. These small non-coding molecules (20–25 nucleotides in length) are implicated in the post-transcriptional regulation of protein expression by binding to a complementary region on target RNA silencing their
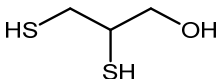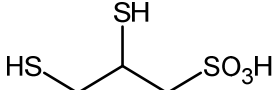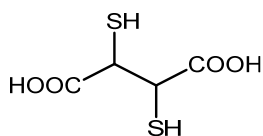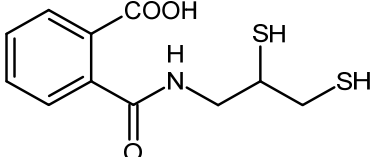
translation. MiRNAs are transcribed within the nucleus from DNA but not translated in proteins [70]. A majority of research on arsenic-induced miRNA expression changes have been conducted in vitro using human bladder carcinoma (T24) and human liver carcinoma (Hep-G2) cell lines. Hep-G2 cells treated for 24 h in the of 4 μM arsenic trioxide (As_2O_3) showed upregulation of miR-24, miR-29a, miR-30a, and miR-210. Among these four miR-NAs, miR-29a had a positive effect in liver cancer therapy by inhibiting cells growth and inducing apoptosis [71]. Cheng et al. (2018) [72] investigated the effects of arsenic exposure (inorganic arsenic, monomethyl arsenic acid, and dimethyl arsenic acid detected in urine) on the expression of AS3MT (arsenite methyltransferase), 3miRNA, and 17 relative mRNA in 43 workers producing arsenic trioxide. The authors found a negative correlation between AS3MT and miR-548c-3p, as well as between the expression of miR-548c-3p and many relative mRNAs. AS3MT and miR-548c-3p may regulate arsenic methylation in arsenic metabolism. DNA methylation pattern in mammals is the most epigenetic modification studied in relation to arsenic exposure. DNA methylation of cytosine-rich region, known as CpG dinucleotide islands, is a covalent addition of a methyl group to cytosine to form 5-methylcytosine (5-MeC). CpG islands can be found in the promoter region of about half of human genes [73]. Methylation of CpG cytosine is allowed by DNA methyltransferase (DNMT) in the presence of SAM (S-adenosyl methionine) as a methyl donor. Actually, five members of DNMT family are known in mammals (DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L); but mammal methylation is mediated only by DNMT1, DNMT3a, and DNMT3b [74]. Arsenic can reduce the activity and the expression of DNMT and the availability of SAM in the methylation of CpG. Literature studies have shown arsenic methylation levels of DNA and several cancer gene promoters both in in vitro cell cultures and in vivo people exposed to arsenic. Gene silencing by CpG methylation directly affects the affinity of transcription factors for binding site of their DNA. Reichard and Puga [75] reported that in vivo or in vitro both hypo- and hyper-methylation at various genetic loci are associated with arsenic exposure. Moreover, both DNA hypo- and hyper-methylation in the promoter region of tumor suppression genes are often associated with carcinogenesis and cancer. Koestler et al. (2013) [76] showed that arsenic exposure during gestation develops congenital malfunctions and disease consequences including cancer. The authors identified DNA methylation of cord blood-derived DNA from 134 infants (New Hampshire, England) exposed to low levels of arsenic, and methylation to individual CpG loci. Their studies demonstrated that, among 44 CpG islands, 75% of them showed higher methylation levels in infants exposed to high arsenic compared to that exposed to low arsenic. It must also be remembered that sex-specific DNA methylation pattern after arsenic exposure have been studied. Pilsner et al. (2012) [77] demonstrated that in a prenatally exposed population of Bangladesh exposed to arsenic in drinking water (up to 660 μg/L), global CpG methylation decreased in females and increased in males. Niedzwiecki et al. (2015) [78] searched the effect of arsenic (up to 300 μg/L in drinking water) on global DNA methylation in an adult population of Bangladesh. Results of the authors indicated that there was no association between arsenic exposure and DNA methylation in females, while in males they found a positively association between arsenic and global DNA methylation.

8. Detoxification from Arsenic

Chelation for heavy metal intoxication (mercury, lead, arsenic et al.) began more than 80–90 years ago. The classic antidote against acute arsenic poisoning, BAL (British Anti-Lewisite, dimercaptopropanol) (Table 3) was synthesized as an antidote for lewisite. Due to high toxicity of BAL, the clinical use of this compound is restricted to only the initial treatment for few days after arsenic intoxication. In the 1950s, water-soluble and less toxic analogs of BAL have been developed for clinical use: dimercaptosuccinic acid (DMSA), 2,3-dimercaptopropane sulfonic acid (DMPS) and *N*-(2,3-dimercaptopropyl)-phthalamidic acid (DMPA). DMSA, DMPS, and DMPA have lower toxicity and higher therapeutic index than BAL when used in an arsenic poisoning in the proportion of 42:14:4:1, respectively. Clinical studies in chelation for the treatment of acute arsenic intoxication established that

the efficacy of chelation therapy is most effective when treatment is started rapidly (within minutes or hours) after arsenic exposure [79]. Analytical and clinical results support that the endogenous dithiol dihydrolipoate, having high affinity for arsenical compounds, are used with success in the therapy of the arsenic intoxication [64]. Arsenic-contaminated drinking water affects hundreds of millions of people in more than 50 countries. Given the high cases of affected individuals, it is not easy to provide infrastructures to remove arsenic from water for daily consumption. The reduction or the removal of arsenic from water can be done in several ways, including harvesting rainwater and digging deep well to harvesting direct groundwater. However, one of the challenges in many water and wastewater treatment plants worldwide is the selective removal of trace elements, such as arsenic, with the presence of higher concentrations of background competing solutes such as main ions. Several methods of selective arsenic removal have been developed, such as precipitation, adsorption, and modified iron and ligand exchange [80]. Besides these water sources, arsenic can be removed from water by various treatments, such as solar oxidation of arsenic in transparent containers that reduces the arsenic load by oxidizing As^{3+} to As^{5+}. The practice of storing water for long time in clear containers reduces the arsenic level through sedimentation. Naturally dissolved $Fe(OH)_2$ in the groundwater undergoes a natural oxidation process to produce a precipitate of $Fe(OH)_3$ which attracts and adsorbs arsenic to stick to it. This adsorption produces a co-precipitate of $Fe(OH)_3/As$ that sediments to the bottom of the container. Alum $[Al_2(SO_4)_3 \cdot 18H_2O]$, ferric chloride $(FeCl_3)$, and ferric sulfate $[Fe_2(SO_4)_3 \cdot 7H_2O]$ are commonly used as coagulants [81]. Rice (*Oryza sativa* L.) is the most arsenic-contaminated cereal found in water and soil. Arsenic is particularly accumulated in rice, because this cereal is grown in flooded soils, thus, the rice absorbs this toxic metal from both water and soil [82]. Rice is the main food for half of the world population, living in Asia (India, Pakistan, China, and Japan) and it grows in places where the water and soil are heavily contaminated with arsenic [83,84]. Irrigation of rice field with arsenic-contaminated groundwater poses a major health problem for those peoples who eat rice with high levels of arsenic [85]. Different agronomic irrigation techniques allow to reduce the accumulation of this toxic element. We should intervene "upstream" at the environmental level by improving irrigation techniques, controlling the arsenic level of the waters that irrigate the rice fields, drawing the water in depth and fertilizing with silica, that is antagonist for arsenic. Rice grown aerobically has lower arsenic levels compared to the one grown in flooded conditions [86]. It is essential to soak the rice overnight before cooking it in plenty of water to allow the arsenic to dissolve in the liquid. Different cooking methods can also reduce the quantity of arsenic in rice, such as the practice of washing the rice thoroughly and then cooking it in large quantities of water in a ratio of 1 to 6 [86]. Percolation cooking allows the arsenic contained in the rice to be removed by passing a continuous stream of boiling water through the grains [86,87]. In addition, rice varieties that accumulate less arsenic have been selected and the possibility of genetically modifying rice to accumulate much less arsenic is being investigated. One of the best ways to prevent health problems bound to arsenic is a diet rich of proteins and antioxidants such as vitamins A, C, and E, and different plants of the traditional Indian medicine like *Mentha piperita* L., *Allium sativum* L., curcumin, quercetin, spirulina, resveratrol, and green tea polyphenol (epigallocatechin-3-gallate) [88–91].

Table 3. Structures of chelating agents.

Structure	Name
HS—⟍—OH with SH	BAL (British Anti-Lewisite; 2,3-dimercapto propanol, dimercaprol)
HS—⟍—SO$_3$H with SH	DMPS (2,3-dimercapto-1-propanesulfonic acid)
HOOC—CH(SH)—CH(SH)—COOH	DMSA (dimercaptosuccinic acid)
phthalamidic structure with COOH, N–H, amide C=O, and dimercaptopropyl SH groups	DMPA (*N*-(2,3-dimercaptopropyl)-phthalamidic acid)

9. Arsenic Phytoremediation

Heavy metals (Cd, Cr, Hg, Pb, Ni, Co), metalloids (As, Si, Se), and organic pollutants (methyl mercury (CH$_3$)Hg$^+$, dimethyl mercury (CH$_3$)$_2$Hg) accumulation in soil and groundwater has been rapidly increased because of various natural processes and anthropogenic activities. Most organic pollutants are biodegradable. Heavy metal and metalloid show greater environmental persistence because they are non-biodegradable and have the possibility to enter the food chain through drinking water, vegetables, and fruits with serious effects on health in humans. Therefore, the removal of these elements had been a challenging task for the scientific community. In the past, many expensive physical, chemical, and biochemical approaches have been used for the removal of arsenic from soil determining the alteration of soil properties and disturbing the soil microflora. Phytoremediation is an eco-friendly, green, cheap, and safer technology that makes use of plants to remove toxic and radioactive metals and organic pollutants (pesticides, herbicides, fertilizers, and detergents) from the environment [92,93]. The results obtained by Ahmad et al. (2018) [94] at the Botanical Garten (University of the Punjab, Lahore) revealed that *Eucalyptus camadulensis* L., *Terminalia arjuna* L., and *Salix tetrasperma* L. can be used for arsenic phytoremediation. Six months old seedling were planted in plastic pots containing loamy soil and treated with diverse doses of arsenic (0.5, 1.0, 2.0, 4.0 mg/L) for 18 months. Arsenic accumulated in all parts of the seedlings with maximum in roots of *Eucalyptus camadulensis* L. (37.25 mg/kg), *Salix tetrasperma* L. (35.76 mg/kg), and *Terminalia arjuna* L. (24.13 mg/kg) in the pots with an arsenic concentration of 4.0 mg/L. Among these three species that can grow in the fields contaminated with arsenic, *Eucalyptus camadulensis* L. is considered an excellent candidate for phytoextraction and phytoremediation as it accumulates maximum level of arsenic in all parts of the plant tissues in the order roots > shoot > leaves. In 2006, Wei and Chen (2006) [95] studied the capability of eight *Pteris cretica* L. and sixteen *Pteris vittata* L. to accumulate arsenic in an area near arsenic mine in Hunan Province of South China. Regarding the arsenic uptake, three factors were determined by the authors: its concentration in fronds, the bioaccumulation factor (BF: ratio of arsenic in fronds to soil), and the arsenic translocation factor (TF: ratio of arsenic in fronds to roots). The results obtained by the authors showed that the arsenic concentration in the fronds of *Pteris cretica* L. were between 3 and 704 mg/kg, the BF factor were 0.06–7.43, and the TF were 0.17–3.98; on the contrary, the values determined in *Pteris vittata* L. were 149–694 mg/kg, 1.34–6.62, and 1.00–2.61 respectively. Between these two ferns, *Pteris cretica* L. showed to be the best candidate for arsenic phytoremediation of contaminated area near arsenic mine. Can-

tamessa and its collaborators (2020) [96] used the fern *Pteris vittata* L. in symbiosis with Arbuscular Mycorrhizal Fungi (AMF) to extract arsenic from an industrial site in north-western Italy contaminated also with other heavy metals due to metallurgic activities. Two series of experiments were performed by the authors. In the first one, which lasted two years, AMF-colonized *Pteris vittata* L. ferns were grown under controlled conditions in pots containing soil coming from the contaminated metallurgic area. In this experiment, an excellent arsenic accumulation in fronds was observed. In a second study, lasting three years, the capacity of *Pteris vittata* L. inoculated with AMF to accumulate arsenic was studied in the contaminated metallurgic field. In these conditions, the level of the metalloid in the soil was reduced from 170 mg/kg to 49 mg/kg, values in agreement with the Italian legislation. Nanophytoremediation is a green technology which includes the nano scale materials used for absorption and degradation of organic and inorganic pollutants [97]. Use of nanomaterial with phytoremediation can have the capability to increase the decontamination energy. It has been reported that TiO_2 nanocomposites showed more affinity for both inorganic forms of arsenic due to high surface area to volume ratio, resistance to corrosion and stability [98]. Numerous metals or metal oxide-based titania nanocomposites, such as $Ce-TiO_2$, $Zr-TiO_2$, and $TiO_2-\alpha Fe_2O_3$ have been used with success for the removal of arsenic in water treatment [98]. It is noteworthy that the use of nanoparticles while enhancing the phytoremediation capability of arsenic, also diminishes the bioaccumulation of this metalloid in crops. Wu and co-authors (2020) [99] used nano-TiO_2 with anatase and rutile structures to reduce arsenic bioaccumulation in rice seedlings of about 40–90% by sorption process without affecting their growth. In 2021, Yan and collaborators (2021) [100] used nano-zinc oxide in agricultural production due to its adsorption capability and as nutrient. An experiment was conducted to study the effect of ZnO nanoparticles on arsenic toxicity and accumulation in rice. The results obtained from the experiments showed that zinc-nanoparticles (100 mg/L) had an important effect on rice seedling growth, decreasing at the same time the accumulation of the xenobiotic in this food.

10. Conclusions

Nowadays, the pollution of water and soil is a major concern. The broad occurrence of arsenic in groundwater threatens human health when groundwater is used as a source for drinking water, agriculture irrigation, and fishery water. Soil pollution due to heavy metals, specifically arsenic, is very harmful to live organisms. Arsenic is the 20th highest natural metalloid found in the earth's crust and it is commonly recognized for adverse effects on human health. It affects many cellular processes and organ functions in the human body. Arsenic is a classical and unique example of a carcinogen in humans associated with the consumption of arsenic-rich drinking water. Development of cancer in skin, lung, bladder, kidney, liver, and prostate due to arsenic is widely accepted. Thus, arsenic removal innovation is direly mandatory. To date, researchers have developed distinctive arsenic remediation/removal techniques including coagulation, precipitation, and nanofiltration membranes. This review tries to highlight the uses and major routes of exposure to arsenic, as well as certain molecular mechanisms related to its toxicity. Moreover, epigenetic studies have been extensively described. In the current review, we also describe some of the most common methods for removing arsenic from soils, such as phytoremediation and the use of nanoparticles. However, further studies are needed in order to develop new remediation/removal methods to reduce recurrent contamination from this dangerous metal.

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