Understanding arsenic toxicity: Implications for environmental exposure and human health

Ravidarshdeep kaur [a], Atul Garkal [b], Lopmudra Sarode [d], Priyanka Bangar [b], Tejal Mehta [b], Dhirendra Pratap Singh [c,*], Rakesh Rawal [a,**,1]

[a] Department of Biochemistry and Forensic Science, University School of Sciences, Gujarat University, Ahmedabad, Gujarat 380009, India
[b] Department of Pharmaceutics, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat 382481, India
[c] Division of Biosciences, ICMR, National Institute of Occupational Health, Meghani Nagar, Ahmedabad, Gujarat 380016, India
[d] Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra 440033, India

ABSTRACT

Arsenic is a trace element and a metalloid which is prominently known as an environmental hazard. At present, rising health apprehensions are linked to emanating from a wide array of industrial, chemical, residential, agricultural, and technological sources, leading to extensive pollution of water, soil, and air ecosystems including flora, fauna and humans. It poses significant harm to biological organisms upon acute and chronic exposure. In this review, we delve into the reported experimental data that elaborates on arsenic as a toxicant, with particular emphasis on its occurrence, metabolism and diverse molecular mechanisms involved. It also includes the major molecular mechanisms leading to systemic toxicity with special emphasis on shedding light on the intricate ways it disrupts the nervous system.

1. Introduction

The term metalloids specify elements with atomic number >20 or atomic mass >23 (Ali and Khan, 2018) and having considerably higher density (>5 g/cm^3, specific gravity: >5) as compared to water (density: 1 g/cm^3, specific gravity: 1) (Ali et al., 2019). These represent the group of elements with properties between metals and non-metals. They have an ionization potential of about 200 kcal/mol and an electronegativity value of 2.0 (Marzo and Mendola, 2021). Certain elements such as Arsenic, Mercury, Lead, Chromium, Cadmium and Vanadium are included in environmental and health studies because of their harmful and ecological effects (Engwa et al., 2019). These are found in trace concentrations (i.e., <10 ppm) in the environment, therefore, termed as trace elements as well (Arora and Chauhan, 2021). Currently, there have been increasing health concerns associated with environmental metal contaminations (Shi and Cai, 2020) and their bioaccumulation in food chains (Shafiuddin Ahmed et al., 2019). Extensive release from various industrial, chemical, domestic, agricultural and technological sources contaminates the water, soil and air environment (Masindi and Muedi,

2018). Anthropogenic activities like metal processing in refineries, coal burning in power plants, petroleum combustion, wood preservation, nuclear power stations, high tension lines, plastics, textiles, microelectronics and paper processing plants along with the natural phenomenon of weathering and volcanic eruptions significantly contribute to metal pollution (He et al., 2005; Nriagu, 1989). These have direct and severe health consequences, which include carcinogenic effects like squamous cell carcinoma, lung cancer, bladder cancer whereasa non-carcinogenic include hyperpigmentation, keratosis, cardiovascular and neurological disorders, diabetes and respiratory issues (Yusuf et al., 2022; Yusuf et al., 2023). Fig. 1 represents the commonly found toxic metals/metalloids and their potential sources, mainly focusing on arsenic as an environmental hazard and its associated health effects.

Epidemiological studies in these countries have shown the negative health impact of arsenic exposure which can vary depending on the level and duration of exposure. Approximately 6 million people are affected by arsenic toxicity in India. It is also majorly present in West Bengal and Bangladesh (>50 ppb) in drinking water (Andrewes et al., 2003). Chronic exposure to low levels of arsenic in drinking water can lead to

skin lesions, including hyperpigmentation, hyperkeratosis, and the development of small warts or nodules. Even low-level exposure to inorganic arsenic has been associated with an increased risk of several cancers, including skin, lung, bladder, and kidney cancers. Emerging research suggests that chronic exposure to low levels of arsenic may contribute to cardiovascular disease, including hypertension and atherosclerosis (Kaur, 2023; Hughes et al., 2011; Drobna et al., 2009). High-level arsenic exposure, typically resulting from accidental ingestion or occupational exposure, can lead to acute arsenic poisoning. Symptoms include severe abdominal pain, vomiting, diarrhea, cardiovascular complications, and, in severe cases, death. Chronic exposure to high levels of arsenic can result in neurological symptoms, including peripheral neuropathy, cognitive impairment, and developmental delays in children (Fatema et al., 2021; Escudero-Lourdes, 2016). Prompt medical intervention is essential in cases of acute arsenic poisoning. Treatment often involves supportive care, such as intravenous fluids to prevent dehydration and administration of chelating agents to remove arsenic from the body. Long-term monitoring and medical care are necessary to manage and treat conditions such as skin lesions, respiratory problems, and cancer that may have developed as a result of past exposure (Lakkis et al., 2023). Post-mortem examinations of individuals exposed to high levels of arsenic often reveal characteristic findings. Skin lesions are prominent features in some cases. While in cases of chronic exposure, it can accumulate in various tissues, including the liver, kidney, and lung, leading to organ damage. Arsenic exposure has been associated with an increased risk of certain cancers, and examinations may reveal cancerous growths in affected organs. In present review, following keywords were used in a literature search on the PubMed database to find full-text articles published: "Metalloids AND environmental toxicity" [All fields], "arsenic exposure AND toxicological effects" [All fields], "arsenic AND neurological dysfunctions" [All fields], "arsenic AND toxicity mechanisms" [All fields]" with a number of 4438, 28, 8, 338 articles respectively for data collection. Publications within the last ten year and some old important articles which were relevant to the goals of the current review were selected. Reviews, conference abstracts, letters to the editors and articles published in languages other than English were excluded.

2. Arsenic and its bioavailability

2.1. Distribution, forms and toxicity

Arsenic is widely distributed throughout the environment. Contaminated groundwater is the principal route of exposure, followed by the smelting of metals, combustion of fossil fuels, manufacture of herbicides and fungicides and their subsequent use in agriculture (Vahidnia et al., 2007). It has a high specific gravity (5.73) and is toxic to both plants and animals even at a low level of exposure (Fatema et al., 2021). It exists in 3 forms organic (oAs), inorganic (iAs) and arsine gas. iAs has further five oxidative states: 3-, 1-, 0, 3 +, 5 + (Ng, 2005) and shows around 60–87 % bioavailability in humans (Mochizuki, 2019). Several arsenicals have been reported in the form of arsenite (arsenous acid), iAsIII; arsenate (arsenic acid), iAsV; (mono) methylarsonous acid, MAsIII; (mono) methylarsonic acid, MAsV; dimethylarsinous acid DMAsIII; dimethylarsinic acid, DMAsV; trimethylarsine oxide, TMAO (Rahaman et al., 2021; Balali-Mood et al., 2021). Its toxicity depends on its nature (inorganic or organic), valence state, solubility, physical state, and purity of the form in which it exists. iAs is considered more toxic than oAs where the former's trivalent form (3+; arsenite) has a slower excretion rate as compared to the pentavalent (5+; arsenate) and organic form (Renu et al., 2020).

2.2. Metabolism, transportation and accumulation

Its metabolism depends on several factors: the form of arsenic entering the system, the species (plant or animal), availability of glutathione or other antioxidant systems, the types of cells being exposed to it in the organism and other biomolecules containing thiol
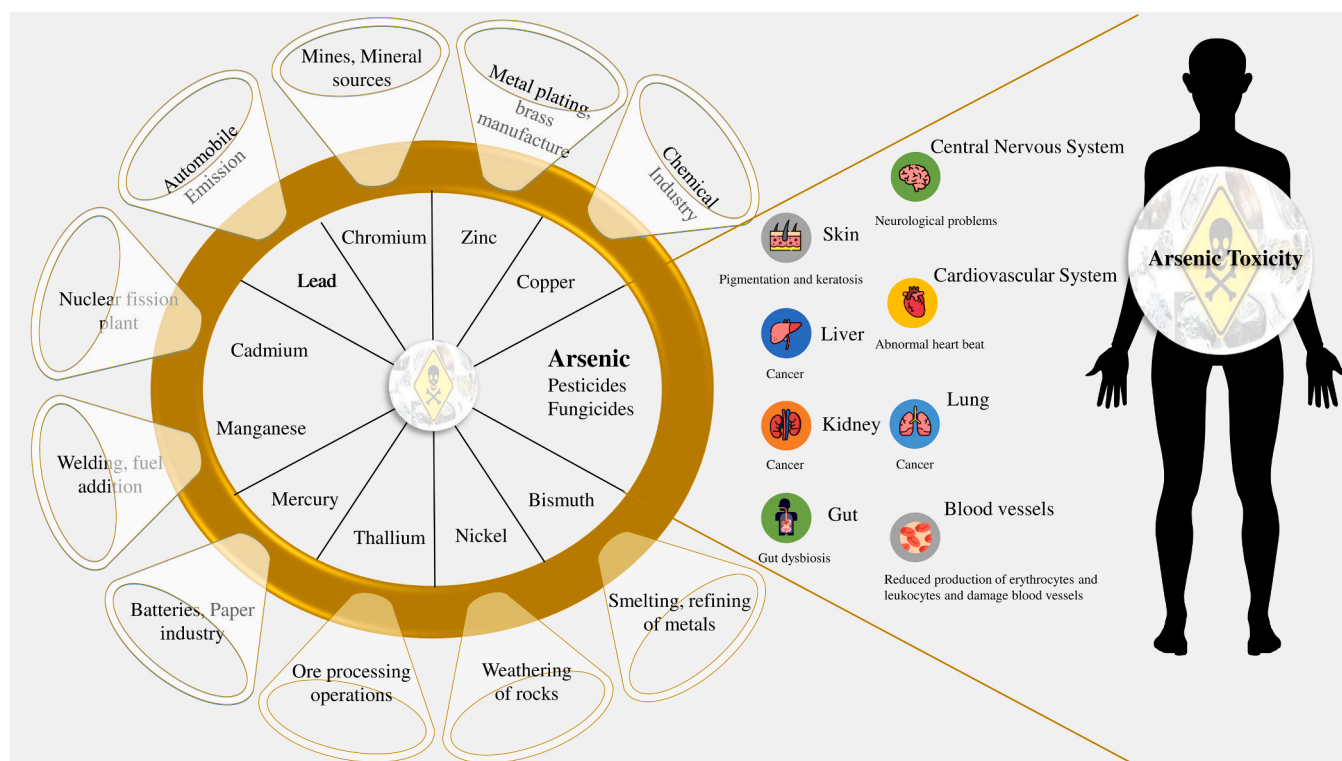

Fig. 1. Commonly observed toxic metals as environmental hazard, their potential sources with special emphasis on the effects of arsenic exposure on the human body (Fu and Xi, 2020; Tchounwou et al., 2012).

group (Dilda and Hogg, 2007; Zhu et al., 2002). Predominantly, arsenic breakdown occurs in the liver (Marafante et al., 1985) where it is methylated in the presence of a methyl donor S-adenosyl methionine and glutathione, a co-factor with arsenic methyltransferase to pertinent monomethylated and simultaneously dimethylated and its metabolites finally being excreted through the urine (Saint-Jacques et al., 2014). Some studies have also demonstrated that other tissues are also capable of its methylation in the cytosol of testes, kidneys and lungs (Aposhian, 1997; Healy et al., 1998). As(OH)$_3$ is usually transported in cells through transporters, like aquaglyceroporins (AQP9 in the brain, liver and bladder, kidney, testes and adipose tissue) or membrane hexose permeases. iAsV, however, is transported in the cells via phosphate transporters and is concentrated to iAsIII, which is then conjugated with glutathione (Watanabe and Hirano, 2013). It is methylated by As(III) methyltransferase (AsIIIMT), making the monomethylated (MMAIIIorV) and dimethylated (DMAIII/V) conjugated metabolites and removed from the system through urine and feces through multidrug-resistance-related proteins I and II (Leslie et al., 2004). AS3MT encodes an enzyme responsible for the methylation of inorganic arsenic (iAs) to its less toxic metabolites, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). This methylation process is a crucial step in arsenic metabolism and detoxification (Andrew et al., 2006). Some genetic variants in AS3MT have been associated with differential arsenic methylation patterns and susceptibility to arsenic-related health effects (Hagenbuch and Dawson, 2004). Individuals with genetic variants that result in reduced AS3MT activity may be less efficient in detoxifying arsenic, potentially increasing their susceptibility to arsenic-related health problems. Studying AS3MT genetics and its role in arsenic metabolism can help identify individuals at higher risk of adverse effects from arsenic exposure (Thomas et al., 2007). Additionally, the exposure of As leads to the accumulation of MMAV (acute exposure), and DMAV (chronic exposure) in different tissues as depicted in Fig. 2.

3. Delving into the molecular mechanisms of arsenic systemic/neuro-toxicity

Arsenic is known for its carcinogenic, neurotoxic, mutagenic properties, oxidative stressor, endocrine system disruption and inflammatory action. The source, species, and concentration of arsenic affect the limit of toxicity (Aljerf et al., 2021). Dosage, duration of exposure, cell/tissue type, and metabolism are additional important factors. Once in the body, arsenic can interfere with cellular processes by disrupting the function of proteins, enzymes, and DNA (Tam, 2020). This leads to oxidative stress and cellular damage, ultimately resulting in cellular death. In humans, biomarkers of its exposure mainly include serum lipid peroxides or changes in DNA methylation (Inesta-Vaquera et al., 2021; Cui et al., 2006). Arsenic exposure is a serious health concern as it can lead to the manifestation of cancer. This is because it stimulates pathways that help in the proliferation and neoplastic transformation of cells while inhibiting apoptotic pathways that prevent carcinogenesis (Medda et al., 2021). In individuals living in arsenic-contaminated areas, overexpression of a mitotic kinase called Aurora A can result in abnormality of chromosomes in lymphocyte and epithelial cells. Aurora A is involved in meiosis, mitosis, and cell proliferation, and its enhanced level can lead to the formation of tumors, metastasis, and cellular invasion (Barchowsky et al., 1996; Trouba et al., 2000; Sen, 2002).

Reactive oxygen species (ROS) are formed as a byproduct of different metabolic pathways, and can help maintain homeostasis by participating in different cellular signaling. However, higher levels of ROS induced by arsenic can cause oxidative damage to proteins, lipids, DNA, and other cellular components. Arsenic administration can initiate a wide range of ROS generation in different cells, and the possible mechanisms include oxidation of arsenite to arsenate, alteration of antioxidant enzymes, NADH oxidase activation, and reducing the mitochondrial membrane potential by cytochrome-c release. Recent studies have demonstrated that the addition of catalase or superoxide dismutase (SOD) can reduce arsenic-induced mutagenic effects in cells (Barchowsky et al., 1996; Nesnow et al., 2002; Zhou et al., 2003; Del Razo et al., 2001; Sajed Ali et al., 2016; Medda et al., 2020; Lee et al., 2013). Oxidative stress is one of the main arsenic poisoning mechanisms while others are increased ROS generation, modifications to signaling pathways like extracellular signal-regulated kinase (Li et al., 2018), mitogen-activated protein kinase signaling pathway (Jou et al., 2019) and nuclear factor erythroid-related factor 2-antioxidant response element signaling pathway (Hu et al., 2018). Arsenic alters the composition and efficiency of proteins, especially SH-proteins (Prakash et al., 2016; Prakash et al., 2022) as well as a breakdown of the antioxidant defense system (Rehman et al., 2019) and promotes the destruction of crucial cellular macromolecules (Rehman et al., 2019;
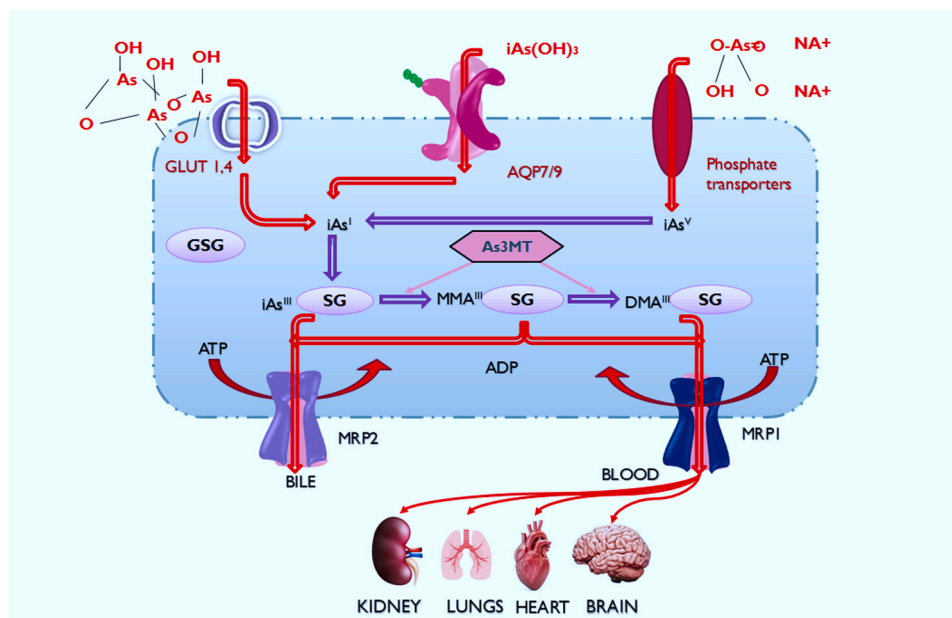

Fig. 2. A Schematic diagram of arsenic metabolism in body (Zhang et al., 2020).

Susan et al., 2019). Targeted disruption or knockout studies involving genes related to arsenic metabolism and detoxification, such as RadS1 (also known as Rad51), provides valuable insights into how the gene function and its potential roles in arsenic toxicity and susceptibility. While Rad51 disruption primarily focuses on DNA repair mechanisms, it indirectly relates to arsenic toxicity because arsenic exposure can lead to DNA damage and genomic instability, potentially exacerbating the effects of Rad51 deficiency (Hughes, 2002). The summary of different reported studies of arsenic concentrations with the exposure time, involvement of metabolites/genes/enzymes/proteins and mode of action with the outcome in a biological model systems is presented in Table 1.

Arsenic toxicity is amplified by free radical formation, glutathione-depleting agents, and oxidant-induced DNA damage. Its exposure results in an increased formation of ROS/RNS, including peroxyl radicals (ROO•), the superoxide radical, singlet oxygen, hydroxyl radical (OH•) via the Fenton reaction, hydrogen peroxide, the dimethyl arsenic radical, the dimethyl arsenic peroxyl radical, and/or oxidant-induced DNA damage. It also induces the formation of oxidized lipids, which generate several bioactive molecules, of which aldehydes [malondialdehyde (MDA) and 4-hydroxy-nonenal (HNE)] are the major end products (Jomova et al., 2011). Plants exposed to arsenic show

morpho-physiological, growth, and developmental disorders, resulting in loss of productivity. At a physiological level, As-induced altered biochemistry in chloroplast, mitochondria, peroxisome, endoplasmic reticulum, cell wall, and plasma membrane causes the overgeneration of reactive oxygen species (ROS), which damage cells by disintegrating the structure of lipids, proteins, and DNA. Plants having an enhanced anti-oxidant defense system show greater tolerance to As toxicity. Therefore, plants' tolerance to ROS-induced oxidative stress is a vital strategy for enhancing As tolerance in plants. Several genotoxic and non-genotoxic mechanisms of arsenic-induced cancer have been proposed at cellular and molecular levels. Oxidative stress induction via reactive oxygen species (ROS) generation, indirect DNA damage due to ROS, epigenetic modifications, and activation of stress and other signaling pathways are some of the proposed mechanisms of arsenic-induced cancers. Inorganic trivalent arsenic is one of the main inducers of ROS in cells. Arsenic metabolism produces different types of ROS like hydroxyl radical, hydrogen peroxide, and superoxide anion radical. Cells convert arsenite to arsenate via oxidation generating two electrons, which are important for hydrogen peroxide production. The hydrogen peroxide further generates hydroxyl radical, a highly active radical by Fenton reaction. The metal has also been found to generate reactive nitrogen species (RNS), and nitric oxide (NO) in arsenic-treated BAEC, and CHO-K1 cells

Table 1
Important molecular mechanism and adverse effects of arsenic toxicity in animal model.

Molecular mechanism	Concentration and type of arsenic	Exposure time	Animal model	Metabolite/ gene/protein/ enzymes	Adverse outcomes	Reference
Oxidative stress	25 ppm sodium arsenite	12 weeks	Male rats	MnSOD	The protein and mRNA which is an expression of MnSOD declined due to an elevation in oxidative damage	(Prakash and Kumar, 2016)
	25 ppm sodium arsenite	10 weeks	Male rats	GSH, SOD, GSH GSSG ratio	Considerable reduction of SOD, reduced GSH: GSSG ratio, elevation in hepatic levels of thiobarbituric acid reactive substances	(Bhadauria and Flora, 2007)
Signaling pathway involved in As-induced apoptosis	7.5 mg/kg arsenic trioxide	62 days	Male rats	AKT	Reduction of AKT protein expression	(Mann et al., 2008)
	2 mg/kg sodium arsenite	6 months	Male rats	PKC and JNK	Phosphorylation of PKC suggests the involvement of PKC in As-induced JNK activation	(Das et al., 2010)
	0.01, 0.05, and 0.1 mg/L sodium arsenite	30 days	Male mice	p53	Activation of p53 leads to oxidative DNA damage to liver cells and elevates the p53 gene expression targets such as Bax and miR-34a	(Mukherjee and Mukhopadhyay, 2009)
Inhibition of spermatogenesis via increased oxidative stress and decreased antioxidants	20 and 40 mg/L sodium arsenite	5 weeks	Male mice	NA	Decreased sperm count in 3β-HSD, 17β-HSD, epididymis and weight of testes through oxidative stress with reduced glutathione	(Chang et al., 2003)
	1, 5, and 25 mg/L sodium arsenite	6 months	Male rats	GPx4	Defect in spermatogenesis	(Muthumani and Prabu, 2012)
	100 ppm sodium arsenite	30 days	Male rats	NA	Increased lipid peroxidation and decreased antioxidant enzymes	(Firkin and Iland, 2013)
Downregulating Ddx3y protein	1, 2, and 4 mg/L arsenic trioxide	6 days	Male mice	Ddx3y	Reduced testes and epididymis mass, reduced motility and number of sperms, malformation ratio of sperm; defective spermatogenesis	(Li et al., 2012)
Repression of transcriptional activity of androgen receptor	0.2 μM sodium arsenite	48 h	Male mice	NA	Complete blockage of androgen-mediated AR transcriptional activity	(Rosenblatt and Burnstein, 2009)
Activation of heat shock proteins	7.5, 15 and 30 mg/kg arsenic trioxide	30, 60 and 90 days	Chickens	NA	Increased Hsp27, Hsp40, Hsp60, Hsp70 and Hsp90 which may have a protective role in inflammation	(Sun et al., 2017)
	50 mg/kg arsenic trioxide	4, 8 and 12 weeks	Chickens	NA	Increased Hsp70 and Hsp90	(Shao et al., 2018)
Effect on the mitochondrial functions	5 mg/kg sodium arsenite	21 days	Male rats	NA	Decreased mitochondria potential, mitochondrial inflammation and inhibition of respiratory chain complex I leading to oxidative stress	(Bodaghi-Namileh et al., 2018)
Apoptosis	6.3, 10.5 mg/kg sodium arsenite	24 h	Male rats	Caspases	Formation of DNA ladder and caspases activation	(Bashir et al., 2006)

Abbreviations: MnSOD= Mitochondrial Superoxide dismutase, SOD= superoxide dismutase, AKT/PKB= protein kinase B, PKC= Protein kinase C, JNK= c-Jun N-terminal kinase, HSD-hydroxysteroid dehydrogenase, GPX4 = Glutathione peroxidase 4, Nrf2 = Nuclear erythroid factor 2, AR= Androgen receptor, SAFB1 = S-caffold attachment factor B1, Hsp= Heat shock protein.

(Gutiérrez et al., 2022). It triggers the NADPH oxidase complex, which generates superoxide anion radicals. Additionally, it is known to disrupt mitochondrial membrane integrity, releasing ROS into the cytosol. This excess of ROS overwhelms the body's natural antioxidant defense system, leading to oxidative stress in cells. The resulting free radicals can cause damage to DNA, RNA, lipids, and proteins, leading to genetic mutations. Arsenic exposure also activates ER stress-UPR and autophagy, causing mitochondrial dysfunction, which influences arsenic-induced cancers and the generation/maintenance of CSCs (Shi et al., 2004; Li and Chen, 2016; Maiti, 2015; Wadgaonkar and Chen, 2021).

Neurological studies indicate that the central (CNS) and peripheral nervous system (PNS) may be affected by arsenic exposure. Various reported studies have demonstrated the effect of its exposure leading to neurological disorders, cognitive and developmental toxicity in which increased anxiety, decreased spatial learning, increased density of pyramidal and granule cells and dendritic length, effect on memory and learning and epigenetic changes have been observed (Mohammed Abdul et al., 2015; Bock et al., 2015; Maekawa et al., 2013). It further reduces the neurofilament protein(s) expression and prompts the disruption of the cytoskeletal framework which causes the axonal degeneration of peripheral nerves. Various studies in patients with arsenic-associated neuropathy have displayed a decreased velocity in nerve conduction in the peripheral nerves, which is a common sign of axonal degeneration. It considerably reduces the serum acetylcholinesterase activity in a dose-dependent manner. Other studies showed oxidative stress with increased generation of ROS, lipid peroxides, and decreased concentration of superoxide dismutase and glutathione levels in the brain leading to DNA damage following brain cell death (Sánchez-Peña et al., 2010; Hughes et al., 2008; Dixit et al., 2020). Its exposure lead to impaired behavioral flexibility and reduced neurite lengths inside the pre-limbic cortex (Aung et al., 2016). Gestational exposure of arsenic to mice (hippocampus and striatum) also led to impaired gene expression of AMPA (GluR2 and GluR3) and NMDA (NR1, NR2A, NR2B) receptor as well as mGluR2 subunits, demonstrating reduced signal transduction in neurons (Wang et al., 2020). It has also been observed that decreased PSD (postsynaptic density) thickness and reduced expression of protein PSD-95 led to considerable impairments in memory and learning behavior (Zhao et al., 2017; Dhas et al., 2021). Further it leads to various neurologic disorders including Alzheimer's disease (Tolins et al., 2014; Niño et al., 2019) Parkinson's disease (Cholanians et al., 2016) and amyotrophic lateral sclerosis (Patti et al., 2020).

Another important reported mechanisms includes the depletion of methyl groups which affects epigenetic profiles, the inhibition of thiol-comprising proteins and enzymes, the uncoupling of oxidative phosphorylation and increased production of reactive oxygen species, reduced DNA repair inducing genotoxicity and altered signal transduction and cell proliferation (Chin-Chan et al., 2015; Rachman, 2018). Metabolites exert their toxic effects by inactivating various enzymes such as carboxylases, dehydrogenases, lipoxygenases, oxidoreductases, kinases, lyases DNA ligase, and helicase involved in the cellular energy pathway as well as DNA synthesis and repair (Ratnaike, 2003). Researchers suggest that arsenic's integrative mode of action could be an increase in gene expression indicative of oxidative stress, a decrease in transcript levels of DNA repair enzymes, and an increase in cell proliferation gene expression. They found that arsenic concomitantly modulates gene expression associated with increased proliferation, decreased DNA repair, and increased oxidative stress in non-transformed NHEK (Hamadeh, 2002). A study hypothesized that alteration of DNA methylation is involved in arsenic-induced carcinogenesis. This mechanism was considered because arsenic's biotransformation pathway overlaps with the DNA methylation pathway, in which donation of methyl groups produces 5-methylcytosine in DNA. The extent of methylation of cytosine, often in long stretches of cytosine-rich sequences known as CpG islands, controls the regulation of expression of many genes, especially in the promoter regions (Chanda et al., 2006).

Inhibition of DNA repair processes is considered one of the main mechanisms of iAs genotoxicity. Nucleotide Excision Repair (NER) and Base Excision Repair (BER) are the processes implicated in the repair of DNA base damage induced by ROS after arsenic exposure. The NER mechanism is the major pathway for repairing bulky distortions in DNA double helix, while the BER mechanism is mainly implicated in the repair of single-strand breaks induced by ROS (Lai et al., 2011). Several studies with cultured human fibroblasts showed reduced DNA repair capacity after arsenic exposure (Faita et al., 2013).

According to another study, it is known to decrease the activities of mitochondrial complexes I, II, III and IV in the rat brain and increase the reactive oxygen species (ROS) levels (Chandravanshi et al., 2014). The ROS accumulation is accountable for the damage of the lipid bilayer leading to mitochondrial swelling and changes to membrane potential (Srivastava et al., 2014). iAs induce alterations in the proteins of the sciatic nerve such as a decrease in NF-L (neurofilament light) expression (Bashir et al., 2006; Mohammed Abdul et al., 2015). Experiments in Wistar rats have shown that exposure to As reduces the neurofilament protein(s) expression and prompts the disruption of the cytoskeletal framework which causes the axonal degeneration of peripheral nerves (Vahidnia et al., 2008). Various studies in patients with As-induced neuropathy have displayed a decreased velocity in nerve conduction in the peripheral nerves, which is a common sign of axonal degeneration (Jomova et al., 2011). The declined activity of acetylcholinesterase induced the cholinergic crisis, which could be linked to damage to the central nervous system or peripheral neuropathy. Moreover, studies performed in hippocampal and subventricular progenitor/stem cells of humans have shown biphasic reactions of adult neurogenesis to cortisol; particularly the enhanced concentration of cortisol that impedes the differentiation and proliferation mediated by the glucocorticoid receptor. The inorganic and organic form of As at environmentally relevant concentrations shows effects such as reduced cell viability and apoptosis (Watcharasit et al., 2007; Garkal and Avachat, 2022; Chivate et al., 2021). The summary of studies demonstrating arsenic-induced neurotoxicity in biological models as depicted in Table 2.

Various experimental models have been developed to understand how arsenic exposure causes these different outcomes. However, converting the laboratory studies of arsenic toxicology to human health is challenging due to inaccurate dose conversion between in vitro, murine, and human exposures, and species-specific metabolic differences. Diseases associated with the lower exposures include coronary artery and ischemic heart disease, carotid atherosclerosis, microcirculatory defects, and prolonged QT intervals. Arsenic may increase associated vascular disease risk factors, such as systolic hypertension and diabetes. Increased systolic hypertension is consistent with the direct stimulatory effects of arsenic on vascular smooth muscle and decreased vasorelaxation. Nutritional, metabolic, and genetic susceptibilities to cardiovascular pathologies caused by arsenic implicate enhanced oxidant signalling as a primary mode of action. This appears as endothelial cell dysfunction and metabolic dysregulation from the loss of nitric oxide or gain of oxidant signalling (States et al., 2011; C.T.- Atherosclerosis, undefined, 2008; Engel and Smith, 1994).

4. Concluding remark and future perspective

Effects related to metalloid exposure are detrimental and therefore considered a major environmental hazard and health concern around the globe. Arsenic among them escalates the susceptibility to develop neurodegenerative disorders. The experimental studies raises the view of various molecular mechanisms involved in metal toxicity. Overall, the review highlights the potential toxicity of arsenic, its relevance to neurodegenerative diseases and developmental disorders. It is important to understand the underlying mechanisms extensively related to arsenic toxicity and to develop strategies for its environmental mitigation and prevention.

Table 2
*S*tudies related to arsenic induced developmental neurotoxicity.

Model	Dose and duration	Adverse effect	References
Human PS cells	–	Angiogenesis in human bronchial epithelium, Downregulation of miR199a-5p	(He et al., 2014)
Mouse Neuronal cells	–	Neuronal apoptosis, necrosis, and inhibited neurite growth in a dose-dependent manner	(Aung et al., 2013)
Human PC12 cells	3 μM arsenic trioxide for 24 hrs	Affect the later stages of differentiation and neurite elongation.	(Wang et al., 2010)
Human mesencephalic cell line 1RB3AN27	Sodium Arsenite at very low concentrations	Oxidative stress	(Felix et al., 2005)
Zebrafish	50 or 500 μg/L Water/iAsIII	activity (F2), anxiety (F0, F2), decreased exploratory behavior (F0, F2), reduced BDNF expression/ methylation (♂ F1), "H3K4 (Histone H3 lysine K4) tri-methylation (♀ F1, F2)	(Valles et al., 2020)
Mouse	10 mg/kg b.w./ d Water/iAsIII	Increased anxiety, decreased memory and learning (stronger in F1), decreased BChE in serum (stronger in F1), reduced SOD activity (stronger in F1)	(Biswas et al., 2020)
Mouse striatum	10 or 100 mg/L water/ iAsIII	Reduced body weight, decreased VGLUT2 and mGluR2	(Sung et al., 2019)
Mouse frontal cortex	85 mg/L water/ iAsIII	Decreased sociability and social novelty preference, reduced 5-HT receptor and BDNF	(Htway et al., 2019)
Rat cortex and hippocampus	7.5 and 200 mM water/ iAsIII	Effect on Hypomethylation (5 mC and 5 hmC), increased Nrf2, NAD+ , decreased BDNF, Egr1, SOD, NADH/NAD$^+$ ratio, DNMT, TET enzymes, learning and memory	(Du et al., 2018)
Mouse telencephalon	50 μg/L water/ iAsV	Increased expression of a master negative regulator of neural-lineage REST/NRSF	(Tyler et al., 2017)
Mouse telencephalon	50 μg/L water/ iAsV	Effect on GD 14 and GD 18, HSD11B1 methylation (♀), increased GSH/GSSH (higher in ♀)	(Allan et al., 2015)
Rat raphe nuclei	50 and 20 mg/kg water/ iAsIII	Decreased number of serotonin-positive cells	(Senuma et al., 2014)

Abbreviations: PND = Post natal day,♂= Male, ♀= Female, BChE = Butyrylcholinesterase, DSR = D-serine, SR = Serine racemase, DAAO = D-amino acid oxidase, VGLUT =Vesicular glutamate transporter, mGluR2 = Metabotropic glutamate receptor 2, 5-HT = 5-hydroxytryptamine receptors, BDNF = Brain derived neurotropic factor, 5-mC = 5-methylcytosine, 5-hmC = 5-hydroxymethylcytosine, DNMT = DNA methyltransferases, TET = Ten-eleven translocation enzymes, REST/NRSF = RE1-Silencing transcription factor/ Neuron-restrictive silencer factor, HSD11B1 = Hydroxysteroid 11-beta dehydrogenase 1, GD = Gestational day, b.w. = Body weight

Funding

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

References

Ali, H., Khan, E., 2018. What are heavy metals? Long-standing controversy over the scientific use of the term 'heavy metals'–proposal of a comprehensive definition. Toxicol. Environ. Chem. 100, 6–19. https://doi.org/10.1080/02772248.2017.1413652.

Ali, H., Khan, E., Ilahi, I., 2019. Environmental chemistry and ecotoxicology of hazardous heavy metals: Environmental persistence, toxicity, and bioaccumulation. J. Chem. 2019, 1–14. https://doi.org/10.1155/2019/6730305.

Aljerf, L., Williams, M., Ajong, A.B., Onydinma, U.P., Dehmchi, F., Pham, V.T., Bhatnagar, S., Belboukhari, N., 2021. Comparative study of the biochemical response behavior of some highly toxic minerals on selenosis in rats. Rev. De. Chim. 72, 9–18. https://doi.org/10.37358/rc.21.2.8415.

Allan, A.M., Hafez, A.K., Labrecque, M.T., Solomon, E.R., Shaikh, M.N., Zheng, X., Ali, A., 2015. Sex-dependent effects of developmental arsenic exposure on methylation capacity and methylation regulation of the glucocorticoid receptor system in the embryonic mouse brain. Toxicol. Rep. 2, 1376–1390. https://doi.org/10.1016/j.toxrep.2015.10.003.

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. Environ. Health Perspect. 114, 1193–1198. https://doi.org/10.1289/ehp.9008.

Andrewes, P., Kitchin, K.T., Wallace, K., 2003. Dimethylarsine and trimethylarsine are potent genotoxins in vitro. Chem. Res. Toxicol. 16, 994–1003. https://doi.org/10.1021/tx034063h.

Aposhian, H.V., 1997. Enzymatic methylation of arsenic species and other new approaches to arsenic toxicity. Annu Rev. Pharm. Toxicol. 37, 397–419. https://doi.org/10.1146/annurev.pharmtox.37.1.397.

Arora, N.K., Chauhan, R., 2021. Heavy metal toxicity and sustainable interventions for their decontamination. Environ. Sustain. 4, 1–3. https://doi.org/10.1007/s42398-021-00164-y.

Aung, K.H., Kurihara, R., Nakashima, S., Maekawa, F., Nohara, K., Kobayashi, T., Tsukahara, S., 2013. Inhibition of neurite outgrowth and alteration of cytoskeletal gene expression by sodium arsenite. Neurotoxicology 34, 226–235. https://doi.org/10.1016/j.neuro.2012.09.008.

Aung, K.H., Kyi-Tha-Thu, C., Sano, K., Nakamura, K., Tanoue, A., Nohara, K., Kakeyama, M., Tohyama, C., Tsukahara, S., Maekawa, F., 2016. Prenatal exposure to arsenic impairs behavioral flexibility and cortical structure in mice. Front Neurosci. 10, 1–12. https://doi.org/10.3389/fnins.2016.00137.

Balali-Mood, M., Naseri, K., Tahergorabi, Z., Khazdair, M.R., Sadeghi, M., 2021. Toxic mechanisms of five heavy metals: mercury, lead, chromium, cadmium, and arsenic. Front. Pharm. 12, 1–19. https://doi.org/10.3389/fphar.2021.643972.

Barchowsky, A., Dudek, E.J., Treadwell, M.D., Wetterhahn, K.E., 1996. Arsenic induces oxidant stress and NF-KB activation in cultured aortic endothelial cells. Free Radic. Biol. Med 21, 783–790. https://doi.org/10.1016/0891-5849(96)00174-8.

Bashir, S., Sharma, Y., Irshad, M., Gupta, S.D., Dogra, T.D., 2006. Arsenic-induced cell death in liver and brain of experimental rats. Basic Clin. Pharm. Toxicol. 98, 38–43. https://doi.org/10.1111/j.1742-7843.2006.pto_170.x.

Bhadauria, S., Flora, S.J.S., 2007. Response of arsenic-induced oxidative stress, DNA damage, and metal imbalance to combined administration of DMSA and monoisoamyl-DMSA during chronic arsenic poisoning in rats. Cell Biol. Toxicol. 23, 91–104. https://doi.org/10.1007/s10565-006-0135-8.

Biswas, S., Banna, H.U., Jahan, M., Anjum, A., Siddique, A.E., Roy, A., Nikkon, F., Salam, K.A., Haque, A., Himeno, S., Hossain, K., Saud, Z.A., 2020. In vivo evaluation of arsenic-associated behavioral and biochemical alterations in F0 and F1 mice. Chemosphere 245, 125619. https://doi.org/10.1016/j.chemosphere.2019.125619.

Bock, J., Wainstock, T., Braun, K., Segal, M., 2015. Stress in utero: prenatal programming of brain plasticity and cognition. Biol. Psychiatry 78, 315–326. https://doi.org/10.1016/j.biopsych.2015.02.036.

Bodaghi-Namileh, V., Sepand, M.R., Omidi, A., Aghsami, M., Seyednejad, S.A., Kasirzadeh, S., Sabzevari, O., 2018. Acetyl-L-carnitine attenuates arsenic-induced liver injury by abrogation of mitochondrial dysfunction, inflammation, and apoptosis in rats. Environ. Toxicol. Pharm. 58, 11–20. https://doi.org/10.1016/j.etap.2017.12.005.

C.T.- Atherosclerosis, undefined 2008, Cardiovascular disease in arsenic-exposed subjects living in the arseniasis-hyperendemic areas in Taiwan, Elsevier. (n.d.). https://www.sciencedirect.com/science/article/pii/S0021915008001056 (accessed September 16, 2023).

Chanda, S., Dasgupta, U.B., Guhamazumder, D., Gupta, M., Chaudhuri, U., Lahiri, S., Das, S., Ghosh, N., Chatterjee, D., Al, C.E.T., 2006. DNA hypermethylation of promoter of gene p53 and p16 in Arsenic-Exposed People with and without Malignancy, 89, 431–437. https://doi.org/10.1093/toxsci/kfj030.

Chandravanshi, L.P., Shukla, R.K., Sultana, S., Pant, A.B., Khanna, V.K., 2014. Early life arsenic exposure and brain dopaminergic alterations in rats. Int. J. Dev. Neurosci. 38, 91–104. https://doi.org/10.1016/j.ijdevneu.2014.08.009.

Chang, F., Lee, J.T., Navolanic, P.M., Steelman, L.S., Shelton, J.G., Blalock, W.L., Franklin, R.A., McCubrey, J.A., 2003. Involvement of PI3K/Akt pathway in cell cycle progression, apoptosis, and neoplastic transformation: a target for cancer chemotherapy. Leukemia 17, 590–603. https://doi.org/10.1038/sj.leu.2402824.

Chin-Chan, M., Navarro-Yepes, J., Quintanilla-Vega, B., 2015. Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. Front Cell Neurosci. 9, 1–22. https://doi.org/10.3389/fncel.2015.00124.

Chivate, A., Garkal, A., Hariharan, K., Mehta, T., 2021. Exploring novel carrier for improving bioavailability of Itraconazole: Solid dispersion through hot-melt extrusion. J. Drug Deliv. Sci. Technol. 63, 102541 https://doi.org/10.1016/j.jddst.2021.102541.

Cholanians, A.B., Phan, A.V., Ditzel, E.J., Camenisch, T.D., Lau, S.S., Monks, T.J., 2016. Arsenic induces accumulation of α-synuclein: implications for synucleinopathies and neurodegeneration. Toxicol. Sci. 153, 271–281. https://doi.org/10.1093/toxsci/kfw117.

Cui, X., Wakai, T., Shirai, Y., Hatakeyama, K., Hirano, S., 2006. Chronic oral exposure to inorganic arsenate interferes with methylation status of p16INK4a and RASSF1A and induces lung cancer in A/J mice. Toxicol. Sci. 91, 372–381. https://doi.org/10.1093/toxsci/kfj159.

Das, J., Ghosh, J., Manna, P., Sil, P.C., 2010. Protective role of taurine against arsenic-induced mitochondria-dependent hepatic apoptosis via the inhibition of PKCδ-JNK pathway. PLoS One 5, 1–19. https://doi.org/10.1371/journal.pone.0012602.

Del Razo, L.M., Quintanilla-Vega, B., Brambila-Colombres, E., Calderón-Aranda, E.S., Manno, M., Albores, A., 2001. Stress proteins induced by arsenic. Toxicol. Appl. Pharm. 177, 132–148. https://doi.org/10.1006/taap.2001.9291.

Dhas, N., Mehta, T., Sharma, S., Garkal, A., Yadav, D., Hariharan, K., Shamjetshabam, B., Khot, S., Kudarha, R., Bangar, P., Arbade, G., Kalyankar, P., 2021. Intranasal gene therapy for the treatment of neurological disorders. In: Direct Nose-to-Brain Drug Delivery. Elsevier, pp. 351–387. https://doi.org/10.1016/B978-0-12-822522-6.00017-5.

Dilda, P.J., Hogg, P.J., 2007. Arsenical-based cancer drugs. Cancer Treat. Rev. 33, 542–564. https://doi.org/10.1016/j.ctrv.2007.05.001.

Dixit, S., Mehra, R.D., Dhar, P., 2020. Effect of α-lipoic acid on spatial memory and structural integrity of developing hippocampal neurons in rats subjected to sodium arsenite exposure. Environ. Toxicol. Pharm. 75, 103323 https://doi.org/10.1016/j.etap.2020.103323.

Drobna, Z., Styblo, M., Thomas, D.J., 2009. An overview of arsenic metabolism and toxicity. Curr. Protoc. Toxicol. https://doi.org/10.1002/0471140856.tx0431s42.

Du, X., Tian, M., Wang, X., Zhang, J., Huang, Q., Liu, L., Shen, H., 2018. Cortex and hippocampus DNA epigenetic response to a long-term arsenic exposure via drinking water. Environ. Pollut. 234, 590–600. https://doi.org/10.1016/j.envpol.2017.11.083.

Engel, R.R., Smith, A.H., 1994. Arsenic in drinking water and mortality from vascular disease: An ecologic analysis in 30 counties in the united states. Arch. Environ. Health 49, 418–427. https://doi.org/10.1080/00039896.1994.9954996.

Engwa, G.A., Ferdinand, P.U., Nwalo, F.N., Unachukwu, M.N., 2019. Mechanism and health effects of heavy metal toxicity in humans. Mech. Health Eff. Heavy Met. Toxic. Hum. 23.

Escudero-Lourdes, C., 2016. Toxicity mechanisms of arsenic that are shared with neurodegenerative diseases and cognitive impairment: role of oxidative stress and inflammatory responses. Neurotoxicology 53, 223–235. https://doi.org/10.1016/j.neuro.2016.02.002.

Faita, F., Cori, L., Bianchi, F., Andreassi, M.G., 2013. Arsenic-induced genotoxicity and genetic susceptibility to arsenic-related pathologies. Int. J. Environ. Res. Public Health 10, 1527–1546. https://doi.org/10.3390/ijerph10041527.

Fatema, K., Shoily, S.S., Ahsan, T., Haidar, Z., Sumit, A.F., Sajib, A.A., 2021. Effects of arsenic and heavy metals on metabolic pathways in cells of human origin: similarities and differences. Toxicol. Rep. 8, 1109–1120. https://doi.org/10.1016/j.toxrep.2021.05.015.

Felix, K., Manna, S.K., Wise, K., Barr, J., Ramesh, G.T., 2005. Low levels of arsenite activates nuclear factor-κB and activator protein-1 in immortalized mesencephalic cells. J. Biochem. Mol. Toxicol. 19, 67–77. https://doi.org/10.1002/jbt.20062.

F. Firkin, H. Iland, protective effect of quercetin, (2013) 1–16.

Fu, Z., Xi, S., 2020. The effects of heavy metals on human metabolism. Toxicol. Mech. Methods 30, 167–176. https://doi.org/10.1080/15376516.2019.1701594.

Garkal, A., Avachat, A., 2022. Development and in-vitro in-vivo characterization of in-situ gelling sustained-release nevirapine suspension. J. Drug Deliv. Sci. Technol. 67, 102938 https://doi.org/10.1016/j.jddst.2021.102938.

Gutiérrez, C., Nahar, K., Rhaman, M.S., Parvin, K., Bardhan, K., Marques, D.N., García-Caparrós, P., Hasanuzzaman, M., 2022. Arsenic-induced oxidative stress and antioxidant defense in plants. Pages 179-209. 2 Stresses 2, 179–209. https://doi.org/10.3390/STRESSES2020013.

Hagenbuch, B., Dawson, P., 2004. The sodium bile salt cotransport family SLC10. Pflug. Arch. 447, 566–570. https://doi.org/10.1007/s00424-003-1130-z.

Hamadeh, H.K., 2002. Coordination of altered DNA repair and damage pathways in arsenite-exposed keratinocytes. Toxicol. Sci. 69, 306–316. https://doi.org/10.1093/toxsci/69.2.306.

He, J., Wang, M., Jiang, Y., Chen, Q., Xu, S., Xu, Q., Jiang, B.H., Liu, L.Z., 2014. Chronic arsenic exposure and angiogenesis in human bronchial epithelial Cells via the ROS/miR-199a-5p/HIF-1α/COX-2 pathway. Environ. Health Perspect. 122, 255–261. https://doi.org/10.1289/ehp.1307545.

He, Z.L., Yang, X.E., Stoffella, P.J., 2005. Trace elements in agroecosystems and impacts on the environment. J. Trace Elem. Med. Biol. 19, 125–140. https://doi.org/10.1016/j.jtemb.2005.02.010.

Healy, S.M., Casarez, E.A., Ayala-Fierro, F., Aposhian, H.V., 1998. Enzymatic methylation of arsenic compounds. V. arsenite methyltransferase activity in tissues of mice. Toxicol. Appl. Pharm. 148, 65–70. https://doi.org/10.1006/taap.1997.8306.

Htway, S.M., Sein, M.T., Nohara, K., Win-Shwe, T.T., 2019. Effects of developmental arsenic exposure on the social behavior and related gene expression in C3H adult male mice. Int. J. Environ. Res. Public Health 16. https://doi.org/10.3390/ijerph16020174.

Hu, Y., Yu, C., Yao, M., Wang, L., Liang, B., Zhang, B., Huang, X., Zhang, A., 2018. The PKCδ-Nrf2-ARE signalling pathway may be involved in oxidative stress in arsenic-induced liver damage in rats. Environ. Toxicol. Pharm. 62, 79–87. https://doi.org/10.1016/j.etap.2018.05.012.

Hughes, M.F., 2002. Arsenic toxicity and potential mechanisms of action. Toxicol. Lett. 133, 1–16. https://doi.org/10.1016/S0378-4274(02)00084-X.

Hughes, M.F., Devesa, V., Adair, B.M., Conklin, S.D., Creed, J.T., Styblo, M., Kenyon, E. M., Thomas, D.J., 2008. Tissue dosimetry, metabolism and excretion of pentavalent and trivalent dimethylated arsenic in mice after oral administration. Toxicol. Appl. Pharm. 227, 26–35. https://doi.org/10.1016/j.taap.2007.10.011.

Hughes, M.F., Beck, B.D., Chen, Y., Lewis, A.S., Thomas, D.J., 2011. Arsenic exposure and toxicology: a historical perspective. Toxicol. Sci. 123, 305–332. https://doi.org/10.1093/toxsci/kfr184.

Inesta-Vaquera, F., Navasumrit, P., Henderson, C.J., Frangova, T.G., Honda, T., Dinkova-Kostova, A.T., Ruchirawat, M., Wolf, C.R., 2021. Application of the in vivo oxidative stress reporter Hmox1 as mechanistic biomarker of arsenic toxicity. Environ. Pollut. 270, 116053 https://doi.org/10.1016/j.envpol.2020.116053.

Jomova, K., Jenisova, Z., Feszterova, M., Baros, S., Liska, J., Hudecova, D., Rhodes, C.J., Valko, M., 2011. Arsenic: toxicity, oxidative stress and human disease. J. Appl. Toxicol. 31, 95–107. https://doi.org/10.1002/jat.1649.

Jomova, K., Jenisova, Z., Feszterova, M., Baros, S., Liska, J., Hudecova, D., Rhodes, C.J., Valko, M., 2011. Arsenic: toxicity, oxidative stress and human disease. J. Appl. Toxicol. 31, 95–107. https://doi.org/10.1002/JAT.1649.

Jou, Y., Wang, S., Dai, Y., Chen, S., Shen, C., Lee, Y., Chen, L., Liu, Y., 2019. Gene expression and DNA methylation regulation of arsenic in mouse bladder tissues and in human urothelial cells. Oncol. Rep. https://doi.org/10.3892/or.2019.7235.

Kaur, R., 2023. Influence of heavy metal exposure on gut microbiota: recent advances. J. Biochem. Mol. Toxicol. 1–7. https://doi.org/10.1002/jbt.23485.

Lai, Y., Zhao, W., Chen, C., Wu, M., Zhang, Z., 2011. Role of DNA polymerase beta in the genotoxicity of arsenic. Environ. Mol. Mutagen. 52, 460–468. https://doi.org/10.1002/em.20643.

Lakkis, N.A., Musharafieh, U.M., Issa, H.G., Osman, M.H., 2023. Lung cancer and risk factors in lebanon: epidemiology, temporal trends, and comparison to countries from different regions in the world. Cancer Control 30, 1–18. https://doi.org/10.1177/10732748231169596.

Lee, C.-H., Wu, S.-B., Hong, C.-H., Chen, G.-S., Wei, Y.-H., Yu, H.-S., 2013. Involvement of mtDNA damage elicited by oxidative stress in the arsenical skin cancers. J. Invest. Dermatol. 133, 1890–1900. https://doi.org/10.1038/jid.2013.55.

Leslie, E.M., Haimeur, A., Waalkes, M.P., 2004. Arsenic transport by the human multidrug resistance protein 1 (MRP1/ABCC1). J. Biol. Chem. 279, 32700–32708. https://doi.org/10.1074/jbc.M404912200.

Li, D., Wei, Y., Xu, S., Niu, Q., Zhang, M., Li, S., Jing, M., 2018. A systematic review and meta-analysis of bidirectional effect of arsenic on ERK signaling pathway. Mol. Med. Rep. https://doi.org/10.3892/mmr.2018.8383.

Li, L., Chen, F., 2016. Oxidative stress, epigenetics, and cancer stem cells in arsenic carcinogenesis and prevention. Curr. Pharm. Rep. 2, 57–63. https://doi.org/10.1007/S40495-016-0049-Y.

Li, Y., Wang, M., Piao, F., Wang, X., 2012. Subchronic exposure to arsenic inhibits spermatogenesisand downregulates the expression of Ddx3y in testisand epididymis of mice. Toxicol. Sci. 128, 482–489. https://doi.org/10.1093/toxsci/kfs169.

Maekawa, F., Tsuboi, T., Oya, M., Aung, K.H., Tsukahara, S., Pellerin, L., Nohara, K., 2013. Effects of sodium arsenite on neurite outgrowth and glutamate AMPA receptor expression in mouse cortical neurons. Neurotoxicology 37, 197–206. https://doi.org/10.1016/j.neuro.2013.05.006.

Maiti, S., 2015. Arsenic-induced mutagenesis and carcinogenesis: a possible mechanism. Handb. Arsen. Toxicol. 233–279. https://doi.org/10.1016/B978-0-12-418688-0.00009-5.

Mann, K.K., Colombo, M., Miller, W.H., 2008. Arsenic trioxide decreases AKT protein in a caspase-dependent manner. Mol. Cancer Ther. 7, 1680–1687. https://doi.org/10.1158/1535-7163.MCT-07-2164.

Marafante, E., Vahter, M., Envall, J., 1985. The role of the methylation in the detoxication of arsenate in the rabbit. Chem. Biol. Inter. 56, 225–238. https://doi.org/10.1016/0009-2797(85)90008-0.

Marzo, T., Mendola, D.La, 2021. Strike a balance: between metals and non-metals, metalloids as a source of anti-infective agents. Inorg. (Basel) 9. https://doi.org/10.3390/inorganics9060046.

Masindi, V., Muedi, K.L., 2018. Environmental contamination by heavy metals. Heavy Met. https://doi.org/10.5772/intechopen.76082.

Medda, N., Patra, R., Ghosh, T.K., Maiti, S., 2020. Neurotoxic mechanism of arsenic: synergistic effect of mitochondrial instability, oxidative stress, and hormonal-neurotransmitter impairment. Biol. Trace Elem. Res. 198, 8–15. https://doi.org/10.1007/s12011-020-02044-8.

N. Medda, S.K. De, S. Maiti, Ecotoxicology and Environmental Safety Different mechanisms of arsenic related signaling in cellular proliferation, apoptosis and neoplastic transformation, 208 (2021).

Mochizuki, H., 2019. Arsenic neurotoxicity in humans. Int. J. Mol. Sci. 20 https://doi.org/10.3390/ijms20143418.

Mohammed Abdul, K.S., Jayasinghe, S.S., Chandana, E.P.S., Jayasumana, C., De Silva, P.M.C.S., 2015. Arsenic and human health effects: a review. Environ. Toxicol. Pharm. 40, 828–846. https://doi.org/10.1016/j.etap.2015.09.016.

Mukherjee, S., Mukhopadhyay, P.K., 2009. Studies on arsenic toxicity in male rat gonads and its protection by high dietary protein supplementation, Al Ameen. J. Med. Sci. 2, 73–77.

Muthumani, M., Prabu, S.M., 2012. Silibinin potentially protects arsenic-induced oxidative hepatic dysfunction in rats. Toxicol. Mech. Methods 22, 277–288. https://doi.org/10.3109/15376516.2011.647113.

Nesnow, S., Roop, B.C., Lambert, G., Kadiiska, M., Mason, R.P., Cullen, W.R., Mass, M.J., 2002. DNA damage induced by methylated trivalent arsenicals is mediated by reactive oxygen species. Chem. Res. Toxicol. 15, 1627–1634. https://doi.org/10.1021/tx025598y.

Ng, J.C., 2005. Environmental contamination of arsenic and its toxicological impact on humans. Environ. Chem. 2, 146–160. https://doi.org/10.1071/EN05062.

Niño, S.A., Morales-Martínez, A., Chi-Ahumada, E., Carrizales, L., Salgado-Delgado, R., Pérez-Severiano, F., Díaz-Cintra, S., Jiménez-Capdeville, M.E., Zarazúa, S., 2019. Arsenic exposure contributes to the bioenergetic damage in an Alzheimer's disease model. ACS Chem. Neurosci. 10, 323–336. https://doi.org/10.1021/acschemneuro.8b00278.

Nriagu, J.O., 1989. A global assessment of natural sources of atmospheric trace metals. Nature 338, 47–49. https://doi.org/10.1038/338047a0.

Patti, F., Fiore, M., Chisari, C.G., D'Amico, E., Lo Fermo, S., Toscano, S., Copat, C., Ferrante, M., Zappia, M., 2020. CSF neurotoxic metals/metalloids levels in amyotrophic lateral sclerosis patients: comparison between bulbar and spinal onset. Environ. Res 188, 109820. https://doi.org/10.1016/j.envres.2020.109820.

Prakash, C., Kumar, V., 2016. Chronic arsenic exposure-induced oxidative stress is mediated by decreased mitochondrial biogenesis in rat liver. Biol. Trace Elem. Res 173, 87–95. https://doi.org/10.1007/s12011-016-0622-6.

Prakash, C., Soni, M., Kumar, V., 2016. Mitochondrial oxidative stress and dysfunction in arsenic neurotoxicity: a review. J. Appl. Toxicol. 36, 179–188. https://doi.org/10.1002/jat.3256.

Prakash, C., Chhikara, S., Kumar, V., 2022. Mitochondrial dysfunction in arsenic-induced hepatotoxicity: pathogenic and therapeutic implications. Biol. Trace Elem. Res 200, 261–270. https://doi.org/10.1007/s12011-021-02624-2.

Rachman, T., 2018. Mechanisms of arsenic toxicity in humans. Angew. Chem. Int. Ed. 6 (11), 951–952, 10–27.

Rahaman, Md.S., Rahman, Md.M., Mise, N., Sikder, Md.T., Ichihara, G., Uddin, Md.K., Kurasaki, M., Ichihara, S., 2021. Environmental arsenic exposure and its contribution to human diseases, toxicity mechanism and management. Environ. Pollut. 289, 117940 https://doi.org/10.1016/j.envpol.2021.117940.

Ratnaike, R.N., 2003. Acute and chribuc arsebuc toxicity. Post. Med. J. 391–397.

Rehman, K., Fatima, F., Akash, M.S.H., 2019. Biochemical investigation of association of arsenic exposure with risk factors of diabetes mellitus in Pakistani population and its validation in animal model. Environ. Monit. Assess. 191, 511. https://doi.org/10.1007/s10661-019-7670-2.

Renu, K., Saravanan, A., Elangovan, A., Ramesh, S., Annamalai, S., Namachivayam, A., Abel, P., Madhyastha, H., Madhyastha, R., Maruyama, M., Balachandar, V., Valsala Gopalakrishnan, A., 2020. An appraisal on molecular and biochemical signalling cascades during arsenic-induced hepatotoxicity. Life Sci. 260, 118438 https://doi.org/10.1016/j.lfs.2020.118438.

Rosenblatt, A.E., Burnstein, K.L., 2009. Inhibition of androgen receptor transcriptional activity as a novel mechanism of action of arsenic. Mol. Endocrinol. 23, 412–421. https://doi.org/10.1210/me.2008-0235.

Saint-Jacques, N., Parker, L., Brown, P., Dummer, T.J., 2014. Arsenic in drinking water and urinary tract cancers: a systematic review of 30 years of epidemiological evidence. Environ. Health 13, 44. https://doi.org/10.1186/1476-069X-13-44.

Sajed Ali, S., Acharyya, N., Maiti, S., 2016. Promising anti-oxidative therapeutic potentials of edible freshwater snail Bellamya bengalensis extract against arsenic-induced rat hepatic tissue and DNA damage. Int. J. Aquat. Biol. 4, 239–255.

Sánchez-Peña, L.C., Petrosyan, P., Morales, M., González, N.B., Gutiérrez-Ospina, G., Del Razo, L.M., Gonsebatt, M.E., 2010. Arsenic species, AS3MT amount, and AS3MT gen expression in different brain regions of mouse exposed to arsenite. Environ. Res 110, 428–434. https://doi.org/10.1016/j.envres.2010.01.007.

Sen, S., 2002. Amplification/overexpression of a mitotic kinase gene in human bladder cancer. Cancer Knowl. Environ. 94, 1320–1329. https://doi.org/10.1093/jnci/94.17.1320.

Senuma, M., Mori, C., Ogawa, T., Kuwagata, M., 2014. Prenatal sodium arsenite affects early development of serotonergic neurons in the fetal rat brain. Int. J. Dev. Neurosci. 38, 204–212. https://doi.org/10.1016/j.ijdevneu.2014.09.005.

Shafiuddin Ahmed, A.S., Sultana, S., Habib, A., Ullah, H., Musa, N., Mahfujur Rahman, M., Shafiqul Islam Sarker, M., 2019. Bioaccumulation of heavy metals in commercially important fish species from the tropical river estuary suggests higher potential child health risk than adults. BioRxiv 1–21. https://doi.org/10.1101/681478.

Shao, Y., Zhao, H., Wang, Y., Liu, J., Li, J., Chai, H., Xing, M., 2018. Arsenic and/or copper caused inflammatory response via activation of inducible nitric oxide synthase pathway and triggered heat shock protein responses in testis tissues of chicken. Environ. Sci. Pollut. Res. 25, 7719–7729. https://doi.org/10.1007/s11356-017-1042-7.

Shi, H., Shi, X., Liu, K.J., 2004. Oxidative mechanism of arsenic toxicity and carcinogenesis. Mol. Cell Biochem 255, 67–78. https://doi.org/10.1023/B:MCBI.0000007262.26044.E8.

Shi, J., Cai, Y., 2020. Environmental chemistry and toxicology of heavy metals. Ecotoxicol. Environ. Saf. 202, 110926 https://doi.org/10.1016/j.ecoenv.2020.110926.

Srivastava, P., Yadav, R.S., Chandravanshi, L.P., Shukla, R.K., Dhuriya, Y.K., Chauhan, L.K.S., Dwivedi, H.N., Pant, A.B., Khanna, V.K., 2014. Unraveling the mechanism of neuroprotection of curcumin in arsenic induced cholinergic dysfunctions in rats. Toxicol. Appl. Pharm. 279, 428–440. https://doi.org/10.1016/j.taap.2014.06.006.

States, J.C., Barchowsky, A., Cartwright, I.L., Reichard, J.F., Futscher, B.W., Lantz, R.C., 2011. Arsenic toxicology: translating between experimental models and human pathology. Environ. Health Perspect. 119, 1356. https://doi.org/10.1289/EHP.1103441.

Sun, X., Li, S., He, Y., Zhao, H., Wang, Y., Zeng, X., Xing, M., 2017. Arsenic-induced testicular toxicity in Gallus gallus: Expressions of inflammatory cytokines and heat shock proteins. Poult. Sci. 96, 3399–3406. https://doi.org/10.3382/ps/pex073.

Sung, K., Kim, M., Kim, H., Hwang, G.W., Kim, K., 2019. Perinatal exposure to arsenic in drinking water alters glutamatergic neurotransmission in the striatum of C57BL/6 mice. Biol. Trace Elem. Res. 187, 224–229. https://doi.org/10.1007/s12011-018-1374-2.

Susan, A., Rajendran, K., Sathyasivam, K., Krishnan, U.M., 2019. An overview of plant-based interventions to ameliorate arsenic toxicity. Biomed. Pharmacother. 109, 838–852. https://doi.org/10.1016/j.biopha.2018.10.099.

Tam, L.M., 2020. Repair. Chem. Res. Toxicol. 33, 709–726. https://doi.org/10.1021/acs.chemrestox.9b00464.Molecular.

Tchounwou, P.B., Yedjou, C.G., Patlolla, A.K., Sutton, D.J., 2012. Heavy Met. Toxic. Environ. https://doi.org/10.1007/978-3-7643-8340-4.

Thomas, D.J., Li, J., Waters, S.B., Xing, W., Adair, B.M., Drobna, Z., Devesa, V., Styblo, M., 2007. Arsenic (+3 oxidation state) methyltransferase and the methylation of arsenicals. Exp. Biol. Med. 232, 3–13.

Tolins, M., Ruchirawat, M., Landrigan, P., 2014. The developmental neurotoxicity of arsenic: Cognitive and behavioral consequences of early life exposure. Ann. Glob. Health 80, 303–314. https://doi.org/10.1016/j.aogh.2014.09.005.

Trouba, K.J., Wauson, E.M., Vorce, R.L., 2000. Sodium arsenite-induced dysregulation of proteins involved in proliferative signaling. Toxicol. Appl. Pharm. 164, 161–170. https://doi.org/10.1006/taap.1999.8873.

Tyler, C.R., Labrecque, M.T., Solomon, E.R., Guo, X., Allan, A.M., 2017. Prenatal arsenic exposure alters REST/NRSF and microRNA regulators of embryonic neural stem cell fate in a sex-dependent manner. Neurotoxicol. Teratol. 59, 1–15. https://doi.org/10.1016/j.ntt.2016.10.004.

Vahidnia, A., Van Der Voet, G.B., Wolff, F.A.De, 2007. Arsenic neurotoxicity - a review. Hum. Exp. Toxicol. 26, 823–832. https://doi.org/10.1177/0960327107084539.

Vahidnia, A., Romijn, F., van der Voet, G.B., de Wolff, F.A., 2008. Arsenic-induced neurotoxicity in relation to toxicokinetics: effects on sciatic nerve proteins. Chem. Biol. Inter. 176, 188–195. https://doi.org/10.1016/j.cbi.2008.07.001.

Valles, S., Hernández-Sánchez, J., Dipp, V.R., Huerta-González, D., Olivares-Bañuelos, T.N., González-Fraga, J., Bardullas, U., 2020. Exposure to low doses of inorganic arsenic induces transgenerational changes on behavioral and epigenetic markers in zebrafish (Danio rerio). Toxicol. Appl. Pharm. 396, 115002 https://doi.org/10.1016/j.taap.2020.115002.

Wadgaonkar, P., Chen, F., 2021. Connections between endoplasmic reticulum stress-associated unfolded protein response, mitochondria, and autophagy in arsenic-induced carcinogenesis. Semin. Cancer Biol. 76, 258–266. https://doi.org/10.1016/J.SEMCANCER.2021.04.004.

Wang, X., Meng, D., Chang, Q., Pan, J., Zhang, Z., Chen, G., Ke, Z., Luo, J., Shi, X., 2010. Arsenic inhibits neurite outgrowth by inhibiting the LKB1-AMPK signaling pathway. Environ. Health Perspect. 118, 627–634. https://doi.org/10.1289/ehp.0901510.

Wang, Y., Yang, X., Yu, H., Wang, H., Qi, Y., Geng, M., 2020. Effects of arsenic exposure on d-serine metabolism in the hippocampus of offspring mice at different developmental stages. Arch. Toxicol. 94, 77–87. https://doi.org/10.1007/s00204-019-02616-1.

Watanabe, T., Hirano, S., 2013. Metabolism of arsenic and its toxicological relevance. Arch. Toxicol. 87, 969–979. https://doi.org/10.1007/s00204-012-0904-5.

Watcharasit, Piyajit, Thiantanawat1, Apinya, Satayavivad, Jutamaad, 2007. GSK3 promotes arsenite-induced apoptosis via facilitation of mitochondria disruption. J. Appl. Toxicol. 27, 511–518. https://doi.org/10.1002/jat.

Yusuf, A.A., Dankwa Ampah, J., Elahi, M., Soudagar, M., Veza, I., Kingsley, U., Afrane, S., Jin, C., Liu, H., Elfasakhany, A., Buyondo, K.A., 2022. Effects of hybrid nanoparticle additives in n-butanol/waste plastic oil/ diesel blends on combustion, particulate and gaseous emissions from diesel engine evaluated with entropy-weighted PROMETHEE II and TOPSIS: environmental and health risks of plastic waste. Energy Convers. Manag. 264, 115758 https://doi.org/10.1016/j.enconman.2022.115758.

Yusuf, A.A., Dankwa Ampah, J., Veza, I., Atabani, A.E., Hoang, A.T., Nippae, A., Powoe, M.T., Afrane, S., Yusuf, D.A., Yahuza, I., Lr,) Yusuf, A.A., 2023. Investigating the influence of plastic waste oils and acetone blends on diesel engine combustion, pollutants, morphological and size particles: dehalogenation and catalytic pyrolysis of plastic waste. Energy Convers. Manag. 291, 117312 https://doi.org/10.1016/j.enconman.2023.117312.

Zhang, R.Y., Tu, J.B., Ran, R.T., Zhang, W.X., Tan, Q., Tang, P., Kuang, T., Cheng, S.Q., Chen, C.Z., Jiang, X.J., Chen, C., Han, T.L., Zhang, T., Cao, X.Q., Peng, B., Zhang, H., Xia, Y.Y., 2020. Using the metabolome to understand the mechanisms linking chronic arsenic exposure to microglia activation, and learning and memory impairment. Neurotox. Res. https://doi.org/10.1007/s12640-020-00286-x.

Zhao, P., Guo, Y., Zhang, W., Chai, H., Xing, H., Xing, M., 2017. Neurotoxicity induced by arsenic in Gallus gallus: regulation of oxidative stress and heat shock protein

response. Chemosphere 166, 238–245. https://doi.org/10.1016/j.chemosphere.2016.09.060.

Zhou, Y., Hileman, E.O., Plunkett, W., Keating, M.J., Huang, P., 2003. Free radical stress in chronic lymphocytic leukemia cells and its role in cellular sensitivity to ROS-generating anticancer agents. Blood 101, 4098–4104. https://doi.org/10.1182/blood-2002-08-2512.

Zhu, J., Chen, Z., Lallemand-Breitenbach, V., De Thé, H., 2002. How acute promyclocytic leukaemia revived arsenic. Nat. Rev. Cancer 2, 705–713. https://doi.org/10.1038/nrc887.