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Nitish Kumar
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# Arsenic Toxicity Remediation: Biotechnological Approaches

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# Arsenic Toxicity Remediation: Biotechnological Approaches

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# Chapter 1
# The Journey of Arsenic from Soil to Plant


**Aritri Laha, Sudip Sengupta, Jajati Mandal, Kallol Bhattacharyya, and Somnath Bhattacharyya**

**Abstract** The presence of Arsenic (As) in food is a serious human health hazard. The primary pathway of As is mediated by dietary uptake. The problem warrants more severe attention in countries of South Eastern Asia, especially India, Bangladesh, China, etc., because of the high population density. A coordinated study effort is necessary to understand the fluctuations of the metalloid throughout the soil–plant system as well as the ability of plants to naturally absorb, transfer, and retain As in edible parts. Numerous elements in the metalloid's natural habitat, soil, affect its chemistry, occurrence, chemical species, etc. Several transporters in the plant system can enable the entry of the contaminant from the root to shoot, and thereafter the xylem and phloem mediate the As uptake in the grain. The organic form of arsenic, especially DMA(V) has higher mobility allowing it to accumulate in edible grains in amounts much higher than the inorganic forms of As. Particular emphasis has also been provided to establish strategies to simulate the uptake of the metalloid in the edible grains through the soil. This chapter's major goal is to identify the As pathway in the soil–plant system, final accumulation in edible grain, and draw strategic approaches to reduce such uptake in the plant system.

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## 1.1 Introduction

Metalloid arsenic (As) has caused serious apprehension for environment and human health. More than 70 countries throughout the world have this metalloid in their groundwater (Zhao et al. 2010). As groundwater pollution has been recorded from numerous nations, the worst issues being in Asia, specifically Bangladesh, West Bengal, India, China, and Taiwan (Sengupta et al. 2022, 2023a). Broader exposure to it has become a global public health issue affecting millions worldwide.

The toxic inorganic and organic forms of arsenic exist, with arsenite (AsIII) constituting the majority species in paddy fields (63% of all As), followed by arsenate (AsV, 36%) and methylated forms (Abedin et al. 2002). The regular physiological functions of the plants are hampered when specific As forms enter through particular transporter proteins. Elevated As levels in plants have an impact on phosphate metabolism, protein activity, and catalytic processes. In addition to these, high As can cause lower root extension, chlorosis, shrinkage, and necrosis, severely reduced biomass accumulation, and lower fertility, yield, and grain output. Even under more elevated As due to induced stress conditions, plants may develop reactive oxygen species (ROS), which can damage membranes, cause general protein and lipid oxidation, and even damage DNA (Awasthi et al. 2017).

Metalloids accumulate in soils as a result of both anthropogenic and natural (geochemical) processes, including mining operations, the use of insecticides containing As, irrigation of crops with As-polluted water, and fertilization with municipal solid wastes (Meharg et al. 1992). Arsenic is categorized as a class I human carcinogen by the US Environmental Protection Agency (EPA) (Mandal et al. 2021; Sengupta et al. 2021), which can have significant health consequences, such as skin cancers, lungs, bladder, liver, numerous other cardiovascular, neurological, hematological, and respiratory diseases. Arsenate (AsV) and arsenite (AsIII), two inorganic As species, are highly cytotoxic to humans and can cause cancer and hyperkeratosis of the skin (Awasthi et al. 2017).

As-contaminated groundwater was considered the major pathway of human arsenic exposure. However, current study have telled that food crops, especially rice, can be a potential route of human exposure (Sengupta et al. 2023a, b; Mandal et al. 2023). In the groundwater system, it is primarily found in the inorganic forms of arsenate and arsenite, with very few levels of methylated arsenic-species.

Diets based on plants and animals are another manner in which humans are exposed to As. Significant quantities of As are found in the shoot tissues and grains of rice produced on polluted soil. Because rice straw has a considerably greater As concentration than grains (Bhattacharya et al. 2010), it can cause arsenic to build up in livestock, which can enter the human food chain. Arsenic solubility and availability to plants can be altered by altering plant growth situations through water management techniques and raising the quantity of other mineral nutrients in soil solution

(Bhattacharyya and Sengupta 2020; Bhattacharyya et al. 2021). The exchangeable percentage of As can be altered by certain mineral nutrients, such as phosphorus (P), silicon (Si), iron (Fe), and sulfur (S), which can lower the arsenic concentration in the soil solution.

## 1.2 Origin and Forms of Arsenic in Soil and Groundwater

Four important hypotheses for the mobilization and transportation of arsenic in groundwater have been put forth in an effort to identify the root causes of the problem with groundwater As (Bhattacharya et al. 2015). These hypotheses include oxidation of pyrite, competitive ion exchange, reductive dissolution of iron oxyhydroxides, and reduction and reoxidation. Pyrite oxidation is the primary underlying process causing the widespread pollution of the alluvial plains in Eastern India and Bangladesh. The competitive ion exchange theory deals with the competition among the As oxyanions and phosphate ions that decipher the release of arsenic in the aquifers (Fakhreddine et al. 2015). But the principle of reductive dissolution of metal oxides and Fe hydroxides, which releases As, is the main reason for As contamination in Bangladesh and India. The reduction and reoxidation theory is the fourth explanation for the As menace. Although this combination of processes makes As immobile, a constrained environment prevents this process from making arsenic bioavailable (Shukla et al. 2020). Arsenic mobilization from arsenic-bearing sediments to the groundwater aquifer is thought to occur when the subsurface aquifer is anoxic, according to the background information on As pollution. A large number of As-bearing minerals are present in the environment, including arsenical pyrite (FeAsS), realgar (AsS), and orpiment ($As_2S_3$) (Khosravi et al. 2019). Further anthropogenic contributions like As-based pesticides, herbicides, wood preservatives, mining and smelting, and coal combustion processes also build up As in soil (Hussain et al. 2021).

There are both inorganic and organic forms of arsenic in the environment. The most common inorganic form of as that is phyto-available is arsenate (AsV). It exists in four forms in an aqueous solution based on pH: $H_3AsO_4$, $H_2AsO_4^-$, $HAsO_4^{2-}$, and $AsO_4^{3-}$. Similarly, As (III) exists in five forms: $H_4AsO_3^+$, $H_3AsO_3$, $H_2AsO_3^-$, $HAsO_3^{2-}$, and $AsO_3^{3-}$. The toxicity follows the order: arsine (−3) > organo-arsine compounds > arsenites ($As^{3+}$) and oxides ($As^{3+}$) > arsenate ($As^{5+}$) > arsonium metals (+1) > native arsenic metal (0) (Sanyal et al. 2015).

## 1.3 As Occurrence in Soil as Affected by Various Factors

A number of variables, particularly the kind of clays and soil organic matter, influence the transmission of As in its natural environment (Fig. 1.1). The amount of arsenic and other soil characteristics such as pH, organic C, CEC, amorphous Fe content, and sorption are different factors that affect how much As is retained in soils (Sengupta

et al. 2023a). The sorbed arsenic content rises with an increase in the soil free iron oxide, magnesium oxide, aluminium oxide, or clay content (Mandal et al. 2023). Carbonate-bearing minerals are important for As sorption in calcareous soils, when the pH exceeds 9. The formation of Ca bridges, the precipitation of calcium arsenates, the formation of soluble $Ca(H_2AsO_4)_2$, $CaAsO_4^-$, and $CaH_2AsO_4^+$ complexes, or any combination of these processes results in the Ca-based Adsorption of arsenic from soil on the surface of kaolinite (Cornie et al. 2003).

Arsenate adsorption reduces with increasing pH in soils with a pH of 8.5 or above, but arsenite adsorption increases with increasing pH. For arsenate, the adsorption maxima on FeOOH are located about pH 4.0, whereas they are located at pH 7.0 to 8.5 for arsenite (Fitz and Wenzel 2002). Jain and Loeppert (2000) also reported similar decrease in arsenate adsorption at higher pH values and undermined electrostatic repulsion among negatively charged iron oxide surface sites and arsenate species ($H_2AsO_4^-$, $HAsO_4^{2-}$). Majumdar and Sanyal (2003) observed that arsenate adsorption decreased with increasing pH, but only at lower concentrations of arsenate. This effect was reversible at higher equilibrium concentrations of arsenate, which may be related to changes in the electrostatic potential of colloidal soil surfaces with pH, solubility product principles, and the buffering effects of the used arsenate salt.

Soil-As and sediments are invariably held by oxides of Fe, Al, and Mn through inner-sphere complexes via a ligand exchange process, according to studies based on the chemical equilibrium of As in soil (Majumdar and Sanyal 2003). The redox potential of the soil has a significant impact on the sorption of arsenic. As is not very soluble at higher soil redox values (500–200 mV) and usually resides as As (V). As-bioavailability occurs from the solubility of iron oxyhydroxides at a redox potential of 0–100 mV (moderately decreased).

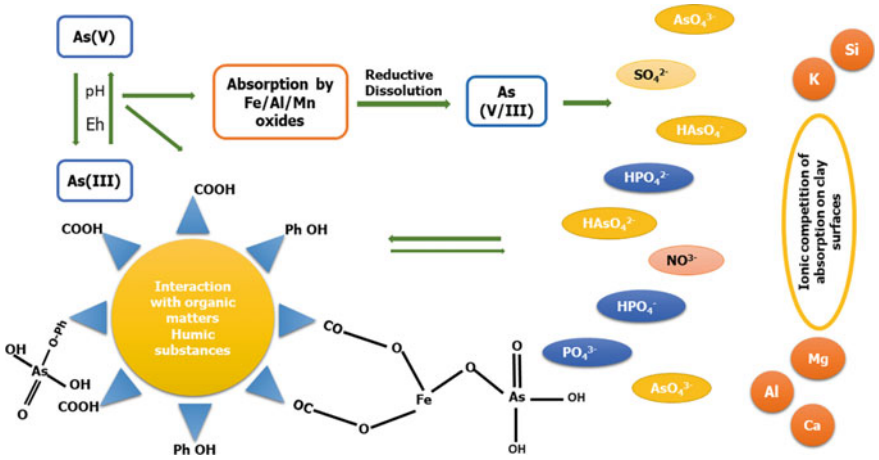


**Fig. 1.1** Arsenic pathway in soil

Numerous researchers have noted that the amount of phosphate in the soil affects arsenic adsorption. Due to the anion $AsO_4^{3-}$'s comparable chemical behaviour to that of $PO_4^{3-}$, they are in a competitive relationship (Liu et al. 2001). According to Lin and Puls (2000), long-term aging of the clay minerals leads to a more considerable degree of As bonding to the clay minerals as a result of an increase in levels caused by increased dehydrations and arsenic diffusion at the soil water interface to internal pores of the clay aggregates.

The application of organic matter can affect the availability of As in the soil–plant system. Humic acid (HA) and fulvic acid (FA) in soil organic fractions operate as an efficient As-accumulators by forming metal-humate complexes with varied stability (Sengupta et al. 2021, 2022). Through the activity of the arsenite oxidase enzyme, the soil microbial population also affects the microbial transformations of As in the soil. These reduce As stress and promote plant development (Laha et al. 2021).

## 1.4 Arsenic Uptake Mechanism Under an Anaerobic Environment

Rice is the leading food consumed by 50 percent of the world's population, and it also provides a significant amount of arsenic in the diet (Sengupta et al. 2021). Rice makes up over 50% of the total dietary intake for people in West Bengal and Bangladesh and up to 60% of Chinese people (Li et al. 2011). Rice is a hydrophilic plant and requires a lot of water to thrive, so it accumulates a higher quantity of As in grains than other cereals like wheat and barley (Williams et al. 2007). Groundwater tainted with arsenic has been widely used to irrigate paddy rice, which is mainly farmed during the dry season (Sengupta et al. 2021; Mandal et al. 2021).

On the surface of the roots, iron plaque (IP) production is a regular occurrence. It has a crystalline or amorphous structure and contains lepidocrocite, goethite, and iron hydroxides (Fe). Numerous studies demonstrate that IP contains mixed-phase Fe hydroxides; the crystalline and weakly crystalline phases are frequently found close together on aquatic roots. The local biogeochemical factors at particular places are what lead to the distinct phases that are present. Lepidocrocite [g-FeO(OH)] and siderite ($FeCO_3$) have been discovered in numerous studies, although ferrihydrite [$(Fe^{3+})_2O_3.5H_2O$] and goethite [a-FeO(OH)] is most prevalent (Tripathi et al. 2014). Like wetland plants, rice is a semi-aquatic plant with abundant aerenchyma in its roots. This aerenchyma permits oxygen to enter from shoots so that roots can breathe. A portion of the oxygen is released from the aerenchyma of rice roots to the rhizosphere in order to combat the anaerobic conditions in submerged soil. Radial oxygen loss (ROL), which varies from genotype to genotype and is influenced by soil waterlogging and/or $O_2$ availability, is what is meant by this (Colmer et al. 2006). Iron oxides and hydroxides precipitate on the root surface as a result of ferrous iron ($Fe^{2+}$) being oxidized by released oxygen to ferric iron ($Fe^{3+}$). This artifact is referred to as an iron plaque and is a distinctive orange color (Fig. 1.2). The oxides and hydroxides

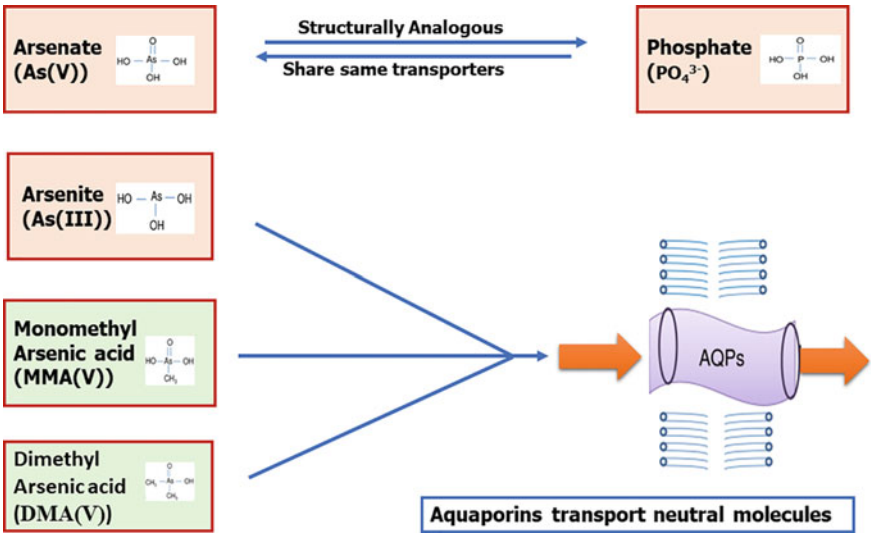


**Fig. 1.2** The graphical representation of different arsenic species and their uptake and transport through Aquaporins channel

of Fe are strong sorbents for As; hence, iron plaque becomes a major sink of As and contains even greater amounts of As than roots (Awasthi et al. 2017).

Rice plants absorb arsenic from the soil solution into the root cells by two different methods. The phosphate ($PO_4^{3-}$) transport route is crucial in the initial mechanism of absorption (Sengupta et al. 2023a). The phosphate transporters absorb arsenate from the soil solution and then deliver it to the plant's aerial portions (Wu et al. 2011). Aquaporin channels mediate the second method of As absorption in rice plants (Fig. 1.3); the As species that are taken up are As(III) (silicic acid analog) and methylated As species (Ma et al. 2008). The arsenite uptake in the rice root cells is highly favored by Si transporter as acidic forms of As(III) owing to its similarities with silicic acid; both possessing high pKa and also similar sized tetrahedral structure. After the root cell-mediated As(III) uptake, a portion of it is instantly released into the rhizosphere through the partial activity of the Lsi1 serving as a bidirectional channel; while the remaining As is sequestered into the root vacuoles and/or translocated to the shoots and thereafter it is distributed to various organs. Monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA), two methylated As species, comprise a small portion of the total soil As. As opposed to inorganic As species, the absorption processes of methylated species have not been the subject of as many studies. The plant often absorbs MMA and DMA through an intrinsic protein that resembles nodulin 26. This causes a high translocation from the root to the shoot, increasing phytotoxicity and improving herbicidal action. Although the translocation efficiency of inorganic arsenic is lower than that of methylated species, Raab et al. (2007) believed that inorganic As species (AsIII and AsV) have considerably larger absorption efficiency than methylated As species (DMA and MMA). It

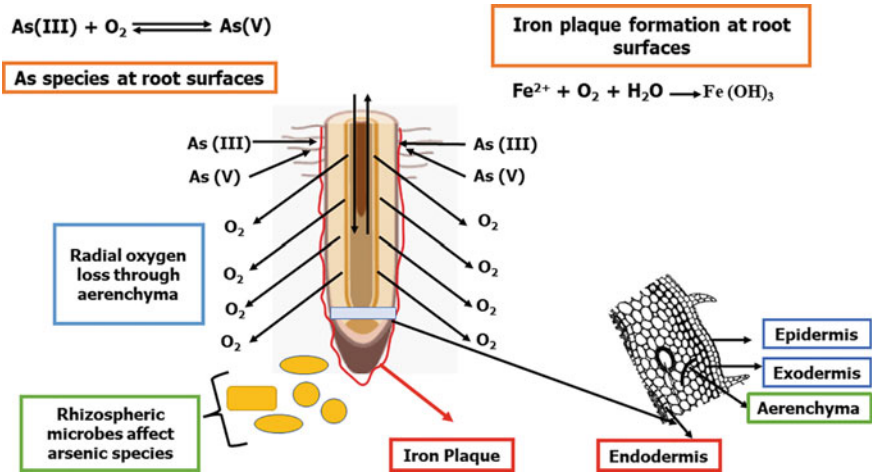


**Fig. 1.3** Arsenic species availability to paddy and subsequently arsenic uptake by roots are influenced by radial oxygen loss and iron plaque development on paddy root surface

is well known that inorganic As is far more hazardous than pentavalent methylated As by several orders of magnitude.

As(III) and DMA are the two main species in rice grains. However, comparing the two forms shows that the proportion of DMA between the two increases as the total As concentration in the grain rises. Additionally, studies have shown that DMA is less hazardous than its inorganic As equivalents (Syu et al. 2015). Independent of rice variety, further analysis of the various plant components of rice reveals that As accumulation in the root is between 28 and 75 times higher than that in the shoot and grain, respectively (Rahman et al. 2005). Arsenic is sequestered in nodal phloem cells, where it is retained at higher concentrations, and less of it travels to the grain. Different cultivable rice types are thought to over-express the vacuolar transporter OsABCC1 as a way to lower As concentrations in grain (Wang et al. 2015). In terms of mobility once more, methylated As species, particularly DMA, move more quickly toward rice grain than inorganic species (Carey et al. 2010), and the potential acquisition of As in aleurone, endosperm, and embryo are the leading causes of decreased seed setting and spikelet sterility, which ultimately results in yield losses (Zheng et al. 2013).

## 1.5 Uptake of as from the Soil to Edible Grains of Aerobic Crops

The cultivation of crops restricted to an aerobic environment faces the primary form of As as the oxidized As(V). Arsenate marks its entry into the plant system through P-cell channels that are usually present at the root level. After the entry, the As

is subsequently reduced to arsenite in the root system of maize plant through the formation of complexes with phytochelatins and thereafter has a vacuolar storage as arsenite-tris thiolate complex. The remaining portion of As, which has not been reduced, has an upward translocation into the aerial portion of the plant via the xylem and the cell phosphate transporter into the shoot and is most commonly stored as arsenite-tris glutathione complex (Rosas-Castor et al. 2014). In some cases, methylated inorganic-As are found, although it is debatable whether it is taken up in that form or has undergone detoxification (Abbas and Meharg 2008). In his study, Lomax et al. (2012) further escalated the debate by suggesting that plants cannot absorb methylated organic forms; instead, they are produced by microorganisms in the agricultural soil.

Maize plants generally have a lower translocation efficiency than other cereal crops (Su et al. 2009). The translocation of As to higher parts of the plants, especially the grains, is affected by several factors, including the soluble fraction of soil As, root-chelating agents, crop age, and soil type. Higher As concentration may often limit its translocation in the grains (Mallick et al. 2011). If the crop has a short period of growth, relatively high translocation efficiency may be observed. An elevated concentration of chelating agents in the root can curtail the As translocation, as evident from the sequestration of As on Fe oxide plaques and thiol ligands of maize roots. The presence of arbuscular mycorrhizal fungi (Yu et al. 2009) can effectuate a high reduction of As in the above-ground portions of the maize plant. The stage of a plant can also affect As-uptake (Zheng et al. 2011), as the total As was found to increase after flowering, and inorganic As has a greater incidence in caryopsis when the plant reaches the stage of grain development. Studies have revealed soil properties to play an important role in As translocation (Gulz et al. 2005), as evident from low As-transfer in finer-textured soil rather than coarse-textured one. Raab et al. (2007) in a study to reveal the species of As that is translocated in maize, showed the translocation pattern as DMA(V) > As(V) > MMA(V), though substantial arsenite recovery has also been reported.

## 1.6 Mobilization of as Through Root-Shoot-Grain

A fascinating viewpoint emerges if we contrast the intake and translocation of As-species. Compared to organic As, which exhibits the opposite pattern, inorganic arsenic has higher absorption but lower translocation (Sengupta et al. 2023a). Studies have also shown that DMA (V) only absorbs one-tenth as much as As(III) but that it relocates 100 times as much (Lomax et al. 2012). Therefore, As species follow the trend of DMA(V) > MMA(V) > inorganic arsenic in terms of mobility.

Arsenic moves from the root tissues to the above-ground plant (shoot) either directly (with no energy needed) or through the xylem sap through transporter-mediated As loading (Suriyagoda et al. 2018). Pi transporters are used for loading arsenate, while aquaporins are used for loading arsenite (Verbruggen et al. 2009). It was reported that phosphate transporter OsPht1;8, OsPHF1 (phosphate transporter

traffic facilitator 1), and PHR2 (phosphate starvation response 2) are responsible for xylem loading of arsenate, while arsenite uptake is facilitated by OsLsi2 (Ma et al. 2008) transporter or OsNRAMP1—natural resistance-associated macrophage protein transporter.

Phloem transporters in the upper stem nodes are highly crucial for translocation to the grain (Chen et al. 2015); however, the role of the xylem is less obvious since transpiration is restricted in this area. The phloem loading mechanism for arsenate is regulated by OsPHT1;8 and OsPHT1;1, while OsPTR7 has been reported for DMA(V) and MMA(V). Despite frequently being referred to as inositol transporters (INT), arsenite transporters for phloem are still unknown (Duan et al. 2016). Stem nodes mostly regulate the grain transport of As from the shoot, which is further accentuated by the symplastic discontinuity between the maternal (plant) and the filial (seed) tissues (Zhao et al. 2013). Despite the substantial uptake of DMA(V) in edible cereal grains, there may be some good news: organic DMA is significantly less toxic than inorganic versions, which lowers the dietary risk of the carcinogen (de Oliveira et al. 2020).

## 1.7 Conclusion and the Future Perspective of the Research

From a global perspective, the natural occurrence of arsenic in soils, sediments, and aquatic bodies, as a toxic metalloid has raised serious alarms over the decades. The current chapter primarily focuses on amalgamating plenty of research initiatives that have been undertaken to effectuate the understanding of As behavior in soil and the possible mechanism of uptake in edible grains. As the global population is increasing, the consumption of As-laden food materials is crippling people about their normal survival. In several areas, the level of As in water is several folds higher than the WHO-prescribed safe limit of the carcinogen. Using such water in irrigating crops in Asian countries further intensifies soil build-up and results in food chain-mediated human exposure. In this line, a concerted effort is required to assess As in groundwater thoroughly, its uptake-mediated dietary risk, and a predictive model based on the problem to draw possible lines and master plans to amend the arsenic-polluted water, soil, and other environmental compartments.

## References

Abbas MHH, Meharg AA (2008) Arsenate, arsenite and dimethyl arsinic acid (DMA) uptake and tolerance in maize (*Zea mays* L.). Plant Soil 304:277–289

Abedin MJ, Feldmann J, Meharg AA (2002) Uptake kinetics of arsenic species in rice plants. Plant Physiol 128:1120–1128

Awasthi S, Chauhan R, Srivastava S, Tripathi RD (2017) The journey of arsenic from soil to grain in rice. Front Plant Sci 8:1007

Bhattacharya P, Mukherjee A, Mukherjee AB (2015) Groundwater arsenic in India: sources, distribution, effects and alternate safe drinking water sources. In: Reference module in earth systems and environmental sciences. Elsevier B.V. The Netherlands, p 19

Bhattacharya P, Samal AC, Majumdar J, Santra SC (2010) Accumulation of arsenic and its distribution in rice plant (*Oryza sativa* L.) in Gangetic West Bengal, India. Paddy Water Environ 8:63–70

Bhattacharyya K, Sengupta S (2020) Arsenic management options in soil-plant-food chain. In: Prasad Bishun D, Jajati M, Kumar S, Sohane RK (eds) Proceedings of the national webinar on arsenic mitigation: a nexus approach, pp 17–23

Bhattacharyya K, Sengupta S, Pari A, Halder S, Bhattacharya P, Pandian BJ, Chinchmalatpure AR (2021) Characterization and risk assessment of arsenic contamination in soil–plant (vegetable) system and its mitigation through water harvesting and organic amendment. Environ Geochem Health 1–16

Carey AM, Scheckel KG, Lombi E, Newville M, Choi Y, Norton GJ, Charnock JM, Feldmann J, Price AH, Meharg AA (2010) Grain unloading of arsenic species in rice. Plant Physiol 152:309–319

Chen Y, Moore KL, Miller AJ, McGrath SP, Ma JF, Zhao FJ (2015) The role of nodes in arsenic storage and distribution in rice. J Exp Bot 66:3717–3724

Colmer TD, Cos MCH, Voesenek LACJ (2006) Root aeration in rice (*Oryza sativa*): evaluation of oxygen, carbon dioxide, and ethylene as possible regulators of root acclimatizations. New Phytol 170:767–777

Cornie S, Breeze D, Saada A, Barange P (2003) The influence of pH, electrolyte type, and surface coating on arsenic (V) adsorption onto kaolinites. Soil Sci Soc Am J 67:1127–1132

de Oliveira AC, Batista BL, Pegoraro C, Venske E, Viana VE (2020) Mechanisms of Arsenic uptake, transport, and in planta metabolism in rice. In: Arsenic in drinking water and food. Springer, Singapore, pp 371–389

Duan GL, Hu Y, Schneider S, McDermott J, Chen J, Sauer N, Rosen BP, Daus B, Liu Z, Zhu YG (2016) Inositol transporters AtINT2 and AtINT4 regulate arsenic accumulation in Arabidopsis seeds. Nat Plants 2:15202

Fakhreddine S, Dittmar J, Phipps D, Dadakis J, Fendorf S (2015) Geochemical triggers of arsenic mobilization during managed aquifer recharge. Environ Sci Technol 49(13):7802–7809

Fitz WJ, Wenzel WW (2002) Arsenic transformations in the soil-rhizosphere-plant system: fundamentals and potential application to phytoremediation. J Biotechnol 99:259–278

Gulz PA, Gupta SK, Schulin R (2005) Arsenic accumulation of common plants from contaminated soils. Plant Soil 272:337–347

Hussain MM, Bibi I, Niazi NK, Shahid M, Iqbal J, Shakoor MB, Ahmad A, Shah NS, Bhattacharya P, Mao K, Bundschuh J (2021) Arsenic biogeochemical cycling in paddy soil-rice system: interaction with various factors, amendments and mineral nutrients. In: Science of the total environment, p 145040

Jain R, Leoppert RH (2000) Arsenite and arsenate adsorption on ferrihydrite: kinetics, equilibrium, and adsorption envelopes. Environ Sci Technol 32:344

Khosravi R, Zarei M, Sracek O, Bigalke M (2019) Geochemical and hydrological controls of arsenic concentrations across the sediment–water interface at Maharlu Lake, Southern Iran. Appl Geochem 102:88–101

Laha A, Bhattacharyya S, Sengupta S, Bhattacharyya K, GuhaRoy S (2021) Investigation of arsenic-resistant, arsenite-oxidizing bacteria for plant growth promoting traits isolated from arsenic contaminated soils. Arch Microbiol 203:4677–4692

Li G, Sun GX, Williams PN, Nunes L, Zhu YG (2011) Inorganic arsenic in Chinese food and its cancer risk. Environ Int 37(7):1219–1225

Lin Z, Puls RW (2000) Adsorption, desorption and oxidation of arsenic affected by clay minerals and aging process. Environ Geol 39:753–759

Liu F, De Cristofaro A, Violante A (2001) Effect of pH phosphate and oxalate on the adsorption/desorption of arsenate on/from goethite. Soil Sci 166:197–208

Lomax C, Liu WJ, Wu L, Xue K, Xiong J, Zhou J, McGrath SP, Meharg AA, Miller AJ, Zhao FJ (2012) Methylated arsenic species in plants originate from soil microorganisms. New Phytol 193(3):665–672

Ma JF, Yamaji N, Mitani N, Xu X.Y, Su Y.H, McGrath S.P, Zhao F.J (2008) Transporters of arsenite in rice and their role in arsenic accumulation in rice grain. Proc Natl Acad Sci USA 105:9931–9935

Majumdar K, Sanyal SK (2003) pH-dependent arsenic sorption in an Alfisol and an Entisol of West Bengal. Agropedology 13:25–29

Mallick S, Sinam G, Sinha S (2011) Study on arsenate tolerant and sensitive cultivars of *Zea mays* L.: differential detoxification mechanism and effect on nutrients status. Ecotoxicol Environ Saf 74:1316–1324

Mandal J, Sengupta S, Sarkar S, Mukherjee A, Wood MD, Hutchinson SM, Mondal D (2021) Meta-analysis enables prediction of the maximum permissible arsenic concentration in Asian paddy soil. Front Environ Sci 9:760125

Mandal J, Jain V, Sengupta S, Rahman MA, Bhattacharyya K, Rahman MM, Golui D, Wood MD, Mondal D (2023) Determination of bioavailable arsenic threshold and validation of modelled permissible total arsenic in paddy soil using machine learning. J Environ Quality. https://doi.org/10.1002/jeq2.20452

Meharg AA, Macnair MR (1992) Suppression of the high affinity phosphate uptake system: a mechanism of arsenate tolerance in *Holcus lanatus* L. J Exp Bot 43:519–524

Raab A, Williams PN, Meharg A, Feldmann J (2007) Uptake and translocation of inorganic and methylated arsenic species by plants. Environ Chem 4:197–203

Rahman MM, Rahman MA, Miah MA (2005) Arsenic contamination in agricultural soil: effects on nutrient uptake and yield of rice (*Oryza sativa* L.). In: Third international conference on plants and environmental pollution (ICPEP - 3). Organized by International Society of Environmental Botanists and National Botanical Research Institute, 29th Nov–2nd Dec, Lucknow (India)

Rosas-Castor JM, Guzmán-Mar JL, Hernández-Ramírez A, Garza-González MT, Hinojosa-Reyes L (2014) Arsenic accumulation in maize crop (*Zea mays*): a review. Sci Total Environ 488:176–187

Sanyal SK, Gupta SK, Kukal SS, Jeevan Rao K (2015) Soil degradation, pollution and amelioration. In: Pathak H, Sanyal Sk, Takkar PN (eds), State of Indian Agriculture-Soil. National academy of agricultural sciences, New Delhi, pp 234–266

Sengupta S, Bhattacharyya K, Mandal J, Bhattacharya P, Halder S, Pari A (2021) Deficit irrigation and organic amendments can reduce dietary arsenic risk from rice: introducing machine learning-based prediction models from field data. Agric Ecosyst Environ 319:107516

Sengupta S, Bhattacharyya K, Mandal J, Chattopadhyay AP (2022) Complexation, retention and release pattern of arsenic from humic/fulvic acid extracted from zinc and iron enriched vermicompost. J Environ Manage 318:115531

Sengupta S, Roychowdhury T, Phonglosa A, Mandal J (2023a) Arsenic contamination in rice and the possible mitigation options. In: Niazi NK, Bibi I, Aftab T (eds) Global arsenic hazard. Environmental science and engineering. Springer, Cham

Sengupta S, Bhattacharyya K, Mandal J, Bhattacharya P, Chattopadhyay AP (2023b) Zinc and iron enrichment of vermicompost can reduce the arsenic load in rice grain: an investigation through pot and field experiments. J Cleaner Prod 138267. https://doi.org/10.1016/j.jclepro.2023.138267

Shukla A, Awasthi S, Chauhan R, Srivastava S (2020) The status of arsenic contamination in India. In: Arsenic in drinking water and food. Springer, Singapore, pp 1–12

Su YH, McGrath SP, Zhao FJ (2009) Rice is more efficient in arsenite uptake and translocation than wheat and barley. Plant Soil 328:27–34

Suriyagoda LDB, Dittert K, Lambers H (2018) Mechanism of arsenic uptake, translocation and plant resistance to accumulate arsenic in rice grains. Agric Ecosyst Environ 253:23–37

Syu CH, Huang CC, Jiang PY, Lee CH, Lee DY (2015) Arsenic accumulation and speciation in rice grains influenced by arsenic phytotoxicity and rice genotypes grown in arsenic-elevated paddy soils. J Hazard Mater 286:179–186

Tripathi RD, Tripathi P, Dwivedi S, Kumar A, Mishra A, Chauhan PS, Nautiyal CS et al (2014) Roles for root iron plaque in sequestration and uptake of heavy metals and metalloids in aquatic and wetland plants. Metallomics 6(10):1789–1800

Verbruggen N, Hermans C, Schat H (2009) Mechanisms to cope with arsenic or cadmium excess in plants. Curr Opin Plant Biol 12:364–372

Wang X, Peng B, Tan C (2015) Recent advances in arsenic bioavailability, transport, and speciation in rice. Environ Sci Pollut Res 22:5742–5750

Williams PN, Villada A, Deacon C, Raab A, Figuerola J, Green AJ (2007) Greatly enhanced arsenic shoot assimilation in rice leads to elevated grain levels compared to wheat and barley. Environ Sci Technol 41:6854–6859

Wu C, Ye Z, Shu W, Zhu Y, Wong M (2011) Arsenic accumulation and speciation in rice are affected by root aeration and variation of genotypes. J Exp Bot. https://doi.org/10.1093/jxb/erq462

Yu Y, Zhang S, Huang H, Luo L, Wen B (2009) Arsenic accumulation and speciation in maize as affected by inoculation with arbuscular mycorrhizal fungus *Glomus mosseae*. J Agric Food Chem 57:3695–3701

Zhao FJ, Zhu YG, Meharg AA (2013) Methylated arsenic species in rice: geographical variation, origin, and uptake mechanisms. Environ Sci Technol 47:3957–3966

Zhao K, Liu X, Xu J, Selim HM (2010) Heavy metal contaminations in a soil–rice system: identification of spatial dependence in relation to soil properties of paddy fields. J Hazard Mater 181:778–787

Zheng MZ, Li G, Sun GX, Shim H, Cai C (2013) Differential toxicity and accumulation of inorganic and methylated arsenic in rice. Plant Soil 365(1–2):227–238

Zheng MZ, Cai C, Hu Y, Sun GX, Williams PN, Cui HJ, Li G, Zhao FJ, Zhu YG (2011) Spatial distribution of arsenic and temporal variation of its concentration in rice. New Phytol 189(1):200–209

# Chapter 2
# Speciation of Arsenic in Environment: Biotransformation and Techniques


**Avinash Gaur and Surabhi Yadav**

**Abstract** Arsenic found in environmental segments like lithosphere, hydrosphere and in atmosphere in various inorganic and organic forms like Arsenate ($As^{V}$), Arsenite ($As^{III}$), Monomethylarsine (MMA), Dimethylarsine (DMA), Trimetylarsine (TMA, Gossiogas), Trimethylarsineoxide (TMAO), AB (Arsenobetaine), AC (Arsenocholine) etc. Some forms are toxic while others are less toxic. In this review, we studied about biotransformation of various organic and inorganic arsenic species in aqueous environment, soil and atmosphere. Marine organisms like fishes, lobsters, fungi, bacteria, cytoplasm of microorganisms, yeast, some enzymes like, ArsC, algae, genes like aos, aio, aox, photosynthetic microorganisms etc., do biotransformation of arsenic as oxidation and reduction in inorganic arsenic species and do methylation in organic arsenic. Many researchers proposed different pathways of arsenic biotransformations. Arsenic speciation generally completes in three steps i.e. extraction, separation, and detection. There are several techniques for arsenic extraction, separation and detection. Voltametric methods i.e. DPP (Differential pulse polarography), CSV (Cathodic stripping Voltametry), ASV (Anodic stripping Voltametry) and Hydride generation (HG) are the main techniques for extraction. Similarly for separation and detection chromatography are used with spectroscopic detection systems.

**Keywords** Arsenic biotransformation · Arsenic speciation · Methylation of arsenic · Speciation techniques

## Abbreviations

| | |
|---|---|
| AB | Arsenobetaine |
| AC | Arsenocholine |
| ASV | Anodic stripping Voltametry |
| CSV | Cathodic stripping Voltametry |

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|---|---|
| CZE | Capillary zone electrophoresis |
| CZE-UV | Capillary zone electrophoresis-Ultraviolet spectroscopy |
| DIN | Direct injector nebulizer |
| DMA | Dimethylarsine |
| DMAA | Dimethyl arsinoyl acetatic acid |
| DMAE | Dimethylarsenoylethanol |
| DPP | Differential pulse polarography |
| DPV | Differential pulse voltametry |
| GC- FID | Gas chromatography- Flame ionization detector |
| HPLC–HG–AAS | High performance liquid chromatography–Hydride generation–Atomic absorption spectroscopy |
| HPLC-ICP-MS | High performance liquid chromatography-Inductively coupled plasma- Mass spectrometry |
| HPLC-HG-MIP-AES | High performance liquid chromatography–Hydride generation Hydride generation–Microwave induced plasma-Atomic emmision spectroscopy |
| HPLC–USN–AFS | High performance–ultrasonic nebulizer–atomic fluorescence spectroscopy |
| HPLC–UV–HG–AAS | High performance–Ultraviolet–Hydride generation–Atomic absorption spectroscopy |
| HG | Hydride generation |
| HG-GC-PID | Hydride generation-Gas chromatography-photoionisation detection |
| IC-HG–AAS | Inductively coupled–hydride generation–atomic absorption spectroscopy |
| IEC–PID | Ion exchange chromatography–Potential induced degradation |
| ICP–AES | Inductively coupled plasma–Atomic emmision spectroscopy |
| ICP–MS | Inductively coupled plasma–mass spectrometry |
| LCFAB–MS | Liquid chromatography fast atom bombardment–Mass spectrometry |
| LNCT | Liquid-nitrogen-cooled trapping |
| LSV | Linear sweep voltammetry |
| MMA | Monomethylarsine |
| NPV | Normal pulse voltammetry |
| AQSTCV | Staircase voltammetry |
| SWV | Square wave voltammetry |
| TMA | Trimethylarsine |
| TMAO | Trimethylarsineoxide |

## 2.1 Introduction

Arsenic is 20th most abundant element on the earth's crust which is associated with sedimentary rocks of sulfide ores (National Research Council 1977; Boyle and Jonasson 1973). Emission of arsenic depends of some natural phenomena i.e. volcanic activity, biological activity, weathering and some anthropogenic input (Chilvers and Peterson 1987).The environmental behavior of arsenic is dependent on chemical and physical properties, biotransformation of arsenic, toxicity, and mobility. Unique heavy metalloid, arsenic is mostly poisonous in inorganic trivalent arsenite which also occurs in 0, +5, and −3 oxidation states in environment. Arsenic poisoning in ground water events is familiar to the world but the consequences of soil contamination are still unrevealed to the community, especially the people of contaminated countries (Cullen and Reimer 1989a, b).

Arsenic is present in soil in both inorganic and organic forms. The inorganic forms of arsenic are more prevalent than the organic forms. When inorganic arsenic enters the food chain, get methylated and forms less toxic organic forms like Monomethylarsine (MMA), Dimethyl arsine (DMA) and Trimethylarsine (TMA) (Kossoff and Hudson 2012; Srivastava et al. 2015). Trimethylarsine (TMA) is known as " Gosio gas" which is toxic and volatile arsenic species, produced by molds development on wallpaper coloured with arsenic pigments such as Copper arsenite or Scheele's green and Schweinfurt- green (copper arsenite + copper acetate) (Challenger 1942; Gossio 1893; Gossio 1901).

Besides these arsenic species, there are some other species which are known as Thiolated arsenicals viz. Monomethyl monothioarsonic acid ($MMMTA^V$), Dimethylarsinothioyl glutathione ($DMMTA^V(GS)$), Dimethylmonothioarsinic acid ($DMMTA^V$), Dimethyldithioarsinic acid ($DMDTA^V$) (Sun et al. 2016). Arsenosugars are Glycerol arsenosugar (arsenosugar- OH), Thio- arsenosugar glycerol (Thio-OH), Thio- arsenosugar phosphate (Thio-$PO_4$), phosphate arsenosugar (Arsenosugar $PO_4$), sulfonate-arsenosugar (Arsenosugar–$SO_3$), Thio-arsenosugar-sulfonate (Thio-$SO_3$), sulfate arsenosugar (Arsenosugar-SO4), Thio-arsenosugar sulfate (Thio-SO4), some Trimethylarsonium compounds like TMAsSugar-Sulfonate, TMAsSugar-Sulfate, TMAsSugar-glycerol, TMAsSugar-phosphate (Luvonga et al. 2020). There are some Arsenolipid compounds like Arsenosugar phospholipids i.e. AsPL958, AsPL978, AsPL1006, and Arsenic containing hydrocarbons i.e. AsHC332, AsHC360. (Glabonjat et al. 2020).

Now a day, various techniques are available to speciate the arsenic species in hydrosphere and lithosphere samples. This new arsenic speciation analysis improves knowledge about arsenic toxicity, biogeochemistry and metabolism and arsenic cycle in environment. The complete isolation of arsenic compounds is very challenging work (Jackson 2015). Therefore a simple and frequent method is necessary for the analysis of arsenic species in various matrices. From the exact determination of arsenic species in environment samples (i.e. water, soil, and plants), we get a help to accurate assessment of the harmful impacts caused by arsenic. In this way, for exact identification of various species of arsenic, appropriate pretreatment techniques are

necessary. Various studies have been done regarding speciation analysis of arsenic till now (Reid et al. 2020; Liu et al. 2018; Reis and Duarte 2018). Yet, this overview includes translocation of arsenic species in plants, soil, and water, arsenic biotransformation, methods of determination of speciation of arsenic and techniques of arsenic species like extraction techniques, separation techniques with their detection systems. This study will give wide discussion in the latest improvements in speciation of arsenic and challenges for further research.

## 2.2 Translocation of Arsenic Species in Environment

Speciation means determination of specific ions of any element in aqueous and other solutions. Arsenic in environment is mainly speciated into plants, soil and water. Thus, on this base we can categories arsenic speciation as arsenic speciation in plants, soil and water. Arsenic is reached into the environmental segments either anthropogenically or naturally. Its degradation from environmental segments is almost impossible. The availability of arsenic depends on speciation, geological source, oxidation state and other environmental factors (Pfeiffer et al. 2002; Jang et al. 2016). In earth crust arsenate ($As^{V}$) form present almost 60% and 20% in the form of arsenites, oxides, silicates and as elemental form and remaining 20% present as sulfonates and sulfides (Onishi and Wedepohl 1969).

### *2.2.1 Arsenic Speciation in Plants*

Although there is no need of arsenic in plants yet it's concentration in plants should be less than one mg/kg dry weight (Adriano 2001). Plants absorb both the organic and inorganic arsenic by different mechanisms. Inorganic arsenic reaches in plants by mainly two mechanisms. In first mechanism phosphate ($PO_4$) transporter uptake arsenate ($As^{V}$) from soil and transfer it into other parts of plants. This is called Phosphate transport pathway (Catarecha et al. 2007; Shin et al. 2004; Wu et al. 2011). In second mechanism aqua channels of plants roots absorbs arsenic species like DMA, MMA and $As^{III}$ silicic analog (Ma et al. 2008). $As^{III}$, in root cells of rice uses Si transporter due to its similarity with silicic acid. ACR2 (Arsenic reductase) also reduced $As^{V}$ into $As^{III}$ (Kumar et al. 2015). The detoxification of arsenate is obtained by forming complexes with thiol-rich peptides (Liu et al. 2010). The organic arsenic species such as DMA and MMA are found in soil in less quantity.

Raab et al. (2007) removed and translocated inorganic and methylated arsenic species by plants with the use of intrinsic protein of Oncokin. They found that organic arsenic species (methylated) like MMA and DMA are more absorbed in comparison to inorganic species like $As^{V}$ and $As^{III}$ while the translocation efficiency of methylated As species is less in comparison to inorganic species in plant stems. The reason of better translocation in methylated arsenic species in the roots may be

the decrease in formation of arsenic complex with the ligands like glutathione (Raab et al. 2007). In rice, $As^{III}$ and DMA are mostly found. Similarly MMA and $As^{V}$ are found either in lower concentration or may be undefined (Huang et al. 2012). Abedin and their companions gave the uptake kinetics of arsenic species in rice plants and showed that $As^{V}$, $As^{III}$ and DMA predominantly found in rice straw (Abedin et al. 2002).

### *2.2.2 Arsenic Speciation in Soil*

Various arsenic species in soil are present in the precipitated solids, free ions, absorbed on inorganic constituents or soil organic, exchangable and structural components of secondary and primary minerals (Shahid et al. 2017; Niazi et al. 2011). Both the organic and inorganic arsenic species are present in soil. Organic species are DMA and MMA while inorganic species are $As^{III}$ and $As^{V}$ in soil. The order of toxicity of arsenic species is DMA < MMA< $As^{V}$ < $As^{III}$. The transformation of arsenic in soil may be via adsorption, precipitation, dissolution, volatilisation, oxidation and reduction. The inorganic species like arsenite and arsenate Present in the form of arsenous acid or protonated arsenic acids (Sadiq et al. 1997). Arsenate and Arsenite are the main thermodynamically stable form in soil. They are present as $H_3AsO_3$, $H_2AsO_4^-$, $HAsO_4^-$. This existence of different forms of arsenic in soil mainly depends on redox potential, pH value, organic matter and texture of the surrounding environment. In oxidised soil (aerobic conditions) the arsenic present as $As^{V}$ and it is quickly adsorbed on Fe/Mn oxides/hydroxides and clay minerals. In paddy fields (reducing environment), $As^{III}$ dominates and its toxicity, solubility and mobility are almost sixty times that of $As^{V}$ (Khalid et al. 2017). Under anaerobic conditions arsenic present in the form of arsenic sulfate and allow to leave excess arsenic into the environment (Koyama 1975). Reduction and oxidation of As species takes place chemically and biologically in water and soil (Rhine 2006). In organic and alluvial soil arsenic concentration is higher while in sandy soil, arsenic concentration is very less (Mandal and Suzuki 2002). Arsenic fixation is seen on clay. Clay particles present in soil absorbed $As^{V}$ with neutral pH. At lower pH value arsenic forms compounds with iron (i.e. $FeAsO_4$) and alluminium *(*i.e. $AlAsO_4$). At neutral pH, $As^{V}$ present in the form of oxygen anions while $As^{III}$ gets a neutral charge at pH 7.0. It tends to the formation of $FeAsO_4$, $Mn_3(AsO_4)_2$ and $Ca_3(AsO_4)_2$ (Sadiq et al. 1982). As the pH value increases over 8.5 adsorption capacity of $As^{III}$ increases while $As^{V}$ decreases. About pH 4, the adsorption of arsenate is maximum on FeOOH (Mahimairaja et al. 2005). In reducing conditions, as $As^{V}$ reduced to $As^{III}$, it binds loosely to the hydroxide solids, thus bioavailability of arsenic increases (Marquez et al. 2011). On the other hand, organo-arsenic complex formed due the high arsenic sorption capacity and solubility of arsenic decreases in soil (Rahaman et al. 2011). Generally, arsenic reaches in soil via oxidation and hydrolysis of sulfide minerals (e.g. *Arsenopyrite)* and absorbed by $Fe(OH)_2$. Similarly phosphate plays an important role in absorption of arsenic from contaminated soil. A group of researchers

reported that in acidic soil which consists of iron oxides, $H_2PO_4$ do displacement of sixty percent absorbed trivalent arsenic and seventy percent pentavalent arsenic. Microbes present in soil affect the desorption/adsorption, bioavailability, solubility, mobility of arsenic with changing in chemical speciation of arsenic in soil. Due to the microbial activities dimethyl sulfoxide, pesticides of DMA, methylated arsenic compounds like DMA and MMA may be accumulated in soil (Willium et al. 2003; Mishra et al. 2017; Ayangbenro et al. 2017).

### *2.2.3 Arsenic Speciation in Water*

In water, arsenic may be present in either particulate or dissolved form. Arsenate ($As^V$) and arsenite ($As^{III}$) are most common forms of arsenic species i.e. $As_3O_4{}^{4-}$, $H_2AsO_4{}^-$, $HAsO_4{}^{2-}$ and $H_3AsO_3$ are also present in natural water (Wilkin et al. 2003). Aquatic organisms do biomethylation of arsenic, they reduce $As^V$ to soluble $As^{III}$ species (Bhattacharya et al. 2002). In seawater, $As^V$ considered as main form of arsenic. Beside this, MMA and DMA found in less quantity in seawater (Cabon and Cabon 2002).

## 2.3 Arsenic Biotransformation

Aquatic animals are able to stockpilling arsenic and they are capable to catalyse the oxidation of As (III) to As (V) and also including the Methylarsine formation via biomethylation reaction (Johnson and Braman 1975). McBride and Wolfe (1971) demonstrated methylarsine production under aerobic conditions by methogenic bacteria. They reported that $CH_3AsO(OH)_2$ (Methyl Arsenic acid) and dimethylarsinic acid act as intermidiate in this reductive methylation of dimethyl arsine from inorganic Arsenic. They also reported that under aerobic conditions Methanobacterium do methylation of Arsenic into Dimethyl arsine (McBride and Wolfe 1971). Saxena and Howard gave reaction of this methylation. In this reductive methylation reaction, first of all Arsenate gives arsenite by accepting two electrons. Now arsenite reacts with methylcobalamin (3+) and forms methylarsonic acid. Here methylcobalamin acts as methyl donor. Again methylcobalamin donates Methyl to methylarsonic acid yields to dimethylarsinic acid (Cacodylic acid). This dimethylarsinic acid accepts four electrons and gives finally trimethylarine (Saxena and Howard 1977; Kumaresan and Riyazuddin 2001) (Fig. 2.1).

Ridley et al. (1977) proposed the formation of methylarsonic acid and dimethylarsinic acid by the reaction of volatile arsines with molecular oxygen (Ridley et al. 1977). Generally in marine organisms, organic arsenic compounds are present but J.S. Edmonds isolated AB (Arsenobetaine) from rock lobster of western sea. This is isolated from the tail muscles of that lobster (Edmonds et al. 1977). Cox and Alexander (1973) reported that *Candida humicola* (a sewage fungi) transforms

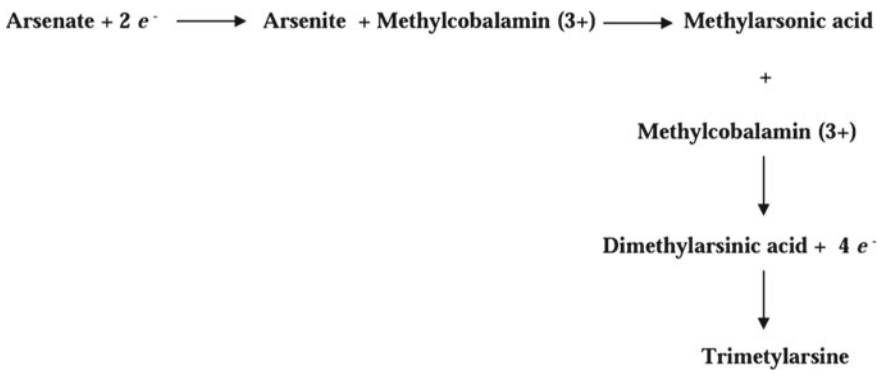


**Fig. 2.1** Reductive methylation reaction of arsenite to dimethylarsinic acid

trimetylarsine from Arsenate. Incubation of fungi with methyl arsonate, arsenite and dimethylarsine form trimetylarsine in lessar amount. These arsenic species act as intermediates in the alkylation and reduction As (V) (Arsenate) to trimetylarsine. (Cox and Alexander 1973).

A researcher reported that *Gliocaninum roseum, Penicilium* and *Candida humicola* are the fungi which are able to generate trimethylarsine, $(CH_3)_3As$, from the pesticides of dimethyl arsine and monomethylarsonate (Alexander 1974). Thayer and Brinckman reported that *C. Humicola* reduces the formation rate of trimethylarsine as molds get its resting form (Thayer and Brinckman 1982). The alkyl arsines which are toxic in nature have a different odour like garlic and have a property of the rapid oxidation into less toxicity in the atmosphere. Wood et al. (1974) demonstrated the biological cycle of arsenic in sediments, water and air. In sediments, arsenate reacts with bacteria and yields arsenite. The arsenite then yields methylarsonic acid with bacteria and finally dimethylarsinic acid. This reaction completes in sediments. Now these arsenic species like arsenite, arsenate, methylarsonic acid and dimethylarsinic acid reach in water. In water methylarsonic acid and dimethylarsinic acid react with molds and bacterias and form trimetylarsine and dimethylarsine. Now these dimethylarsine and trimethylarsine come in contact with air ($O_2$) from water and again dimethylarsinic acid. From air this Dimethylarsinic acid again reaches in sediments (Wood et al. 1974).

Rahman et al. (2007) reported in their work that inorganic arsenic species like arsenate and arsenite are mainly absorbed by aquatic species. These inorganic species may be oxidised, reduced or methylated to form organic arsenic species. In inorganic arsenic biotransformation process mainly interconversion between arsenite and arsenate is drastic. The microorganisms play important role in environment (Rahman et al. 2007). Mitra and their companions reported that microorganisms reduce arsenate in anaerobic conditions. Arsenite works as terminal electron acceptor. They also reported that microorganisms reduce arsenate ($AS^V$) and in anaerobic condition arsenite ($As^{III}$) works as terminal electron acceptor. Further, they reported that thermus (strain HR13) a prokaryotic microorganism could oxidise arsenite under

anaerobic conditions in water (Mitra et al. 2017). Murphy and Saltikov reported that reduction of arsenate ($As^V$) occurs in cytoplasm of microorganisms and ARM (Arsenate reduction mutant) acts as intermidiate under aerobic conditions (Murphy and Saltikov 2009). Cytoplasmic arsenate reductases are found in some microorganisms like *Halophilicarchaea* (Wang et al. 2004), *E. Coli* (Gladysheva et al. 1994) and *S*. Cerevisiae (Bobrowicz et al. 1977)**,** In some marine fishes like *L. Jappnicus*, S. *Fuscescenes* and *S. Cucullata* (a Bombay oyester) reduction of arsenate to arsenite occurs (Zhang et al. 2015b; Zhang et al. 2016; Zhang et al. 2020)**.** In freshwater, *C. Reinhardtii* (a green algae) shows arsenite oxidation (Qin et al. 2009)**.** *Cyanidioschyzon* species of algae exhibit As (III) oxidation outside its cytoplasm in presence of carbonic anhydrase and phosphatase enzymes. Cyanidioschyzon species (an eukaryotic alga) do both reduction and oxidation between arsenate and arsenite simultaneously (Mitra et al. 2017; Qin et al. 2009). In different organisms, inorganic arsenic undergoes oxidation or reduction and various enzymes are involved in these processes. As (V) reductases have been isolated from many microbes. Recently Mukhopadhyay and their associates studied the presence of *Arsoperon* in yeast and *Archaea* gives resistance to As (V) and As (III) (Mukhopadhyay et al. 2002), for example in *E. Coli* bacteria glutaredoxin and GSH is used by arsenate reductases (ArcC). In B. Subtilis arsenate reductase uses thioredoxin as reductants (Zhu et al. 2014a, b) and during this catalysis thioredoxin acts as electron donor while As (V) is electron acceptor (Silver et al. 2001). In *E. Coli* arsenate reductase (cytoplasmic) acts as arsenite membrane pump so it controlls As (V) reduction (Zhang et al. 2017a). Various algae like *Clostridiumaciculare*, *C. Salina*, and *Dunaliella* species reduce arsenate to arsenite regulated by *ArsB* which is arsenite effux proteins (Mitra et al. 2017). Some genes are involved in reduction and oxidation of arsenic: *aos, aio, aox* which are used by microorganisms to oxidised As (III) (Cai et al. 2009; Santini and Hoven 2004; Silver and Phung 2005). Genes *arr*, and *ars* are used to reduce As (V) in detoxification or catabolic purposes (Saltikov and Newman 2003; Wu and Rosen 1993).

Organic biotransformation of arsenic includes mainly methylation which plays an important role in organic arsenic biotransformation (Bhattacharjee and Rosen 2007). Microorganisms like yeast, fungi, algae, bacteria etc. do arsenic methylation (Frankenberger and Arshad 2002). Some different groups of scientists reported in their work that methylation by bacteria and fungi like microorganisms is about over fourty years old study (Chang and Focht 1979; Cullen and Reglinski 1984). Phytoplankton and cyanobacteria are the photosynthetic microbes; they reduce arsenate to arsenite followed by methylation to methylarsenic species (Guo et al. 2016; Xue et al. 2014; Ye et al. 2012). Nostoc bacteria do methylation of arsenite ($As^{III}$) to trimetylarsine oxide (TMAO) and Dimethylarsenate (DMA) (Yin et al. 2011). *C. Asylase* a clone of Nostoc species is responsible for monomethylarsonous acid ($MMA^{III}$) and monomethylarsenic acid ($MMA^V$) demethylation. *Rhodopseudomonas palustris* and *Cyanidioschyzon* species are eukaryotic microalgae (thermoacidophilic) do bacterial methylation of TMA. There are several arsenic biotransformation pathways known through arsenic methylation. One possibility is that biomethylation process changes toxic inorganic As to less toxic methylated arsenic species, such as trimethylarsine

gas (gosio gas), $DMA^{V}$, TMAO and $MMA^{V}$ (Qin et al. 2009, 2006; Ye et al. 2012). Yet more toxics like dimethylarinous acid ($DMA^{III}$) and monomethyl arsonous acid ($MMA^{III}$) are also produced by biomethylation. In this process $DMA^{V}$ and $MMA^{V}$ are intermidiate. This process follows the biosynthetic pathways (Kumagai and Sumi 2007; Rahman and Hassler 2014). Inorganic arsenic species do biomethylation (enzymatic) in many methylated metabolites as follows: arsenate → arsenite → monomethylarsenic acid → dimethylarsinic acid. This pathway is known as classical metabolic pathway of Challenge (Cullen 2014; Hayakawa et al. 2015; Naranmandura et al. 2006; Suzuki et al. 2004). Another possible organic arsenic bioaccumulation pathway through methylation is reductive methylation more than stepwise methylation process (oxidative). Here arsenite do direct methylation of DMA. In these conditions $DMA^{III}$ is directly methylated by aresite through arsenite–monomethylarsonous acid–dimethylarsonous acid process, and is then oxidised to As (V). Kunito and their companions proposed two hypothesized methylated pathways of inorganic arsenic; one reductive and other oxidative (Kunito et al. 2008; Le et al. 2000). Further $DMA^{V}$ reduced to $DMA^{III}$ in presence of TMAO intermediate and followed by the methylation till the formation of $TMA^{III}$ (Zhu et al. 2014a, b). Some enzymes also participate in arsenic methylation more than a stepwise methylation. They are *ArsM (arsenite methyltransferases)*, *SAM* (S- *adenosylmethionine*) and *As3MT* (Arsenite methyltransferase) etc. SAM acts as methyl donor to form intermediates, such as dimethylated and mono- methylated forms of As (III) and As (V) (Cullen et al. 1995). In the marine algae and fungi like *Polyphysa periculus* and *Apiotrichum humicola* respectively, *SAM* donates methyl group (Zhang et al. 2022). In microalgae *ArsM* acts as methyl donor for the methylation arsenite into $DMA^{V}$ and $MMA^{V}$ (Ajees et al. 2012). Arsenic biotransformation mainly goes through a series of methylation and oxidative reactions which are catalyzed by*As3MT* enzyme (Chen et al. 2011; Lin et al. 2002; Thomas et al. 2007; Cullen and Reimer 1989a, b). *As3MT* enzyme also gives addition of methyl groups oxidatively in a stepwise reduction of arsenate ($As^{V}$) to arsenite ($As^{III}$) (Cullen 2014; Cullen and Reimer 1989a, b). Some special type of genes like *arsH* participate in methylation of arsenic (Guo et al. 2016; Qin et al. 2006; 2009; Zeng et al. 2018; Zhang et al. 2018, 2015a). Yang and Rosen (2016) illustrated a global cycle regarding arsenic methylation. They showed that *ArsH oxidoreductase* and *ArsH methyltransferases* play an important role in methylation of arsenic biotransformation (Yang and Rosen 2016).There are many speculated synthesis pathways regarding the formation of AB (Arsenobetaine). AB can be synthesized from trimethylated arsenosugars and dimethylated arsenosugars. First of all dimethylated arsenosugars were converted into AB through Dimethylarsinoyl acetate and dimethylarsinoyl ethanol. Similarly trimethylated arsenosugars were directly converted into AB (Kunito et al. 2008). Edmonds et al. (1982) reported a route of biological formation of AB (Arsenobetaine) from dimethylarsenoylethanol (DMAE) in which AC is converted to AB by sedimental microorganisms (Edmonds et al. 1982). Similarly Hoffman and their fellow researchers also proposed a pathway for the formation of AB from AC, here *B. Subtililis* (a microorganism) converts AC into AB (Hoffman et al. 2018). AC acts as metabolic predecessor of AB and after insertion of AC in aquatic mussels and fishes, it is transformed into AB quickly (Borak

and Hosgood 2007; Gailer et al. 1995; Kaise et al. 1992; Marafante et al. 1984). Foster and Maher (2016) used DMAE as an intermediate for the methylation of AB from dimethylarsinylacetic acid (Foster and Maher 2016).Similarly two separate groups of researchers reported that trimethylarsonioribosides methylate transformed into AC followed by the methylation of AB (Devesa et al. 2005; Francesconi and Edmonds 2003). Ritchie and their associates found that DMAA (dimethyl arsinoyl acetatic acid) is used in synthesis of AB and blue mussels are used for the isolation of SAM, a methyl donor (Ritchie et al. 2004). Fungi can store AB while SAM promotes biotransformation of AB and is synthesized from 2-oxo acids, DMA $^{III}$, pyruvate and glyoxylate (Caumette et al. 2012; Edmonds and Francesconi 2003). AB can be synthesized from microorganisms, bacteria etc. In marine sediments microbial degradation of As-Sug is consumed by herbivores and derisiveness (Francesconi and Edmonds 1993; Kirby and Maher 2002). Similarly Pseudomonas species of bacteria convert dimethylarsenoyl acetate to AB in marine microorganisms (Ritchie et al. 2004). AB can also be synthesized from degradation of trimethylarsinoribosides, dimethylarsenoribosides, thioarsenoribosides in different arsenic species (Francesconi et al.1998; Kirby et al. 2005). AB can be degraded to As (V), TMAO and DMA. DMAA acts an intermediate to degrade AB into DMA (Jenkins et al. 2003; Khokiattiwong et al. 2001). Hanaoka et al. (1997), first investigated the AB in marine environment in which degradation pathway was AB → TMAO → MMA or As (V) (Hanaoka et al. 1988).The degradation of AB to arsenate ($As^V$) might be possible in deep sea microorganisms (Hanaoka et al. 1997).The degradation and synthesis process of AB is very complex. The minor process of arsenic biotransformation utilize future and present methods of metaproteomics, metagenomics, metabolomics and metatranscriptomics which would increase our knowledge regarding arsenic biotransformation process (Zhu et al. 2017) (Table 2.1).

## 2.4 Methods of Determination of Speciation of Arsenic

The term speciation means determination of specific ions of any element in aqueous and other solutions. In soil and sediments, the first step of arsenic speciation is extraction. Speciation of arsenic includes three major processes i.e. extraction, separation and detection. For extraction generally Voltametry and HG are used. For separation, chromatography and capillary electrophoresis methods are used. Similarly for detection, spectroscopic methods are there. For extraction, the extracting solution should be in specific form and during this process As (V) should not be reduced to As (iii). Similarly oxidation of As (iii) should not be done to As (V) (Melanie et al. 2009).

Commonly four extraction procedures are used:

1. Soil and 10 M Hydrocholric acid are taken in the ratio of 1:30 and this solution is shaken for 30 min (Chappell et al. 1995);
2. Soil and 15% Phoshoric acid ($H_3PO_4$) are taken in the ratio of 1:200 and this solution is heated at above 95 °C for one hour (CEAEQ 2004).

**Table 2.1** Oraganic arsenic biotransformation (methylation) by enzymes and genes

| Enzymes and genes | Organic species | Methylation process | References |
|---|---|---|---|
| ArsM gene | Microalgae synechoystis species | Converts arsenite into MMA $^{V}$ and DMA $^{V}$ | Mitra et al. (2017) |
| arsM gene | Rhodopseudomonas palustris | Convertion of arsenite into MMA $^{V}$ and DMA $^{V}$ and TMAO | Qin et al. (2006) |
| arsM genes (SparsM) | spirulina platensis (Microbes) | Converts arsenite into MMA and DMA | Guo et al. (2016) |
| arsH and arsM | Bacteria | Converts arsenite into MMA $^{V}$, DMA $^{V}$, TMAO And | Zeng et al. (2018) |
| AS3MT | Mouse | Converts arsenite into DMA and MMA | Chen et al. (2011) |
| CmarsM7 & CmarsM8 | Cyanidioschyzon sp. (eukaryotic alga) | Converts arsenite into DMA $^{V}$, MMA $^{III}$, TMA and TMA | Qin et al. (2009) |
| SAM | Polyphysapeniculus (marine alga), Apiotrichum humicola (fungi) | Methyl arsenic formation | Cullen et al. (1995) |
| SAM | Microbes | Conversion of As (III) and As (V) into MMA and DMA | Zhu et al. (2014a, b) |

3. First of all a 10 mM Phosphate solution is prepared from 0.5 M $K_2HPO_4$ and 0.5 M $KH_2PO_4$ in equal amounts. In this solution now add 0.5% Sodium diethylthiocarbamate. This resulting solution is taken in the ratio of 1:40 and shaken for 60 min (Geogiadis et al. 2006).
4. Soil and solution of 1 M Phosphoric acid and 0.5 M ascorbic acid are taken in the ratio of 1:150 and kept in microwave for 10 min at 60 W (Garcia–Maryes et al. 2002; Ruiz-Chancho et al. 2005; Ruiz-Chancho et al. 2007).

## 2.5 Techniques for Arsenic Speciation

Cullen and their fellow researchers reported in their work that there was not enough litrature related with speciation of arsenic before year 1980 but in 1984 Maher extracted Arsenic species from English estuarine and African coast by using solvent extraction and ion-exchange chromatography and determined by AAS, Atomic absorption spectroscopy (Maher 1981). Now a days there are some techniques, famous for arsenic speciation i.e. Voltametric methods which include Differential pulse polarography (DPP), Anodic stripping voltametry (ASV), Cathodic stripping voltametry (CSV), Differential pulse Cathodic stripping voltametry (DPCSV).

Electrophoresis include capillary electrophoresis (CE) and Capillary zone electrophoresis. Similarly Chromatographic methods are High performance liquid Chromatography (HPLC), Gas chromatography (GC), Ion-exchange chromatography, ion-exclusion chromatography, and superficial fluid chromatography. Spectroscopic methods used for detection consists of Atomic absorption spectroscopy (AAS), Atomic fluorescence spectroscopy (AFS), Inductively coupled plasma–atomic emission spectrometry (ICP–AES), Inductively coupled plasma–mass spectrometry (ICP–MS) (Kumaresan and Riyazuddin 2001).

### *2.5.1 Techniques for Extraction System*

#### 2.5.1.1 Voltametric Methods

In Voltametric methods the differential pulse polarography (DPP) is extensively used. Although these methods are not able to extract ultratrace concentration of arsenic. For ultratrace concentration extraction, stripping Voltametric methods are better option. Generally CSV (Cathodic stripping voltametry) and ASV (Anodic stripping Voltametry) methods are used. In CSV, Hg electrode or glassy carbon electrodes are used whereas in ASV, gold, platinum and Hg (as HDME) electrodes are used (Salaun et al. 2007; Zima and Van den Berg 1994; Hussain et al. 2002; Locatelli 2001). Sadana used DPCSV (differential pulse Cathodic stripping voltametry) for arsenic extraction in drinking water with Cu (ii) and in this process HDME is used as working electrode and Ag/AgCl as reference electrode. First of all drinking water samples of arsenic are heated with conc. HCl and 48% solution of HBr in steam bath at almost 100 °C for 45 min so that As (V) is reduced to As (III). (So that electro- inactive species As (V) becomes electro active As (III). After 45 min solution is cooled and diluted with hydrazinium chloride (0.25%) then Cathodic stripping voltametry is carried out. This method detects upto 1 mg/ml. Cu (II) concentration is 4 to 6 μg/ml, 0.75 M HCl and −0.6 V deposition potential are taken as optimized analytical conditions (Sadana 1983). Forsberg and their companions used both DPASV and ASV for total arsenic determination in water samples. Water samples of arsenic are heated with $Na_2SO_3$ (Sodium sulphite) in acid solutions (Concentrated). So that electro- inactive As (V) becomes electro- active As (III). 1 M HBr or 1 M HCl and 0.5 V deposition potential are taken as optimized analytical conditions. This method detects upto 0.02 mg/ml by both DPASV and ASV (Forsberg et al. 1975). Henze and their colleagues extracted both As (III) and As (V) in fresh water by Cathodic stripping voltametry (CSV). First of all 10 ml fresh water is mixed with 100 μg/ml $H_2O_2$ and 50 μg/ml Conc. $H_2SO_4$. Now all organics are removed from this resulting solution by digesting it in UV digestor. Then sample is analysed through CSV by using HMDE and Ag/AgCl/3M KCl (double junction) as reference electrodes with an auxiliary electrode (glassy—Carbon). After de-aeration, at –550 mili volt, preconcentration process is completed and stripping is completed at 25 mili volt per second scan rate with a—50 mili volt of pulse amplitude. $0.22^0$ M Mannitol, 0.4 M

$H_2SO_4$, 70 mg/L Se (IV) and 10 mg/L Cu (II) are taken as supporting electrolytes. The determination and detection limits are 0.93 and 0.52 μg/ml As, respectively (Henze et al. 1997). Besides it some advanced Voltametric methods are recently introduced to increase sensitivity, speed and potential modules in different forms. These techniques are NPV (Normal pulse voltametry), LSV (Linear sweep voltametry), STCV (Staircase voltametry), SWV (Square wave voltametry) and DPV (Differential pulse voltametry) (Hussam 2007).

In NPV, potential pulses are used serially in increasing order. At the end of each pulse the current measurement is found. In this voltametry a plot is found with current vs potential. In LSV, potential varies linearly with time which is applied on working electrode. This is simplest voltametry technique. A peak of current signal at potential produced by redox processes of species. When the current is flowing through the electrode, a current difference vs reducing potential exhibit the graph. Similarly a technique derivitized from LSV named as STCV in which a series of stair steps is a potential sweep. At the end of every potential change, the current is measured. A further improvement in Staircase voltametry is SWV. In this voltametry a superimposition of a symmetrical square wave is on a staircase waveform corresponding to the staircase step. In DPV, a superimposition of a series of terminal constant potential pulse containing small amplitude to a linear scanning gives a consistent signal. In this voltametry for every pulse, at two points, current is measured. Just before the pulse application the first point appears while at the end of pulse second point is found and a graph is plotted against base potential (Shah Rukh et al. 2015).

#### 2.5.1.2 Hydride Generation (HG) or Derivitization

Derivitization is a process to improve separation process of elements in chromatography for thermal stability or their identification. Shrain and their companions derivitized total arsenic by hydride generation, using $NaBH_4$/HCl for assay by atomic absorption spectroscopy (AAS) or ICP- MS. In derivitization process reduction of As (V) to As (iii) takes place, then in second step arsine production takes place (Shrain et al. 1999).

$$C_2H_5\text{-As-O-OH} + H^+ + BH_4^- \rightarrow C_2H_5\text{-As-OH} + BH_3 + H_2O \quad (2.1)$$

$$C_3\text{-As-OH} + BH_4^- + H^+ \rightarrow (C_2H_5\text{-As-H}) + BH_3 + H_2O \quad (2.2)$$

Howard A.G. (Boro) cleared production of Arsine from above hydride technique which is pH sensitive (Howard 1997). The arsine is formed during this second step in AAS or ICP–MS for measurement driven by $N_2$ gas (Goessler and Kuehnelt 2001), due to which detection limit improves upto 1000 times over the generally used derivitization process (Anawar 2012). Amino acids of arsenic and arsenosugars (AS) like $Me4As^+$ are not derivatized by sodium borohydride ($NaBH_4$). For their derivitization they must be separated and decomposed first into inorganic species

**Table 2.2** Arsenic speciation of arsenic species by hydride derivatization at different pH values

| pH value | Analyte | Product |
|---|---|---|
| 0.3 to 1 (in hydrochloric acid) | $(CH_3)_2AsO(OH)$ | Dimehtyl arsine ($Me_2AsH$) |
| Greater than 0.3 | $AsO(OH)_2$ | Arsine ($AsH_3$) |
| 0.3 to 1 (in hydrochloric acid) | $(Me)_3AsO$ | Trimetylarsine ($Me_3As$) |
| 0.3 to 1 (in hydrochloric acid) | $MeAsO(OH)_2$ | Monomethyl arsine ($MeAsH_2$) |

of As. During derivitization different arsenic compounds show different pH values and at pH 5 they show different types of sensitivities. This problem is commonly found during derivitization (Table 2.2). A group of researchers found a solution for this problem. They added 2% aqueous solution of L-cysteine with NaBH4 (Sodium borohydride) before derivitization. By this addition of L-cysteine As (V) compounds are reduced to As (III) compounds. But inorganic species of arsenic are not separated by this method ( Le et al. 1994).

$$CH_3As(OH) \rightarrow (CH)_2As(SR) \rightarrow (CH3)_2As$$
$$CH_3AsO(OH)_2 \rightarrow CH_3As(SR)_2 \rightarrow CH_3AsH_2$$
$$AsO(OH)_3,As(OH)_3 \rightarrow As\ (SR)_3 \rightarrow AsH_3$$

Hydride generation experiment mainly includes five steps. First step is sample insertion which follow batch process. In second step hydride derivitization by sodium borohydride is done. The third step involves water trapping and in fourth is atomization in quartz furnace. The last step is detection which may be by AFS (Atomic fluorescence spectrometry), AAS (Atomic absorption spectroscopy), AES (Atomic emission spectroscopy) and ICP-MS (Inductively coupled plasma – mass spectrometry).

### *2.5.2 Techniques for Separation and Detection*

For separation of arsenic, generally chromatography and electrophoresis techniques are used. In Chromatographic techniques, Liquid chromatography, HPLC, gas chromatography, ion exchange chromatography, ion-exclusion chromatography and supercritical fluid chromatography are used. For Electrophoresis, generally capillary and capillary zone electrophoresis are extensively used. Different spectroscopies are merged with separation systems; thus their studies should be combined with separation systems.

### 2.5.3 *Liquid Chromatographies with Spectroscopic Detection Systems*

Akhtar et al. (2005) reported that in liquid chromatography, there are excellent possibilities for separation in comparison to Gas chromatography. Generally Arsenic compounds are non-volatile in nature thus gas chromatography is less applicable to environmental samples of arsenic. The commonly used liquid chromatographies are ion chromatography, High performance liquid chromatography (HPLC) and ion interaction chromatography (Akhtar et al. 2005). Arsenic species show different dissociation constants because they form weak acids. These different dissociation constants are speciated by HPLC. TMA, DMA, MMA, AS (V), and As (III) these are the molecular and ionic forms of arsenic which are separated by HPLC. Anion exchange HPLC and Cation exchange HPLC are generally used to separate arsenic species. To separate anionic and cationic species of arsenic in a single run, a combination of reversed–phase separation and anion-exchange has been developed. After separation by liquid chromatography i.e. HPLC, on-line detection can be done by AAS, UV, ICP-AES, HG-AAS, ICP-MS and off-line detection by ETA–AAS (Electrothermal atomic absorption spectroscopy). Hansen and their fellow researchers used a combined on-line system of HPLC–AAS for DMA, MMA, As (V) and As (III) like arsenic species are separated and detected from each other. Cationic arsenic compounds are co- injected on an anionic-exchange column with carbonate of 0.1 M strength at 10.3 pH as mobile phase. AC, TMA, and AB are separated from the co-injected anionic species on cation-exchange column of Silica with a mobile phase of Pyridine at pH 2.65. A method containing HPLC-HG-AAS gives better sensitivity. From this method only volatile arsines are detected (Hansen et al. 1992). Hakala and their colleagues also used HPLC- HG-AAS system for arsenic separation in urine samples. The separation of arsenic species like DMA, MMA, As (V), and As (III) are done on a reverse-phase column of C18 with 20 mM phosphate and 10 mM TBA (Tetrabutylammonium) at the pH of 6.0. Although hydrides are not generated by AC (Arsenocholine) and Arsenobetaine (AB) so there is a need to a pre- oxidation of AC and AB into an inorganic arsenical by the on-line combination of $K_2Cr_2O_8$ with ultraviolet light (Hakala and Pyy 1992). Lopez used phosphate (17 mM) at pH 6.0 as mobile phase to separate AC, AB, DMA, MMA, As (V) and As (III) by thermal oxidation. A Per-sulphate stream is added with this HPLC effluent before the entrance in thermo- reactor which consists of a loop of PTFE tube. This PTFE tube is dipped in a oven of powdered- graphite at 140 °C. After heating, it was cooled in ice bath. HCl and NaBH4 are added on–line to produce Arsine (Lopez et al. 1993). Some researchers used previously same column for the separation of DMA, MMA, As(V) and As (III) (Stummeyer et al. 1996). Raurret et al. (1991) used Hydride generation (HG) and ICP between the HPLC and AES for the detection of Arsine in gaseous phase. To improve volatile hydrides separation and to decrease the volume of solution approaching the plasma torch, they use a liquid–gas separator. A silica based anion-exchanger is used to separate AC, AB, DMA, MMA, As (V) and As (III) with a mobile phase of Phosphate buffer of 6.75 (Rauret et al. 1991). For Arsenic

separation, Beauchemin et al. (1989) coupled different forms of HPLC–ICP–MS. They studied ion-exchange and ion-pairing HPLC to separate AB, DMA, MMA, As (III) and As (V). They found that ion-pairing chromatography has resolution superior to anion exchange (Beuchemin et al. 1989). Demesmay and their fellow researchers used ICP–MS–HPLC detection system to determine AC, AB, MMA, DMA, As (III) and AS (V). Phosphate buffer (with 2% Acetonitrile) is used as mobile phase with an anion-exchange column (Demesmay et al. 1994).

### 2.5.4 *Gas Chromatography with Spectroscopic Detection Systems*

Beckerman used Gas chromatography for separation of DMA and MMA for biological samples. In most of the methods Sodium borohydride ($NaBH_4$) of arsenic species is converted into methylarsine compounds but due to volatile nature conversion of methylarsine compounds into DMA and MMA is necessary. Thioglycolic acid methyl ester (derivative of methyl arsine) yield a lipophilic species. This species is determined by Gas chromatography with FID (Flame ionization detector) (Bakerman 1982). Two separate groups of authors used gas chromatography for the determination of As (III) under both strong and weak acid conditions. In this method the authors use HG, LNCT (Liquid-nitrogen-cooled trapping) and GC with Helium discharge based PID (Photoionization detection). From this method Sb (III) and Sb (V) are also determined (Yamamoto et al. 1992; Cutter et al. 1991). Talmi and their associates used GC-MES system for the separation of Arsenic in environmental samples. This procedure is completed in following steps: Pretreatment of samples; II. As (III) co-crystallization with thio-analide;III. Phenylation reaction in which the reaction of dry precipitate with Ph–Mg–Br (Phenyl magnesium bromide = PMB). After Phenylation the Ph–Mg–Br become decomposed in $Ph_3As$ (Triphenylarsine) and now small amount of this organic compound is injected into the column and determined by MES (Talmi and Norvell 1975).

### 2.5.5 *Ion- Exchange Chromatography with Spectroscopic Detection System*

Ricci et al. (1981) applied ion-exchange chromatography with HG- AAS system for separation of p-APA (para-Phenyl arsine), MMA, DMA, As (III) and As (V). In this method, a dionex 8 × 500 mm column (anion- separator) is used to separate above arsenic species. $Na_2B_4O_7$ and $NaHCO_3$ are mixed with each other and this mixture is used as mobile phase to separate p-APA, As (V) and MMA while only $Na_2B_4O_7$ mobile phase is used to separate DMA and As (III) (Ricci et al. 1981). McGeehan and their companions also used a suppressed ion chromatography of 4000i

dionex and mobile phase is $Na_2CO_3$ and $NaHCO_3$ mixture. Conductometric and electrochemical detectors are used to quantify As (V) and As (III). The detection limit of SIC (Suppressed ion chromatography) is very low in comparison to ion-exchange chromatography. Besides it, this chromatography does not have good sensitivity to analyze environmental samples. The only advantage of this chromatography (SIC) is that it can separate and quantify Arsenic species (ionic) without reduction or oxidation (Mcgeehan and Naylor 1992). Some researchers used ion-exchange-ICP-MS System to separate As species like As(III) and As (V) in water samples. This method determines the less lethal MMA, DMA and AC, AB (do not occur in drinking water). The detection limit for all species is 0.4 to 0.5 μg/L (Pantsar-Kallio et al. 1997).

### *2.5.6 Ion-Exclusion Chromatography with Spectroscopic Detection System*

Hemmings et al. (1991) utilized ion- exclusion chromatography to determine As (V) and As (III). With this chromatography a photometric detector is used in which a lack of sensitivity occurs during Arsenic speciation (Hemmings et al. 1991).

### *2.5.7 Supercritical Fluid Chromatography with Spectroscopic Detection System*

Laintz et al. (1992) employed supercritical fluid chromatography with FID to separate As (V) and As (III) (Laintz et al. 1992).

### *2.5.8 Refractory Method with Spectroscopic Detection System*

Battencourt et al. (1992) used solvent extraction with Methanol, HPLC—Dynamic flow fast atom bombardment—MS to separate refractory arsenic. Refractory arsenic doesn't form hydrides. The detection of arsenic is by HG or Gas furnace AAS and the final detection is done by LCFAB–MS (Liquid chromatography fast atom bombardment- MS) (De Battencourt et al. 1992).

### *2.5.9 By Resin with Spectroscopic Detection*

Suzuki et al. (1997) manipulated the resins of monoclinic Zirconium oxide (hydrous). Resins used, are porous and spherical. First of all $ZrOCl_2$ solution is saturate with Amberlite XAD-7, dried and then agitated with 28% Ammonia for 5 h. Separate the precipitate after dilution with water. For hydrothermal treatment the pH of resin water pulp made up is allowed to stand for 2 to 15 h at 150 °C. This resin consists of good separation property with a distribution ratio 2:4. This ratio depends on pH of solution and the oxidation state of Arsenic (Suzuki et al. 1997).

#### 2.5.9.1 Electrophoresis Separation with Spectroscopic Detection System

The term electrophoresis means separation and migration of ions under the influence of electric field (Fritsch and Krause 2003). This technique is used to separate arsenic species like As (V), As (III), DMA, ABA (p-aminobenzene arsonate) with spectroscopic, conductometric and photometric detection systems. Most of the authors suggested that electrophoresis is of two types: Capillary electrophoresis (CE) and Capillary zone electrophoresis (CZE). Schlegel and their fellow researchers used high performance CE and CZE followed by conductometric detection system to separate ABA, As (V), DMA, PhAs and Photometric detection system to separate DMA, As (V) and As (III) (Schlegel et al. 1996). Lin and their companions used a CE technique for the separation of DMA, MMA, As (V) and As (III) with a different ICP-MS detection system. This is based on DIN (Direct injector nebulizer) (Lin et al. 1995). Magnuson and their associates gave a method to separate and detect As (V), As (III), MMA and DMA by hydrodynamically modified EOF (electro-osmotic flow) capillary electrophoresis followed by HG-ICP-MS system (Magnuson et al. 1997). Vanifatova et al. (1997) used capillary zone electrophoresis followed by photometric detection to separate As (V) (Vanifatova et al. 1997). Tian et al. (1998) proposed CZE-ICP-AES system for the speciation of As (V), As (III), DSMA, and DMA. For As (V), As (III) and DSMA the detection limits are 0.32 μg/ml and for DMA it is 0.35 μg/ml (Tian et al. 1998). Instrumental techniques used in speciation of Arsenic are presented in Table 2.3.

## 2.6 Conclusions

The aquatic environment of India, Nepal, China, Bangladesh, Pakistan is mainly affected by arsenic contamination. Environmental and biological factors affect both the assimilation and absorption of arsenic. Arsenic enters in the bodies of organisms or microorganisms and does biotransformation of one arsenic species into another. Enzymes, marines fishes, bacteria, fungi, genes etc.; transform inorganic arsenic into

**Table 2.3** Instrumental techniques used in speciation of Arsenic

| Method for speciation | Determination of Arsenic species | LOD ((μgl–1) | References |
|---|---|---|---|
| Ion-exchange ICP-MS | As $^{V}$, As $^{III}$ | 0.40, 0.40 | Pantsar-Kallio et al. (1992) |
| IC-HG-AAS | DMA, MMA, P-APA, As $^{III}$, As $^{V}$ | 6.50, 3.20, 9.30, 4.0, 20.0 | Ricci et al. (1981) |
| IEC- PID | As $^{V}$, As $^{III}$ | Greater than 3000 | Hemmings and Jones (1991) |
| HPLC–AAS | DMA, MMA, As $^{V}$, As $^{III}$, TMA, AB, AC | 700, 1400, 1400, 1100, 400, 500, 300 | Hansen et al. (1992) |
| HPLC-HG-AAS | MMA, DMA, As $^{V}$, As $^{III}$ | 1.20,4.70, 1.60, 1.0 | Hakala and Pyy (1992) |
| HPLC with UV-HG-AAS | DMA, MMA, AC, As $^{V}$, As $^{III}$, As $^{V}$ | 6.0, 6.0, 4.0, 4.0, 8.0, 5.0 | Lopez et al. (1993) |
| Spectrophotometric | As $^{V}$, As $^{III}$<br>As $^{V}$, As $^{III}$ | 100, 100<br>1.0, 0.03 | Howard and Arbab-avar (1980)<br>Palanivelu et al. (1992) |
| SIC–electrochemical | As $^{III}$ | 114 | Mcgeehan and Naylor (1992) |
| CZE with ICP- MES | Cacodylic acid, As $^{V}$ As $^{III}$, DSMA | 350, 320, 320, 320 | Tian et al. (1998) |
| CZE with UV | DMA, As $^{III}$, As $^{V}$ | 120, 90, 60 | Schlegel et al. (1996) |
| GC–FID | As $^{V}$, As $^{III}$ | 10.0, 10.0 | Backerman (1982) |
| CZE | DMA, As $^{III}$, As $^{V}$ | 1130, 150, 1100 | Vanifatova et al. (1997) |
| GC with MES | As $^{III}$ | 0.05 | Talmi and Norvell (1975) |
| ICP–MS (Voltametric) | As $^{III}$ | 0.13 | – |
| ICP–AES (Voltametric) | As $^{III}$ | 5.0 | – |
| CSV | As $^{V}$, As $^{III}$ | 0.520, 0.520 | Henze et al. (1997) |
| SFC with FID | As $^{V}$, As $^{III}$ | 87.50, 87.50 | Laintz et al. (1992) |
| DPCSV | As $^{V}$, As $^{III}$ | 1.0, 1.0 | Sadana (1983) |
| DPCSV / ASV | As $^{V}$, As $^{III}$ | 0.020, 0.020 | Forsberg et al. (1975) |
| HG with GC- PID | As $^{V}$, As $^{III}$ | 0.00180 | Yamamoto et al. (1992) |
| HPLC-HG system with MIP – AES | DMA, MMA, As $^{V}$, As $^{III}$ | 6.0, 1.20, 5.0, 1.0 | Costa-Fernandez et al. (1995) |

(continued)

**Table 2.3** (continued)

| Method for speciation | Determination of Arsenic species | LOD ((μgl–1) | References |
|---|---|---|---|
| HPLC with ICP- MS | AB, $As^{III}$<br>DMA, MMA, $As^{III}$, $As^{V}$<br>AC, AB, DMA, MMA, $As^{III}$, $As^{V}$ | 5.0, 1.0<br>1.20, 3.60, 4.90, 6.0<br>0.50, 0.50, 1.0, 1.0, 0.50, 0.30 | Beuchemin et al. (1989)<br>Sheppard et al. (1992)<br>Demesmay et al. (1994) |
| SIC (conductometric) | $As^{V}$ | 120.00 | – |
| HPLC–HG system with ICP- AES | DMA, MMA, $As^{V}$, $As^{III}$ | 21.30, 3.80, 9.20, 3.50 | Rauret et al. (1991) |
| HPLC with USN–AFS | DMA, MMA, $As^{V}$, $As^{III}$ | 0.08, 0.08, 0.20, 0.14 | Woller et al. (1995) |

organic arsenic. This review gives information about better understanding regarding biotransformation of many arsenic species, their formation pathways as well as the techniques of arsenic speciation. There are diverse techniques for arsenic extraction, detection and separation. Every technique possess its advantages and disadvantages with respect to laboratory facilities and scope of the study.

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## References

Abedin MJ, Feldmann J, Meharg AA (2002) Uptake kinetics of arsenic species in rice plants. Plant Physiol 128(3):1120–1128

Adriano DC (2001) Arsenic. In: Trace elements in terrestrial environments. Springer, Berlin, pp 219–261

Ajees AA, Marapakala K, Packianathan C, Sankaran B, Rosen BP (2012) Structure of an As(III) S-Adenosylmethionine methyltransferase: insights into the mechanism of arsenic biotransformation. Biochemistry 51(27):5476–5485

Akhter KF, David GO, Davey E, Naidu R (2005) Arsenic speciation and toxicity in biological systems. Environ Contamination Toxicol 184:97–149

Alexander M (1974) Adv Appl Microbiol 18:1

Anawar HM (2012) Arsenic speciation in environmental samples by hydride generation and electrothermal atomic absorption spectrometry. Talanta 88:30–42

Beauchemin D, Siu KWM, McLaren JW, Berman SS (1989) J Anal Atom Spectrum 4:285

Beckerman B (1982) Anal Chim Acta 135:77

Bhattacharjee H, Rosen BP (2007) Arsenic metabolism in prokaryotic and eukaryotic microbes. In: Nies DH, Silver S (eds) Molecular microbiology of heavy metals. Springer, Heidelberg, pp 371–406

Bhattacharya P, Jacks G, Frisbie SH, Smith E, Naidu R, Sarkar B (2002) Arsenic in the environment: a global perspective. In: Sarkar B (ed) Heavy metals in the environment. Marcel Dekker Inc., New York, pp 147–215

Bobrowicz P, Wysocki R, Owsianik G, Goffeau A, Ułaszewski S (1997) Isolation of three contiguous genes, ACRl, ACR2 and ACR3, involved in resistance to arsenic compounds in the yeast Saccharomyces cerevisiae. Yeast 13:819–828

Boyle RW, Jonasson I (1973) R. J Geochem Explor 2:251

Cabon JY, Cabon N (2000) Speciation of major arsenic species in seawater by flow injection hydride generation atomic absorption spectrometry. Fresenius J Anal Chem 368(5):484–489

Cai L, Rensing C, Li XY, Wang GJ (2009) Novel gene clusters involved in arsenite oxidation and resistance in two arsenite oxidizers: Achromobactersp SY8 and Pseudomonas sp TS44. Appl Microbiol Biotechnol 83(4):715–725

Catarecha P, Segura MD, Franco-Zorrilla JM, García-Ponce B, Lanza M, Solano R, Paz-Ares J, Leyva A (2007) A mutant of the Arabidopsis phosphate transporter PHT1; 1 displays enhanced arsenic accumulation. Plant Cell 19:1123–1133

Caumette G, Koch I, Reimer KJ (2012) Arsenobetaine formation in plankton: a review of studies at the base of the aquatic food chain. J Environ Monit 14(11):2841–2853

CEAEQ (2004) Centre d'expertise en analyse environnementale du que´bec. DE' termination des me´taux: Me´thode par spectrome´triede masse a' source ionisante au plasma d¢argon. MA. 200-Me´t.1.1; Ministe'rede l'EnvironnementduQue´bec: Que´bec, QC, Canada, p 37

Challenger F (1942) Chem Rev 36:315

Chappell J, Chiswell B, Olszowy H (1995) Speciation of arsenic in a contaminated soil by solvent-extraction. Talanta 1995(42):323–329

Chen BW, Arnold LL, Cohen SM, Thomas DJ, Le XC (2011) Mouse arsenic (+3 Oxidation State) methyltransferase genotype affects metabolism and tissue dosimetry of arsenicals after arsenite administration in drinking water. Toxicol Sci 124(2):320–326

Cheng CN, Focht DD (1979) Production of arsine and Methylarsine in soil and in culture. Appl Environ Microbiol 38:494–498

Chilvers DC, Peterson, P J (1987) Lead, Mercury, Cadmium and Arsenic in the environment. In: Hutchinson TC, Meema KM (eds). Wiley, New York, p 279

Costa-Fernandez JM, Lunzer F, Pereiro-Garcia R, SanzMedel A, Bordel-Garcia N (1995) J Anal Atom Spectrom 10:1019

Cox DP, Alexander M (1973) Appl Microbiol 25:408

Cullen WR, Reimer KJ (1989a) Arsenic speciation in the environment. Chem Rev 89:713–764

Cullen WR (2014) Chemical mechanism of arsenic biomethylation. Chem Res Toxicol 27(4):457–461

Cullen WR, Li H, Pergantis SA, Eigendorf GK, Mosi AA (1995) Arsenic biomethylation by the microorganism Apiotrichum Humicola in the presence of L-Methionine-Methyl-D(3). Appl Organomet Chem 9(7):507–515

Cullen WR, Mcbride BC, Reglinski J (1984) The reaction of methylarsenicals with thiols: some biological implications. J Inorg Biochem 21:179–194

Cullen R, Reimer KJ (1989b) Arsenic speciation in the environment. Chem Rev 713–764

Cutter LS, Cutter Gam(1991) San Diego-McGlone, MLC. Anal Chem 63:1138

De Battencourt AMM, Florencio MHFS, Vilas-Boas LF (1992) Mikrochim Acta 109: 53

Demesmay C, Olle M, Porthault M (1994) Fres J Anal Chem 348:205

Devesa V, Loos A, Suner MA, Velez D, Feria A, Martinez A, Montoro R, Sanz Y (2005) Transformation of organoarsenical species by the microflora of freshwater crayfish. J Agric Food Chem 53(26):10297–10305

Edmonds JS, Francesconi KA, Cannon JR, Ratson CL, Skelton BW White AH (1977) Tetrahedron Lett 1543

Edmonds JS, Francesconi KA (2003) Organoarsenic compounds in the marine environment. In: Craig PJ (ed) Organometallic compounds in the environment. Wiley, New York, pp 195–222

Edmonds JS, Francesconi KA, Hansen JA (1982) Dimethyloxarsylethanol from anaerobic decomposition of brown kelp Ecklonia radiata: a likely precursor of arsenobetaine in marine fauna. Experientia 38:643–644

Forsberg G, O'Laughlin JW, Megargle RG, Koirtyohann SR (1975) Anal Chem 47:1586

Foster S, Maher W (2016) Arsenobetaine and thio-arsenic species in marine macro-algae and herbivorous animals: accumulated through trophic transfer or produced in situ? J Environ Sci 49:131–139
Francesconi KA, Edmonds JS (1993) Arsenic in the sea. Oceanogr Marine Biol Ann Rev 31:111–151
Francesconi KA, Goessler W, Panutrakul S, Irgolic KJ (1998) A novel arsenic containing riboside (arsenosugar) in three species of gastropod. Sci Total Environ 221:139–148
Frankenberger WT, Arshad MA (2002) Volatilisation of arsenic. In: Frankenberger WT (ed) Environmental chemistry of Arsenic. Marcel Dekker, New York, pp 363–380
Fritsch RJ, Krause I (2003) Electrophoresis. Encyclopedia of food sciences and nutrition, 2nd edition, pp 2055–2062. https://doi.org/10.1016/B0-12-227055-X/01409-7
Gailer J, Francesconi KA, Edmonds JS, Irgolic KJ (1995) Metabolism of arsenic compounds by the blue mussel Mytilus-Edulis after accumulation from seawater spiked with arsenic compounds. Appl Organomet Chem 9(4):341–355
Garcia-Manyes S, Jimenez G, Padro A, Rubio R, Rauret G (2002) Arsenic speciation incontaminated soils. Talanta 2002(58):97–109
Georgiadis M, Cai Y, Solo-Gabriele HM (2006) Extraction of arsenate and arsenite species from soils and sediments. Environ Pollution141: 22–29
Glabonjat RA, Raber G, Holm HC, Van Mooy BAS, Francesconi KA (2021) Arsenolipids in plankton from high- and low-nutrient oceanic waters along a eTransect in the North Atlantic. Environ Sci Technol 55(8):5515–5524
Gladysheva TB, Oden KL, Rosen BP (1994) Properties of the arsenate reductase of plasmid R773. Biochemistry 33:7288–7293
Goessler W, Kuehnelt D (2001) Analytical methods for the determination of As and As compounds in the environment. In: Franjzenberzer WT (ed) Environmental chemistry of Arsenic. Dekker, New York, p 27
Gosio B (1893) Arch Ital Biol 18:253
Gosio B (1901) Arch Ital Biol 35:201
Guo YQ, Xue XM, Yan Y, Zhu YG, Yang GD, Ye J (2016) Arsenic methylation by an arsenite S-adenosylmethionine methyltransferase from Spirulina platensis. J Environ Sci 49:162–168
Hakala E, Pyy L (1992) J Anal Atom Spectrom 7:191
Hanaoka K, Kaise T, Kai N, Kawasaki Y, Miyasita H, Kakimoto K, Tagawa S (1997) Arsenobetaine-decomposing ability of marine microorganisms occurring in particles collected at depths of 1100 and 3500 meters. Appl Organomet Chem 11(4):265–271
Hanaoka K, Yamamoto H, Kawashima K, Tagawa S, Kaise T (1988) Ubiquity of arsenobetaine in marine animals and degradation of arsenobetaine of sedimentary microorganisms. Appl Organomet Chem 2(4):371–376
Hansen SH, Larsen EH, Pritzl G, Cornett C (1992) J Anal Atom Spectrom 7:629
Hayakawa T, Kobayashi Y, Cui X, Hirano S (2005) A new metabolic pathway of arsenite: arsenic-glutathione complexes are substrates for human arsenic methyltransferase Cyt19. Arch Toxicol 79(4):183–191
Hemmings MJ, Jones EA (1991) Talanta 38:151
Henze G, Wagner W, Sander S, Fres J (1997) Anal Chem 1997(358):741
Hoffmann T, Warmbold B, Smits SHJ, Tschapek B, Ronzheimer S, Bashir A, Chen CL, Rolbetzki A, Pittelkow M, Jebbar M, Seubert A, Schmitt L, Bremer E (2018) Arsenobetaine: an ecophysiologically important organoarsenical confers cytoprotection against osmotic stress and growth temperature extremes. Environ Microbiol 20(1):305–323
Howard AG (1997) (Boro) Hydride techniques in trace element speciation. J Anal Atomic Spectrom 12:267–272
Howard AG, Arbab-Zavar MH (1980) Analyst (london) 105:338
Huang JH, Fecher P, Ilgen G, Hu KN, Yang J (2012) Speciation of arsenite and arsenate in rice grain—verification of nitric acid based extraction method and mass sample survey. Food Chem 130(2):453–459

Hussam A, Rasul H, Hossain SB, Munir Z, Alauddin AKM, Khan M (2002) Electrochemical measurement and speciation of inorganic arsenic in groundwater of Bangladesh. Talanta 58:33–43

Hussam A (2007) Voltammetry: dynamic electrochemical techniques in comprehensive analytical chemistry. In: Ahuja S, Jesperen N (eds), vol 47. Elsevier BV, p 663

Jackson BP (2015) Fast ion chromatography-ICP-QQQ for arsenic speciation. J Anal Spectrom 30(6):1405–1407

Jang YC, Somanna Y, Kim H (2016) Source, distribution, toxicity and remediation of arsenic in the environment—a review. Int J Appl Environ Sci 11(2):559–581

Jenkins RO, Ritchie AW, Edmonds JS, Goessler W, Molenat N, Kuehnelt D, Harrington CF, Sutton PG (2003) Bacterial degradation of arsenobetaine via dimethylarsinoylacetate. Arch Microbiol 180(2):142–150

Johnson DL, Braman RS (1975) Deep Sea Res 22:503

Kaise T, Horiguchi Y, Fukui S, Shiomi K, Chino M, Kikuchi T (1992) Acute toxicity and metabolism of arsenocholine in mice. Appl Organomet Chem 6(4):369–373

Khalid S, Shahid M, Niazi NK, Rafiq M, Bakhat HF, Imran M, Abbas T, Bibi I, Dumat C (2017) Arsenic behaviour in soil-plant system: biogeochemical reactions and chemical speciation influences. In: Enhancing cleanup of environmental pollutants. Springer, Cham, pp 7–140

Khokiattiwong S, Goessler W, Pedersen SN, Cox R, Francesconi KA (2001) Dimethylarsinoylacetate from microbial demethylation of arsenobetaine in seawater. Appl Organomet Chem 15(6):481–489

Kirby J, Maher W (2002) Tissue accumulation and distribution of arsenic compounds in three marine fish species: relationship to trophic position. Appl Organomet Chem 16(2):108–115

Kirby J, Maher W, Spooner D (2005) Arsenic occurrence and species in near-shore macroalgae-feeding marine animals. Environ Sci Technol 39(16):5999–6005

Kossoff D, Hudson-Edwards KA (2012) Arsenic in the environment. Chapter 1. In: Santini JM, WardSM (eds) The metabolism of arsenite, Arsenic in the environment, vol 5. CRC Press, London, pp 1–23

Koyama T (1975) Arsenic in soil-plant system. Nippon Dojo Hiryogaku Zasshi 46:491–502

Kumagai Y, Sumi D (2007) Arsenic: signal transduction, transcription factor, and biotransformation involved in cellular response and toxicity. Ann Rev Pharmacol Toxicol 47:243–262

Kumaresan M, Riyazuddin P (2001) Overview of speciation chemistry of arsenic. Curr Sci 80(7):837–846

Kumar S, Dubey RS, Tripathi RD, Chakrabarty D, Trivedi PK (2015) Omics and biotechnology of arsenic stress and detoxification in plants: current updates and prospective. Environ Int 1(74):221–230

Kunito T, Kubota R, Fujihara J, Agusa T, Tanabe S (2008) Arsenic in marine mammals, seabirds, and sea turtles. Rev Environ Contam Toxicol 195(195):31–69

Laintz KE, Shieh GM, Wai CM (1992) J Chromatogr Sci 30:120

Le XC, Cullen WR, Reimer KJ (1994) Anal Chim Acta 285:277

Le XC, Lu XF, Ma MS, Cullen WR, Aposhian HV, Zheng BS (2000) Speciation of key arsenic metabolic intermediates in human urine. Anal Chem 72(21):5172–5177

Lin S, Shi Q, Nix FB, Styblo M, Beck MA, Herbin-Davis KM, Hall LL, Simeonsson JB, Thomas DJ (2002) A novel S-adenosyl-L-methionine: arsenic(III) methyltransferase from rat liver cytosol. J Biol Chem 277(13):10795–10803

Liu Q, Lu X, Peng H, Popowich A, Tao J, Uppal JS, Yan X, Boe D, Le XC (2018) Speciation of arsenic—a review of phenylarsenicals and related arsenic metabolites. TrAC Trends Anal Chem 1(104):171–182

Liu WJ, Wood BA, Raab A, McGrath SP, Zhao FJ, Feldmann J (2010) Complexation of arsenite with phytochelatins reduces arsenite efflux and translocation from roots to shoots in Arabidopsis. Plant Physiol 152(4):2211–2221

Locatelli GT (2001) Voltammetric trace metal determinations by cathodic and anodic stripping voltammetry in environmental matrices in the presence of mutual interference. J Electroanal Chem 2001(509):80–89

Lopez MA, Gomez MM, Palacios MA, Camara C (1993) Fres J Anal Chem 346:643

Luvonga C, Rimmer CA, Yu LL, Lee SB (2020) Organoarsenicals in seafood: occurrence, dietary exposure, toxicity, and risk assessment considerations—a review. J Agric Food Chem 68(4):943–960

Ma JF, Yamaji N, Mitani N, Xu XY, Su YH, McGrath SP, Zhao FJ (2008) Transporters of arsenite in rice and their role in arsenic accumulation in rice grain. Proc Natl Acad Sci 105(29):9931–9935

Magnuson ML, Creed JT, Brockhoff CA (1997) Analyst (London) 122:1057. Maher WA (1981) Anal Chim Acta 125:157

Mahimairaja S, Bolan NS, Adriano DC, Robinson B (2005) Arsenic contamination and its risk management in complex environmental settings. Adv Agron 1(86):1–82

Mandal BK, Suzuki KT (2002) Arsenic round the world: a review. Talanta 58:201–235

Marafante E, Vahter M, Dencker L (1984) Metabolism of arsenocholine in mice, rats and rabbits. Sci Total Environ 34(3):223–240

Marquez EB, Gurian PL, Barud-Zubillaga A, Goodell PC (2011) Corre-lates of arsenic mobilization into the groundwater in El Paso, Texas. Air Soil Water Res 4:19–29

McBride BC, Wolfe RS (1971) Biochemistry 10:4312

McGeehan SL, Naylor DV (1992) J Environ Qual 21:68

Melanie G, Zagury JG, Deschenes L, Blouin J (2009) Comparison of four extraction procedures to assess arsenate and arsenite species in contaminated soils. Environ Pollut 158:18901898

Mitra A, Chatterjee S, Gupta DK (2017) Uptake, transport, and remediation of arsenic by algae and higher plants. Arsenic Contamination Environ 145–170

Mukhopadhyay R, Rosen BP, Pung LT, Silver S (2002) Microbial arsenic: from geocycles to genes and enzymes. FEMS Microbiol Rev 26(3):311–325

Murphy JN, Saltikov CW (2009) The arsR repressor mediates arsenite-dependent regulation of arsenate respiration and detoxification operons of Shewanella sp strain ANA-3. J Bacteriol 191(21):6722–6731

Naranmandura H, Suzuki N, Suzuki KT (2006) Trivalent arsenicals are bound to proteins during reductive methylation. Chem Res Toxicol 19(8):1010–1018

National Research Council (1977) Arsenic; National Academy of Sciences, Washington, DC, p 16

Niazi NK, Singh B, Shah P (2011) Arsenic speciation and phytoavailability in contaminated soils using a sequential extraction procedure and XANES spectroscopy. Environ Sci Technol 45(17):7135–7142

Onishi H, Wedepohl KH (1969) Handbook of geochemistry. vol II-2. Springer, Berlin

Palanivelu K, Balasubramanian N, Rama Krishnan TV (1992) Talanta 39:555

Pantsar-Kallio M, Manninen PKG (1997) J Chromatogr 779:1301

Pfeifer HR, Beatrizotti G, Berthoud J, Rossa MD, Girardet A, Jäggli M, Lavanchy JC, Reymond D, Righetti G, Schlegel C, Schmit V, Temgoua E (2002) Natural arsenic-contamination of surface and ground waters in Southern Switzerland (Ticino). Bull Appl Geol 7:81–103

Qin J, Lehr CR, Yuan CG, Le XC, McDermott TR, Rosen BP (2009) Biotransformation of arsenic by a Yellowstone thermoacidophilic eukaryotic alga. PNAS 106(13):5213–5217

Qin J, Rosen BP, Zhang Y, Wang GJ, Franke S, Rensing C (2006) Arsenic detoxification and evolution of trimethylarsine gas by a microbial arsenite S-adenosylmethioninemethyltransferase. PNAS 103(7):2075–2080

Raab A, Williams PN, Meharg A, Feldmann J (2007) Uptake and translocation of inorganic and methylated arsenic species by plants. Environ Chem 4(3):197–203

Rahaman S, Sinha AC, Mukhopadhyay D (2011) Effect of water regimes and organic matters on transport of arsenic in summer rice (Oryza sativa L.). J Environ Sci 23(4):633–639

Rahman MA, Hassler C (2014) Is arsenic biotransformation a detoxification mechanism for microorganisms? Aquat Toxicol 146:212–219

Rahman MA, Hasegawa H, Rahman MM, Rahman MA, Miah MAM (2007) Accumulation of arsenic in tissues of rice plant (Oryzasativa L.) and its distribution in fractions of rice grain. Chemosphere 69(6):942–948
Rauret G, Rubio R, Prado A (1991) Fres J Anal Chem 340:157
Reid MS, Hoy KS, Schofield JR, Uppal JS, Lin Y, Lu X, Peng H, Le XC (2020) Arsenic speciation analysis: a review with an emphasis on chromatographic separations. TrAC Trends Anal Chem 1(123):115770
Reis VA, Duarte AC (2018) Analytical methodologies for arsenic speciation in macroalgae: a critical review. TrAC Trends Anal Chem 1(102):170–184
Rhine ED, Phelps CD, Young LY (2006) Anaerobic arsenite oxidation by novel denitrifying isolates. Environ Microbiol 8:899–908
Ricci GR, Shepard LS, Colovos G, Hester NE (1981) Anal Chem 53:610. Ridley DW, Dizikes LJ, Wood JM (1977) Science 197:329
Ritchie AW, Edmonds JS, Goessler W, Jenkins RO (2004) An origin for arsenobetaine involving bacterial formation of an arsenic-carbon bond. FEMS Microbiol Lett 235(1):95–99
Ruiz-Chancho MJ, Lopez-Sanchez JF, Rubio R (2007) Analytical speciation as a tool to assess arsenic behavior in soils polluted by mining. Anal Bioanal Chem 387:627–635
Ruiz-Chancho MJ, Sabe R, Lopez-Sanchez JF, Rubio R, Thomas P (2005) New approaches to the extraction of arsenic species from soils. Microchim Acta 151:241–248
Sadana RS (1983) Anal Chem 55:304–307
Sadiq M (1997) Arsenic chemistry in soils: an overview of thermodynamic predictions and field observations. Water Air Soil Pollut 93(1):117–136
Sadiq M, Zaidi TH, Mian AA (1983) Environmental behavior of arsenic in soils: theoretical. Water Air Soil Pollut 20(4):369–377
Salaun P, Planer-Friedrich B, Berg CMGVD (2007) Inorganic arsenic speciation in water and seawater by anodic stripping voltammetry with a gold microelectrode. Analytica Chimica Acta 585:312–322
Saltikov CW, Newman DK (2003) Genetic identification of a respiratory arsenate reductase. PNAS 100(19):10983–10988
Santini JM, vanden Hoven RN (2004) Molybdenum-containing arsenite oxidase of the chemolithoautotrophic arsenite oxidizer NT-26. J Bacteriol 186(6):1614–1619
Saxena J, Howard PH (1977) Adv Appl Microbiol 21:185
Schlegel V, Mattusch J, Wennrich V (1996) Fres J Anal Chem 354:535
Shahid M, Shamshad S, Rafiq M, Khalid S, Bibi I, Niazi NK, Dumat C, Rashid MI (2017) Chromium speciation, bioavailability, uptake, toxicity and detoxification in soil-plant system: a review. Chemosphere 1(178):513–533
Shah Rukh, Akhtar MS, Memon M, Mehmood A, Imran M (2015) An overview of arsenic extraction and speciation techniques in soil and water. Am Chem Sci J 6(1):1–15. Article no. ACSj.2015.032. ISSN: 2249-0205. SCIENCEDOMAIN International. www.sciencedomain.org
Sheppard BS, Caruso JA, Heitkemper DT, Wolnik KA (1992) Analyst (london) 117:971
Shin H, Shin HS, Dewbre GR, Harrison MJ (2004) Phosphate transport in Arabidopsis: Pht1; 1 and Pht1;4 play a major role in phosphate acquisition from both low- and high-phosphate environments. Plant J 39:629–642
Shraim A, Chiswell B, Olszowy H (1999) Speciation of arsenic by hydride generation: atomic absorption spectrometry (HG-AAS) in hydrochlororic acid reaction medium. Talanta 50:1109–1127
Silver S, Phung LT (2005) Genes and enzymes involved in bacterial oxidation and reduction of inorganic arsenic. Appl Environ Microbiol 71(2):599–608
Silver S, Phung LT, Rosen BP (2001) Arsenic metabolism: resistance, reduction, and oxidation. Environ Chem Arsenic 247–272
Srivastava A, Devanita G, Ayushman D, Suatapa B (2015) Arsenic contamination in soil and sediments in India: source, effect and remediation. Springer International Publishing AG. https://doi.org/10.1007/s40726-015-0004-2

Stummeyer J, Harazim B, Wippermann T (1996) Fres J Anal Chem 354:344
Sun YZ, Liu GL, Cai Y (2016) Thiolated arsenicals in arsenic metabolism: occurrence, formation, and biological implications. J Environ Sci 49:59–73
Suzuki KT, Mandal BK, Katagiri A, Sakuma Y, Kawakami A, Ogra Y, Yamaguchi K, Sei Y, Yamanaka K, Anzai K, Ohmichi M, Takayama H, Aimi N (2004) Dimethylthioarsenicals as arsenic metabolites and their chemical preparations. Chem Res Toxicol 17(7):914–921
Talmi Y, Norvell VE (1975) Anal Chem 47:1510
Thayer JS, Brinckman FE (1982) Adv Organomet Chem 20:313
Thomas DJ, Li JX, Waters SB, Xing WB, Adair BM, Drobna Z, Devesa V, Styblo M (2007) Arsenic (+3 oxidation state) methyltransferase and the methylation of arsenicals. Exp Biol Med 232(1):3–13
Tian XD, Zhuang ZX, Chen B, Wang XR (1998) Analyst (london) 123:899
Vanifatova NG, Spirakova YaB, Mattusch J, Wennrich R (1997) J Capillary Electrophor 4:91
Wang GJ, Kennedy SP, Fasiludeen S, Rensing C, DasSarma S (2004) Arsenic resistance in Halobacterium sp strain NRC-1 examined by using an improved gene knockout system. J Bacteriol 186(10):3187–3194
Wilkin RT, Wallschläger D, Ford RG (2003) Speciation of arsenic in sulfidic waters. Geochem Trans 4(1):1–7
Woller A, Mester Z, Fodor P (1995) J Anal Atom Spectrom 10:609
Wood JM (1974) Science 183:1049
Wu JH, Rosen BP (1993) Metalloregulated expression of the ars operon. J Biol Chem 268:52–58
Wu Z, Ren H, McGrath SP, Wu P, Zhao FJ (2011) Investigating the contribution of the phosphate transport pathway to arsenic accumulation in rice. Plant Physiol 157:498–508
Xue XM, Raber G, Foster S, Chen SC, Francesconi KA, Zhu YG (2014) Biosynthesis of arsenolipids by the cyanobacterium Synechocystis sp. PCC 6803. Environ Chem 11(5):506–513
Yamamoto M, Tanaka S, Hashimoto Y (1992) Appl Organomet Chem 6:351
Yang HC, Rosen BP (2016) New mechanisms of bacterial arsenic resistance. Biomed J 39(1):5–13
Ye J, Rensing C, Rosen BP, Zhu YG (2012) Arsenic biomethylation by photosynthetic organisms. Trends Plant Sci 17(3):155–162
Yin XX, Chen J, Qin J, Sun GX, Rosen BP, Zhu YG (2011) Biotransformation and volatilization of arsenic by three photosynthetic Cyanobacteria. Plant Physiol 156(3):1631–1638
Zeng XC, Yang Y, Shi WX, Peng ZF, Chen XM, Zhu XB, Wang YX (2018) Microbially mediated methylation of arsenic in the arsenic-rich soils and sediments of Jianghan Plain. Front Microbiol 9:1–13
Zhang W, Miao AI, Wang NX, Li C, Sha J, Jia J, Daniel SA, Yan B, Ok YS (2022) Arsenic bioaccumulation and biotransformation in aquatic organisms. Environ Int 163(2022):107221
Zhang J, Cao TT, Tang Z, Shen QR, Rosen BP, Zhao FJ (2015a) Arsenic methylation and volatilization by arsenite S-adenosylmethionine methyltransferase in Pseudomonas alcaligenes NBRC14159. Appl Environ Microbiol 81(8):2852–2860
Zhang SY, Su JQ, Sun GX, Yang YF, Zhao Y, Ding JJ, Chen YS, Shen Y, Zhu GB, Rensing C, Zhu YG (2017) Land scale biogeography of arsenic biotransformation genes in estuarine wetland. Environ Microbiol 19(6):2468–2482
Zhang W, Guo ZQ, Song DD, Du S, Zhang L (2018) Arsenic speciation in wild marine organisms and a health risk assessment in a subtropical bay of China. Sci Total Environ 626:621–629
Zhang W, Guo ZQ, Zhou YY, Liu HX, Zhang L (2015b) Biotransformation and detoxification of inorganic arsenic in Bombay oyster Saccostrea cucullata. Aquat Toxicol 158:33–40
Zhang W, Song DD, Tan QG, Wang WX, Zhang L (2020) Physiologically based pharmacokinetic model for the biotransportation of arsenic in marine medaka (Oryziasmelastigma). Environ Sci Technol 54(12):7485–7493
Zhang W, Wang WX, Zhang L (2016) Comparison of bioavailability and biotransformation of inorganic and organic arsenic to two marine fish. Environ Sci Technol 50(5):2413–2423
Zhu YG, Xue XM, Kappler A, Rosen BP, Meharg AA (2017) Linking genes to microbial biogeochemical cycling: lessons from arsenic. Environ Sci Technol 51(13):7326–7339

Zhu YG, Yoshinaga M, Zhao FJ, Rosen BP (2014a) Earth abides arsenic biotransformation. Ann Rev Earth Planet Sci 42:443–467

Zhu YG, Yoshinaga M, Zhao FJ, Rosen BP (2014b) Earth abides arsenic biotransformations. Ann Rev Earth Planet Sci 42:443–467

Zima J, van den Berg CMG (1994) Determination of arsenic in sea-water by cathodic stripping voltammetry in the presence of pyrrolidinedithiocarbamate. AnalyticaChimicaActa. 289:291–298

# Part II
# Arsenic Exposure and Adverse Health Effects

# Chapter 3
# Human Health Effects of Chronic Arsenic Exposure


**A. Hashim**

**Abstract** Arsenic is commonly found in Earth's crust and ranks 20th in terms of abundance. It can enter the human body through drinking water, inhalation, and diet, but drinking water is the most common source. The toxic effects of arsenic are widespread in both developed and developing countries. Arsenic exposure over a prolonged period can lead to skin, lungs, CNS, and reproductive health disorders. Arsenic is a human carcinogen well known for affecting multiple organs. Recent evidence suggests that arsenic exposure causes reproductive toxicity, which leads to teratogenic and developmental effect. Arsenic exposure at high levels increases the chances of developing diabetes mellitus.

**Keywords** Health effects · Chronic arsenic · Multi-organ damage · Reproductive toxicity · Teratogenicity

## 3.1 Introduction

Arsenic exposure can occur through ingestion, inhalation, or skin contact. The most common ways are by ingestion or inhalation, and skin absorption is uncommon (Watanabe and Hirano 2013). Arsenic is more easily absorbed in the digestive tract than most other heavy metals when consumed orally. Arsenic absorbed in the body binds to red blood cells and is stored in various organs like liver, kidneys, muscles, bones, hair, skin, and nails (Hong et al. 2014). It is mainly eliminated through urine. Arsenic exposure interferes with enzymes responsible for cellular respiration, DNA synthesis and glutathione metabolism, and can cross the placenta affecting fetal nervous system (Hanlon et al. 1977). Exposure to arsenic can occur in the workplace or through ingestion of contaminated water, soil, food products from agriculture and fisheries. Arsenic is a confirmed carcinogen causing skin and lung cancers in humans

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(IARC 2004). The maximum allowed limit of arsenic in drinking water in the US has been reduced from 50 to 10 ppb, with a potential for further decrease (EPA 1982; Marchiset-Ferlay et al. 2012).

Features of chronic arsenic poisoning include multi-organ damages such as dermatologic, cardiovascular, neurological changes and the most serious aftermath is malignancy (Tchounwou et al. 2003; Achummantakath et al. 2022). Chronic arsenic poisoning results in numerous and diverse clinical symptoms. These symptoms are non-specific and insidious causing abdominal pain, diarrhea, sore throat, weakness, anorexia, alopecia, dysphonia, cachexia, and dementia (Centeno et al. 2005). Anemia is often caused by suppressed bone marrow, leading to a decrease in white blood cells (leukopenia) and the presence of small dark dots on red blood cells (basophilic stippling). Chronic poisoning can cause renal and liver damage. Arsenic poisoning causes liver cirrhosis which has been reported by different studies (Abernathy et al. 1999; Goyer 2001). Clinical symptoms of arsenic toxicity vary among individuals, populations, and regions (Kapaj et al. 2006; Guha Mazumder 2003). The cause of specific symptoms or affected organs is unclear.

## 3.2 Mechanism of Arsenic Toxicity

Arsenic exists in 2 forms: arsenite (AsIII) and arsenate (AsV). It is toxic by inhibiting mitochondrial enzymes and disrupting oxidative phosphorylation. Arsenate resembles inorganic phosphate and competes with it to produce ATP, leading to disrupted oxidative phosphorylation through arsenolysis (breakdown of an unstable arsenate ester) (Hughes 2002). Absorbed arsenate is mostly converted to arsenite in the blood by arsenate reductase (Radabaugh et al. 2000). Both arsenate and arsenite cause similar toxicity, but arsenite (trivalent species) is believed to be more toxic due to its interaction with thiol groups. Arsenite blocks essential proteins and enzymes by binding to their sulfhydryl groups, disrupting metabolism and signaling mechanisms (Aposhian 1997). Arsenite disrupts the structure of cytoskeleton. Its toxicity has been linked to the formation of reactive oxygen species, causing harm (Zhang et al. 2000; Clarkson 1987). Additionally, it hinders glutathione reductase and reduces the cell's supply of reduced glutathione, a key component in maintaining cellular redox balance and defending against oxidative stress (Thomas et al. 2001). Numerous studies have shown that arsenic accumulation can cause histopathological changes such as vacuolation, swelling, leukocyte infiltration, pyknotic nuclei, nuclear degeneration, and cytoplasmic degeneration in various organs (Achummnatakath et al. 2022).

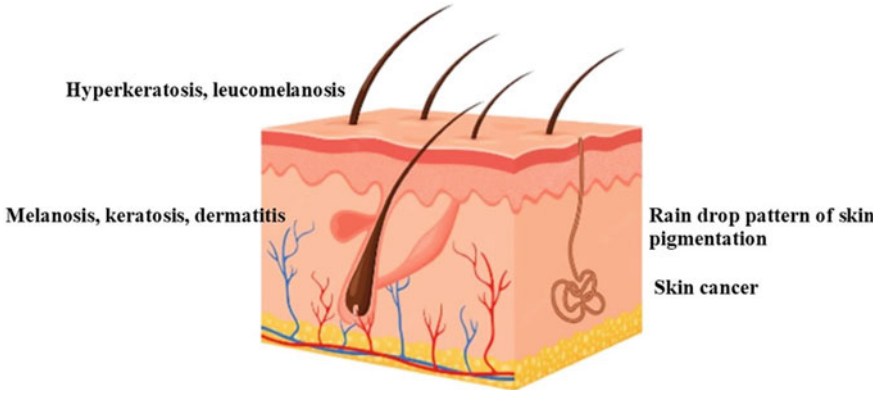


**Fig. 3.1** Effect of arsenic on skin

## 3.3 Effects on Skin

Initial sign of chronic arsenic exposure is often skin lesions, including melanosis, keratosis, dermatitis, hyperkeratosis on palms and soles, painful skin blisters, basal cell carcinoma, and squamous cell carcinoma (Madorsky et al. 1977). Melanosis includes various skin pigmentation disorders including: diffuse melanosis (hyperpigmentation), spotted melanosis (spotted pigmentation), non-melanoma (depigmentation), and leucomelanosis (white and black spots appearing together) (Fig. 3.1). It primarily affects the trunk and extremities or the entire body (Kapaj et al. 2006). Characteristic rain drop pattern, hypopigmentation of skin is another feature of chronic arsenic poisoning (Smith et al. 2000). Keratosis is a late symptom of arsenical dermatitis, (Roggenbeck et al. 2016) which typically appears on the palm and soles of the feet in various forms such as discrete or nodular, spotted, or a combination of both (spotted palmoplanter keratosis) (Roggenbeck et al. 2016) (Ayres et al. 1934; Schwartz 1997). Depigmentation increases the chance of skin cancer (basal cell carcinoma and Bowen's disease) (Lien et al. 1999; Everall et al. 1978) and consuming arsenic over time causes accumulate in keratin-rich body parts, resulting in white lines on nails (known as Aldrich Mee's lines) (Schwartz 1997). Arsenic-induced skin lesions are more common in males than females (Ratnaike et al. 2003, 2006; Ahsan et al. 2000).

## 3.4 Effects on Gastrointestinal System

Arsenic can cause gastrointestinal (GI) effects from ingesting it or heavy exposure through other routes. The main GI sign is increased permeability in small blood vessels, causing fluid loss and low blood pressure (Fig. 3.2). Inflammation and necrosis in the stomach and intestinal mucosa, potentially leading to a perforated

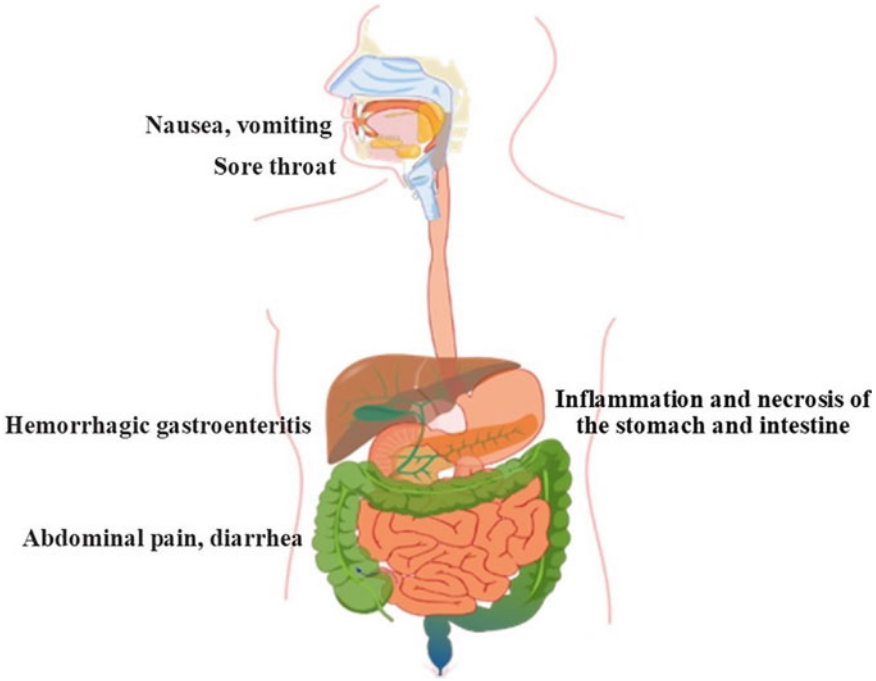


**Fig. 3.2** Effect of arsenic on gastrointestinal system

gut wall. Chronic arsenic toxicity may be associated with nausea, vomiting, abdominal pain, recurrent diarrhea, sore throat, weakness, haemorrhagic gastroenteritis, anorexia, and weight loss (Groschwitz et al. 2009; Ashraf et al. 2022; Dong et al. 2017; Poklis et al. 1990; Santra et al. 1999; Nevens et al. 1994).

## 3.5 Effects on Cardiovascular System

Epidemiological evidence suggests an association between arsenic and cardiovascular disease. The level of cardiovascular injury can be influenced by multiple factors, including age, dose, and individual susceptibility (Navas-Acien et al. 2005; Pinto et al. 1977; Axelson et al. 1978; Lee-Feldstein et al. 1989). Long-term exposure to arsenic has been linked to the development of hypertension (high blood pressure) (Rahman et al. 1999) (Fig. 3.3). This is due to the toxic effects of arsenic on the cardiovascular system. Arsenic leads to direct myocardial damage, cardiomyopathy, arrhythmias, and atypical multifocal ventricular tachycardia (Hsueh et al. 1998; Tsai et al. 1999; Benowitz et al. 1992; Goldsmith et al. 1980). Arsenic exposure is a probable reason for Black Foot Disease, which a rare peripheral vascular ailment is resulting in foot

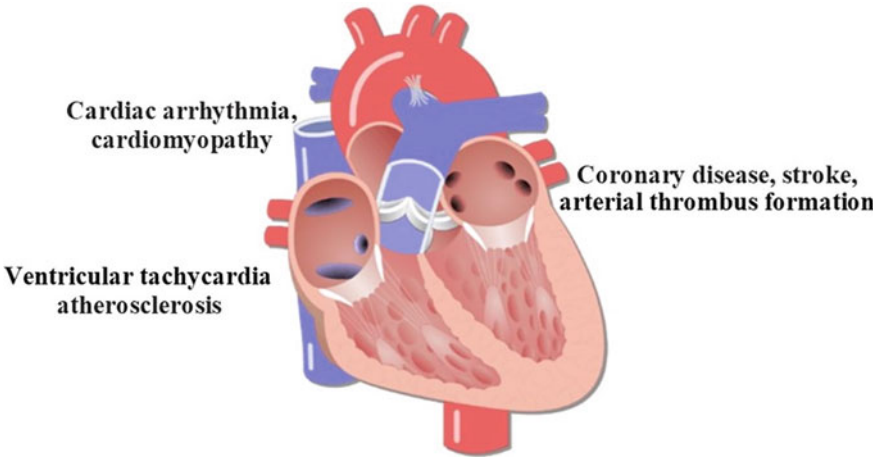


**Fig. 3.3** Effect of arsenic on cardiovascular system

gangrene (Tseng et al. 2005). Arsenic may increase the risk of atherosclerosis, coronary disease, stroke, and peripheral arterial disease (Benowitz et al. 1992; Simeonova et al. 2004). In Bangladesh, a notable rise in death from hypertensive heart disease was seen among both men and women. There have also been reports of ischaemic heart disease among Taiwanese patients. A study reported that intake of drinking water which contains arsenic for a long time can increase thrombocyte agglutination (arterial thrombus formation). Vasospastic changes (Raynaud's disease) have been reported among smelter workers and German vineyard workers exposed to arsenic (Borgono et al. 1977; Hindmarsh et al. 1977; Santra et al. 1999).

## 3.6 Effects on Respiratory System

It is mostly in industrial areas where inorganic arsenic is found as airborne particles (mostly arsenic trioxide) that causes respiratory system damage (Sijko et al. 2021) (Fig. 3.4). Initially, it causes damage to the membranes of respiratory system and intense irritation of the nasal mucosa, larynx, and bronchi, with later reports of nasal septum perforation (Islam et al. 2007; Mazumder et al. 1990). Both crude and refined forms of inorganic arsenic can lead to tracheobronchitis, rhinopharyngolaryngitis, and emphysematous lesions resulting in respiratory insufficiency (Roggenbeck et al. 2016; Mazumder et al. 1998; Saady et al. 1989). Arsenic exposure through other routes can also harm the respiratory system, leading to chronic cough and both restrictive and obstructive lung disease (Borgono et al. 1977; Quatrehomme et al. 1992). Cough, breathlessness, and auscultatory findings in respiratory system increased with age and higher arsenic concentration in water in both males and females in West Bengal and Bangladesh (Mazumder et al. 2000). Arsenic linked to

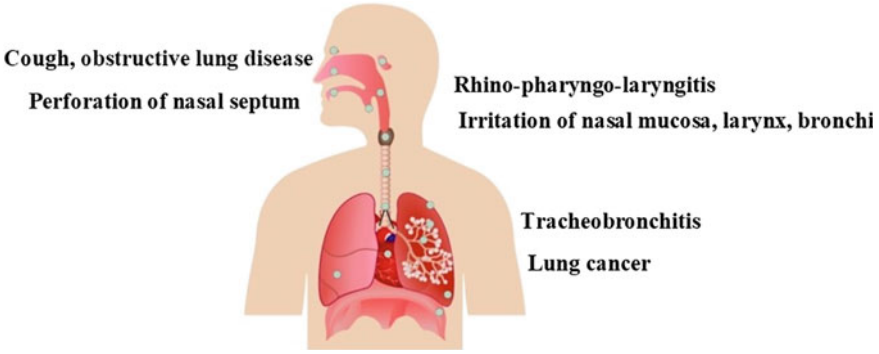


**Fig. 3.4** Effect of arsenic on respiratory system

lung cancer among industrial workers in areas where arsenic-containing pesticides, chemicals, and metals are produced (Ratnaike et al. 2003).

## 3.7 Effects on Liver

Chronic arsenicosis causes liver disease seen in population which drinks arsenic-contaminated water. Non-cirrhotic portal fibrosis is the most common liver lesion in this population (Fig. 3.5). People in West Bengal who consumed arsenic-contaminated water for 1–15 years developed liver enlargement (hepatomegaly), hepatic membrane damage, fatty infiltration, and noncirrhotic portal hypertension. In a separate study, 5 out of 42 patients were found to have liver disease caused by arsenic, leading to incomplete septal cirrhosis and an abnormally high rate of variceal bleeding. Significantly high serum aspartate aminotransferase and alanine aminotransferase and gradual decline of liver glutathione antioxidant enzymes linked to lipid peroxidation were observed in the arsenic-exposed population (Nevens et al. 1990, 1994; Hindmarsh et al. 1986; Ratnaike et al. 2003).

## 3.8 Effects on Genitourinary System

Various sources of arsenic exposure, including the environment, occupational and dietary exposures, have been implicated in the incidence of renal injury and the development of renal disease (Hsueh et al. 2009; Zheng et al. 2013). Chronic exposure of high levels of arsenic leads to the development of chronic kidney disease (CKD), an irreversible condition for which there is no current treatment (Soderland et al. 2010) (Fig. 3.6). Chronic exposure to arsenic leads to several clinical manifestations such as hypercalciuria, albuminuria, proteinuria, hypercalciuria, glomerulonephritis,

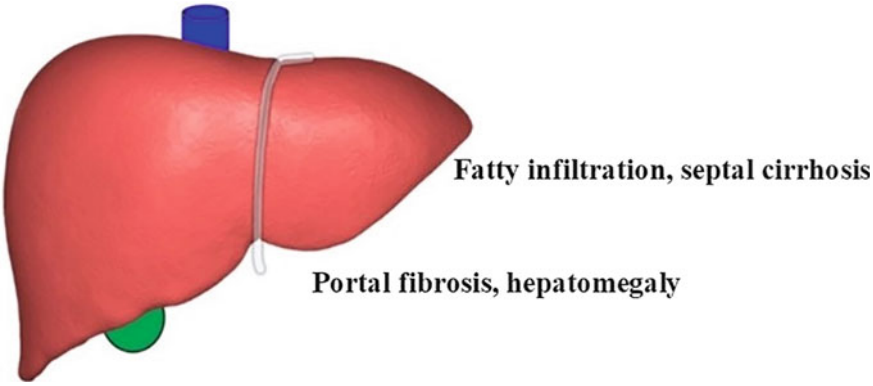


**Fig. 3.5** Effect of arsenic on liver

nephrocalcinosis, nephritis, nephrosis, acute tubular necrosis, nephrotic syndrome and necrosis of the renal papillae (Mayer et al. 1993; Astor et al. 2009; Lewis et al. 1999; Meliker et al. 2007; Karmaus et al. 2008; Zheng et al. 2014). An increase in mortality from nephritis and cancer of bladder, kidney, ureter, and prostate reported from previous studies (Ratnaike et al. 2003).

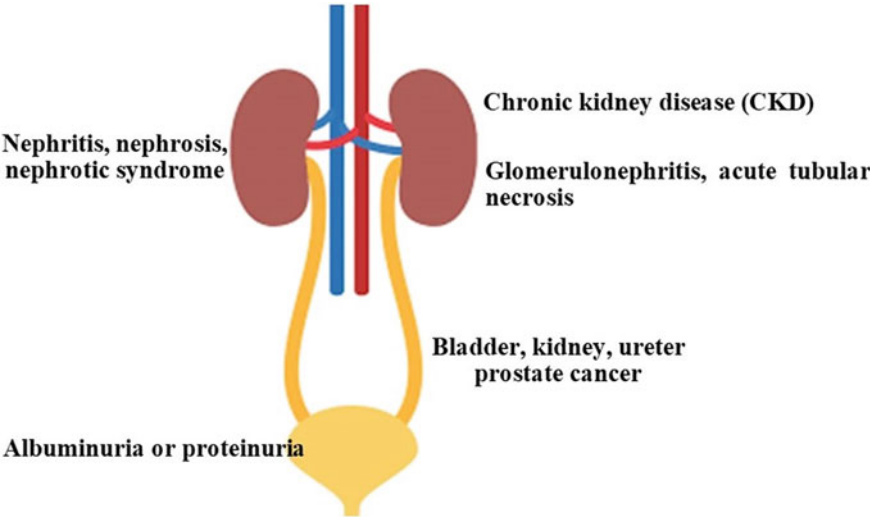


**Fig. 3.6** Effect of arsenic on genitourinary system

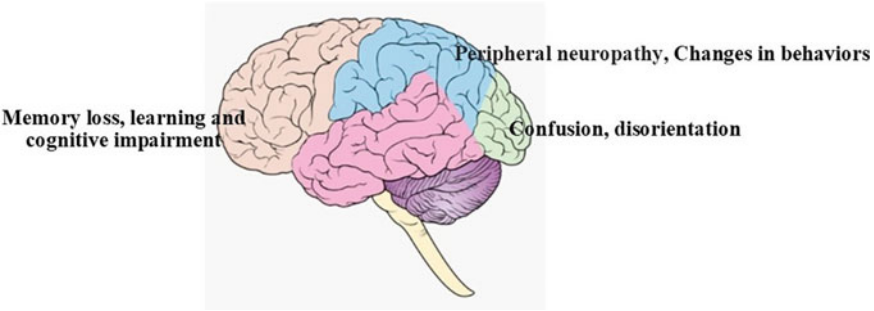


**Fig. 3.7** Effect of arsenic on nervous system

## 3.9 Effects on Nervous System

Toxic metals such as mercury, lead, and arsenic, especially heavy metals, mainly affect the neurological system (ATSDR 1990). Chronic exposure to arsenic-contaminated water can lead to reversible damage to the peripheral nervous system (Fig. 3.7). There are many complex neurological effects caused by arsenic (Lagerkvist et al. 1994; Mazumder et al. 1992; Hashim et al. 2022). The most common finding is the peripheral neuropathy that resembles Guillain-Barré syndrome, as shown by similar electromyographic results (Goddard et al. 1992). It starts with sensory symptoms with a glove-and-stocking anesthesia. In a large study group, behavioral changes, disorientation, confusion, memory loss, and cognitive issues were observed (Heyman et al. 1956; Schenk et al. 1967; Morton et al. 1989; Wasserman et al. 2004). Consumption of water contaminated with arsenic increases the incidence of cerebrovascular disease, especially strokes (Chiou et al. 1997; Tsai et al. 2003). People exposed to arsenic suffer from various neurological disorders, including decreased ability to feel sensations, such as temperature and pressure, as well as functional problems in the autonomic nervous system, such as hypohidrosis, and adiaphoresis (Rodrıguez et al. 2003).

## 3.10 Effects on the Reproductive System

In addition to being toxic to the environment, arsenic is also harmful to the reproductive system and also a developmental toxicant. The toxicity of arsenic depends on its source, form, mode of exposure, dose, and duration (Hopenhayn et al. 2003a, b; Hong et al. 2014). In males, arsenic exposure may cause reduced testosterone production, luteinizing hormone (LH), FSH, gonadotrophins, apoptosis, necrosis, and disruptions of steroidogenesis, and lead to gonadal dysfunction. Mechanism behind arsenic induced arsenic induced male toxicity also includes genotoxic effects, oxidative stress, inflammation, activation of the ERK/AKT/NF-kB signaling pathway

in testes and activation of heat shock proteins (Davila-Esqueda et al. 2012; Pant et al. 2004; Shen et al. 2013) (Fig. 3.8). Arsenic exposure affects sperm production and development, leading to infertility and poor sperm quality. Decreased sperm count and motility, as well as increased abnormal sperm and erectile dysfunction have been reported in males based on recent epidemiological studies (Nie et al. 2006; Hsieh et al. 2008; Meeker et al. 2010). Evidence suggests that arsenic accumulates in male reproductive organs, including the testes, epididymis, seminal vesicle, and prostate (Danielsson et al. 1984; Pant et al. 2001). The testes showed structural damages, such as decreased protein levels, elevated cholesterol levels, and degenerative changes in tubules, as well as damage to germinal epithelial cells. In females arsenic can cause toxicity in the ovaries and uterus, leading to cellular degeneration in the uterine layers. It interferes with follicular maturation, resulting in a decrease in E2 levels. Studies in animals and humans suggest that exposure to arsenic can cause oxidative stress in primordial and preovulatory follicles. In vitro exposure to inorganic arsenic affects all aspects of reproductive physiology, including oocyte maturation, meiotic aberrations in oocytes, ovarian steroidogenesis, prolongs diestrus, interfere corpus luteal function and luteolysis. Arsenic also causes degeneration of ovarian follicular and uterine cells. Arsenic affects female sex hormones and neurotransmitters controlled by the neuroendocrine system. Arsenic exposure in drinking water leading to pregnancy complications has been reported (Hong et al. 2014). Chronic exposure may impact placental growth in the uterus and result in low birth weight (Hopenhayn et al. 2003a, b). Reports of necrosis, apoptosis, and loss of fertilized eggs in animal studies have been documented (Flora et al. 2017). Prenatal arsenic exposure affects urine excretion, metabolite distribution, and fetal development. Arsenic inhibits ovarian gonadotrophin and steroidogenesis secretion (Chattopadhyay et al. 2002), increased adrenal hormone production, and elevated corticosterone levels in the blood (Sun et al. 2016; Hopenhayn et al. 2003a, b).

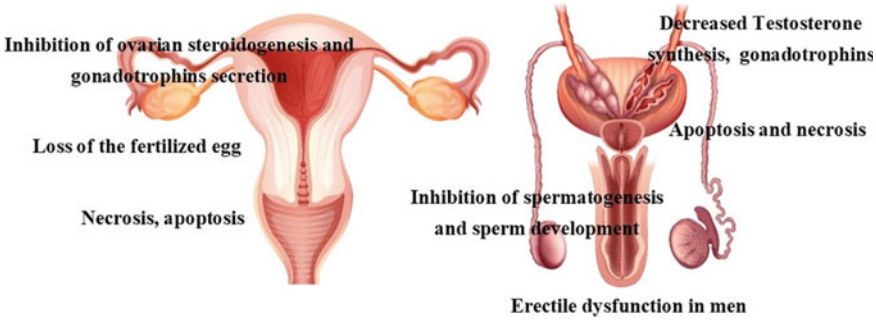


**Fig. 3.8** Effect of arsenic on reproductive system

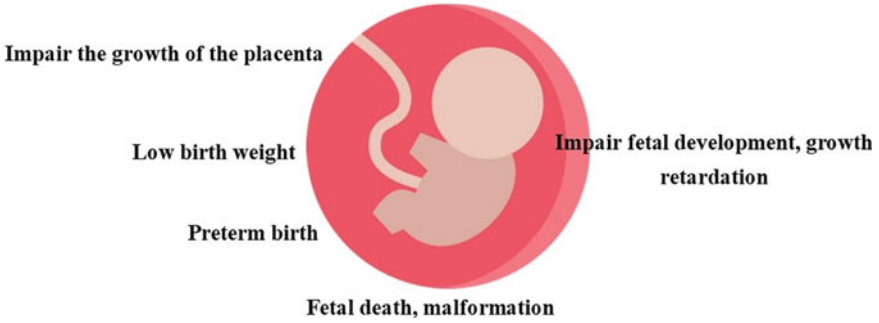


**Fig. 3.9** Developmental and teratogenicity of arsenic

## 3.11 Developmental and Teratogenicity of Arsenic

Infants and children subjected to arsenic toxicity through breastfeeding. Prenatal exposure to arsenic via oral and inhalation routes affects fetal development, including growth retardation, birth defects, decreased birth weight, preterm birth, and fetal death. Arsenic is a well-known teratogen and developmental toxicant in animal models (Tabocova et al. 1996; Golub et al. 1998) (Fig. 3.9). Experiments have shown that arsenic causes a delay in the maturational process during postnatal growth (Ihrig et al. 1998). Developmental toxicity varies based on dose, route of exposure, and gestational day (Tabocova et al. 1996; Ahmed et al. 2001). The possible mechanism may include maternal oxidative/methylated DNA damage (Chu et al. 2014). In Bangladesh. Several studies in Bangladesh, Northeastern Taiwan, and Chile have linked increased exposure to arsenic in drinking water among women to adverse pregnancy outcomes such as premature delivery, spontaneous abortion, stillbirth, and neonatal death (Milton et al. 2005; Yang et al. 2003; Hopenhayn-Rich et al. 2000). Prenatal arsenic exposure is thought to lead to adverse pregnancy outcomes and health issues in children, but the specific mechanism behind its developmental and reproductive toxicity is still unclear.

## 3.12 Malignant Disease

Arsenic can sometimes act as a co-carcinogen, indirect genotoxic carcinogen, and enhance tumerigenicity, and proliferation. Arsenic can cause DNA damage by disrupting DNA repair processes, leading to double strand breaks and cross-link formation. This results in chromosomal abnormalities, interference with micronuclei and sister chromatid exchange in mammalian cells. (Mass 1992; Bustaffa et al. 2014; Wanibuchi et al. 2004; Pershagen 1981). The association between arsenic exposure and cancer is compelling, putting millions of people at risk as the number of potential victims continues to rise. According to studies conducted in Bangladesh,

India and Taiwan, arsenic can lead to skin, lymphoma, stomach, colon, lung, nasal cavity, larynx, liver, kidney, bladder, bone, leukemia, and prostate cancer (Rossman et al. 2004; Hsueh et al. 1997; Luster et al. 2004; Ferreccio et al. 2000). Airborne arsenic exposure at 50 μg/l for a minimum of 25 years can cause a 3 × increase in the risk of lung cancer mortality. In experimental animals arsenic has been shown to induce carcinogenicity (Chiou et al. 1995; Chiu et al. 2004, Garcia-Esquinas et al. 2013; Chiang et al. 1993; Meliker et al. 2010; Morales et al. 2000; Lin et al. 2013).

### *3.12.1 Other Complications*

High levels of arsenic exposure increases the chances of developing diabetes mellitus (Rahman et al. 1998; Lai et al. 1994). Chronic arsenic toxicity causes neutropenia (Ratnaike 2003). Inorganic arsenic is believed to be responsible for hearing loss in children in Czechoslovakia (Benko et al. 1977).

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## References

Abernathy CO, Liu YP, Longfellow D, Aposhian HV, Beck B, Fowler B et al (1999) Arsenic: health effects, mechanisms of actions, and research issues. Environ Health Perspect 107(7):593–597

Achummantakath H, Prasanna KS, Nizamudeen AS (2022) Effect of Phyllanthus amarus in sodium arsenite-induced tissue damage. Bangladesh J Pharmacol 17(3):79–83

Ahmed S, Mahabbat-e Khoda S, Rekha RS, Gardner RM, Ameer SS, Moore S et al (2001) Arsenic-associated oxidative stress, inflammation, and immune disruption in human placenta and cord blood. Environ Health Perspect 119:258–264

Ahsan H, Chen Y, Parvez F, Zablotska L, Argos M, Hussain I (2006) Arsenic exposure from drinking water and risk of premalignant skin lesions in Bangladesh: baseline results from the health effects of arsenic longitudinal study. Am J Epidemiol 163(12):1138–1148

Ahsan H, Perrin M, Rahman A, Parvez F, Stute M, Zheng Y (2000) Associations between drinking water and urinary arsenic levels and skin lesions in Bangladesh. J Occup Environ Med 42(12):1195–1201

Aposhian HV (1997) Enzymatic methylation of arsenic species and other new approaches to arsenic toxicity. Annu Rev Pharmacol Toxicol 37:397–419

Ashraf SA, Elkhalifa AEO, Ahmad MF, Patel M, Adnan M, Sulieman AME (2022) Probiotic fermented foods and health promotion. In: African fermented food products-new trends. Springer, Heidelberg, pp 59–88

Astor BC, Levey AS, Stevens LA, Van LF, Selvin E, Coresh J (2009) Method of glomerular filtration rate estimation affects prediction of mortality risk. J Am Soc Nephrol 20:2214–2222

ATSDR (1990) ATSDR case studies in environmental medicine. Agency for Toxic Substances and Disease Registry, Atlanta GA, USA

Axelson O, Dahlgren E, Jansson CD (1978) Arsenic exposure and mortality: a case-referent study from a Swedish copper smelter. Br J Ind Med 35:8–15

Ayres S Jr, Anderson NP (1934) Cutaneous manifestations of arsenic poisoning. Arch Dermatol Syphilol 30:33–43
Benowitz NL (1992) Cardiotoxicity in the workplace. Occup Med 7:465–478
Bencko VK, Symon V, Chladek J, Pihrt (1977) Health aspects of burning coal with a high arsenic content. II. Hearing changes exposed children. Environ Res 13:386–395
Borgono JM, Vincent P, Venturino H (1977) Arsenic in the drinking water of the city of Antigofasta: epidemiological and clinical study before and after installation of a treatment plant. Environ Health Perspect 19:103–105
Bustaffa E, Stoccoro A, Bianchi F, Migliore L (2014) Genotoxic and epigenetic mechanisms in arsenic carcinogenicity. Arch Toxicol 88(5):1043–1067
Centeno JA, Gray MA, Mullick FG, Tchounwou PB, Tseng C (2005) Arsenic in drinking water and health issues. In: Moore TA, Black A, Centeno JA, Harding JS, Trumm DA (eds) Metal contaminants in New Zealand: sources, treatments, and effects on ecology and hu251 effects of Arsenic exposure man health. Resolutionz Press, Christchurch, pp 195–219
Chattopadhyay S, Bhaumik S, Purkayastha M, Basu S, Nag, Chaudhuri A, Das Gupta S (2002) Apoptosis and necrosis in developing brain cells due to arsenic toxicity and protection with antioxidants. Toxicol Lett 136(1):65–76
Chiang HS, Guo HR, Hong CL, Lin SM, Lee EF (1993) The incidence of bladder cancer in the black foot disease endemic area in Taiwan. Br J Urol 71(3):274–278
Chiou HY, Hsueh YM, Liaw KF, Horng SF, Chiang MH, Pu YS et al (1995) Incidence of internal cancers and ingested inorganic arsenic: a seven-year follow-up study in Taiwan. Cancer Res 55(6):1296–1300
Chiou HY, Huang WI, Su CL (1997) Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. Stroke 28:1717–1723
Chiu HF, Ho SC, Yang CY (2004) Lung cancer mortality reduction after installation of tap-water supply system in an arseniasis-endemic area in Southwestern Taiwan. Lung Cancer 46(3):265–270
Chou WC, Chung YT, Chen HY, Wang CJ, Ying TH, Chuang CY, Tseng YC, Wang SL (2014) Maternal arsenic exposure and DNA damage biomarkers, and the associations with birth outcomes in a general population from Taiwan. PLoS ONE 9(2):e86398
Clarkson TW (1987) Metal toxicity in the central nervous system. Environ Health Perspect 75:59–64
Danielsson BR, Dencker L, Lindgren A, Tjälve H (1984) Accumulation of toxic metals in male reproduction organs. Arch Toxicol Suppl 7:177–180
Davila-Esqueda ME, Jimenez-Capdeville ME, Delgado JM, De la Cruz E, Aradillas-Garcia C, Jimenez-Suarez V et al (2012) Effects of arsenic exposure during the pre- and postnatal development on the puberty of female offspring. Exp Toxicol Pathol 64:25–30
Dong X, Shulzhenko N, Lemaitre J, Greer RL, Peremyslova K, Quamruzzaman Q et al (2017) Arsenic exposure and intestinal microbiota in children from Sirajdikhan, Bangladesh. PLoS ONE 12:e0188487
Everall JD, Dowd PM (1978) Influence of environmental factors excluding ultra violet radiation on the incidence of skin cancer. Bull Cancer 65:241–247
Environmental Protection Agency (1982) An exposure and risk assessment for arsenic [cited 2022 Nov 22]. Available from: https://tinyurl.com/5dv4fdmw
Ferreccio C, Gonzalez C, Milosavjlevic V, Marshall G, Sancha AM, Smith AH (2000) Lung cancer and arsenic concentrations in drinking water in Chile. Epidemiology 11(6):673–679
Flora SJ, Agrawal S (2017) Arsenic, cadmium, and lead. In: Reproductive and developmental toxicology. Academic Press, pp 537–566
Garcia-Esquinas E, Pollan M, Umans JG, Francesconi KA, Goessler W, Guallar E et al (2013) Arsenic exposure and cancer mortality in a US-based prospective cohort: the strong heart study. Cancer Epidemiol Biomarkers Prev 22(11):1944–1953
Goddard MJ, Tanhehco JL, Dau PC (1992) Chronic arsenic poisoning masquerading as Landry-Guillain-Barre syndrome. Electromyogr Clin Neurophysiol 32:419–423

Goldsmith S, From H (1980) Arsenic-induced atypical ventricular tachycardia. N Engl J Med 303:1096–1098
Golub MS, Macintosh MS, Baumrind N (1998) Developmental and reproductive toxicity of inorganic arsenic: animal studies and human concerns. J Toxicol Environ Health B Crit Rev 1:199–241
Goyer RA (2001) Toxic effects of metals. In: Casarett LJ, Doull J, Klaassen CD (eds) Casarett and Doull's toxicology: the basic science of poisons, 6th edn. McGraw-Hill, New York, pp 811–867
Groschwitz KR, Hogan SP (2009) Intestinal barrier function: molecular regulation and disease pathogenesis. J Allergy Clin Immunol 124:3–20
Guha Mazumder DN (2003) Chronic arsenic toxicity: clinical features, epidemiology, and treatment: experience in West Bengal. J Environ Sci Health A Tox Hazards Subst Environ Eng A38:141–163
Hanlon DP, Ferm VH (1977) Placental permeability of arsenate ion during early embryogenesis in the hamster. Experientia 33(9):1221–1222
Hashim A, Ahmed MG, Rahiman NBA, Manikkoth S, Pramod KL (2022) Evaluation of the neuroprotective activity of P. amarus in attenuating arsenic-induced neurotoxicity-an in vivo study. Phytomedicine Plus 2(3):100316
Heyman A, Pfeiffer JB, Willett RW, Taylor HM (1956) Peripheral neuropathy caused by arsenical intoxication. N Engl J Med 254(9):401–409
Hindmarsh JT, McCurdy RF, Savory J (1986) Clinical and environmental aspects of arsenic toxicity. CRC Crit Rev Clin Lab Sci 23(4):315–347
Hindmarsh JT, Mcktchie OR, Heffernan LPM, Hayne OA, Ellenberger HA, McCurdy RF et al (1977) Electromyographic abnormalities in chronic environmental arsenicalism. J Anal Toxicol I 6:270–276
Hong YS, Song KH, Chung JY (2014) Health effects of chronic arsenic exposure. J Prev Med Public Health 47(5):245–252
Hopenhayn C, Ferreccio C, Browning SR, Huang B, Peralta C, Gibb H et al (2003a) Arsenic exposure from drinking water and birth weight. Epidemiology 14(5):593–602
Hopenhayn C, Huang B, Christian J, Peralta C, Ferreccio C, Atallah R et al (2003b) Profile of urinary arsenic metabolites during pregnancy. Environ Health Perspect 111(16):1888–1891
Hopenhayn-Rich C, Browning SR, Hertz-Picciotto I, Ferreccio C, Peralta C, Gibb H (2000) Chronic arsenic exposure and risk of infant mortality in two areas of Chile. Environ Health Perspect 108:667–673
Hsieh FI, Hwang TS, Hsieh YC, Lo HC, Su CT, Hsu HS, Chiou HY, Chen CJ (2008) Risk of erectile dysfunction induced by arsenic exposure through well water consumption in Taiwan. Environ Health Perspect 116:532–536
Hsueh YM, Chiou HY, Huang YL, Wu WL, Huang CC, Yang MH et al (1997) Serum beta-carotene level, arsenic methylation capability, and incidence of skin cancer. Cancer Epidemiol Biomarkers Prev 6(8):589–596
Hsueh YM, Chung CJ, Shiue HS (2009) Urinary arsenic species and CKD in a Taiwanese population: a case-control study. Am J Kidney Dis 54:859–870
Hsueh YM, Wu WL, Huang YL (1998) Low serum carotene level and increased risk of ischemic heart disease related to long-term arsenic exposure. Atherosclerosis 141:249–257
Hughes MF (2002) Arsenic toxicity and potential mechanisms of action. Toxicol Lett 133:1–16
Ihrig MM, Shalat SL, Baynes C (1998) A hospital-based case-control study of stillbirths and environmental exposure to arsenic using an atmospheric dispersion model linked to a geographical information system. Epidemiology 9:290–294
International Agency For Research On Cancer (2004) IARC monographs on the evaluation of carcinogen risks to humans [cited 2022 Nov 16]. Available from: http://monographs.iarc.fr/ENG/Monographs/vol83/mono83.pdf
Islam LN, Nurun Nabi A, Rahman MM, Zahid MSH (2007) Association of respiratory complications and elevated serum immunoglobulins with drinking water arsenic toxicity in human. J Environ Sci Health Part A 42:1807–1814

Kapaj S, Peterson H, Liber K, Bhattacharya P (2006) Human health effects from chronic arsenic poisoning: a review. J Environ Sci Health A Tox Hazard Subst Environ Eng 41(10):2399–2428
Karmaus W, Dimitrov P, Simeonov V, Tsolova S, Bonev A, Georgieva R (2008) Metals and kidney markers in adult offspring of endemic nephropathy patients and controls: a two-year follow-up study. Environ Health 7:11
Lagerkvist BJ, Zetterlund B (1994) Assessment of exposure to arsenic among smelter workers: a 5-year follow-up. Am J Ind Med 25:477–488
Lai MS, Hsueh YM, Chen CJ, Shyu MP, Chen SY, Kuo TL et al (1994) Ingested inorganic arsenic and prevalence of diabetes mellitus. Am J Epidemiol 139(5):484–492
Lee-Feldstein A (1989) A comparison of several measures of exposure to arsenic. Matched case-control study of copper smelter employees. Am J Epidemiol 129:112–124
Lewis DR, Southwick JW, Ouellet-Hellstrom R, Rench J, Calderon RL (1999) Drinking water arsenic in Utah: a cohort mortality study. Environ Health Perspect 107:359–365
Lien HC, Tsai TF, Lee YY (1999) Merkel cell carcinoma and chronic arsenicism. J Am Acad Dermatol 41:641–643
Lin HJ, Sung TI, Chen CY, Guo HR (2013) Arsenic levels in drinking water and mortality of liver cancer in Taiwan. J Hazard Mater 262:1132–1138
Luster MI, Simeonova PP (2004) Arsenic and urinary bladder cell proliferation. Toxicol Appl Pharmacol 198(3):419–423
Madorsky DD (1977) Arsenic in dermatology. Assoc Milit Dermatol 3(2):19–22
Marchiset-Ferlay N, Savanovitch C, Sauvant-Rochat MP (2012) What is the best biomarker to assess arsenic exposure via drinking water? Environ Int 39(1):150–171
Mayer DR, Kosmus W, Pogglitsch H, Mayer D, Beyer W (1993) Essential trace elements in humans. Serum arsenic concentrations in hemodialysis patients in comparison to healthy controls. Biol Trace Elem Res 37:27–38
Mazumder D, Das-Gupta J, Chakraborty AK, Chatterjee A, Das D, Chakraborti D (1990) Environmental pollution and chronic arsenicosis in south Calcutta. Bull World Health Org 70:481–485
Mazumder DN, Das-Gupta J, Santra A (1998) Chronic arsenic toxicity in West Bengal—the worse calamity in the world. J Indian Med Assoc 96:4–7
Mazumder DN, Haque R, Ghosh N (2000) Arsenic in drinking water and the prevalence of respiratory effects in West Bengal, India. Int J Epidemiol 29:1047–1052
Mass MJ (1992) Human carcinogenesis by arsenic. Environ Geochem Health 14(2):49–54
Meeker JD, Rossano MG, Protas B, Padmanahban V, Diamond MP, Puscheck E et al (2010) Environmental exposure to metals and male reproductive hormones: circulating testosterone is inversely associated with blood molybdenum. Fertil Steril 93:130–140
Meliker JR, Slotnick MJ, AvRuskin GA, Schottenfeld D, Jacquez GM, Wilson ML et al (2010) Lifetime exposure to arsenic in drinking water and bladder cancer: a population-based case-control study in Michigan, USA. Cancer Causes Control 21(5):745–757
Meliker JR, Wahl RL, Cameron LL, Nriagu JO (2007) Arsenic in drinking water and cerebrovascular disease, diabetes mellitus, and kidney disease in Michigan: a standardized mortality ratio analysis. Environ Health 6:4
Milton AH, Smith W, Rahman B, Hasan Z, Kulsum U, Dear K et al (2005) Chronic arsenic exposure and adverse pregnancy outcomes in Bangladesh. Epidemiology 16:82–86
Morales KH, Ryan L, Kuo TL, Wu MM, Chen CJ (2000) Risk of internal cancers from arsenic in drinking water. Environ Health Perspect 108(7):655–661
Morton WE, Caron GA (1989) Encephalopathy: an uncommon manifestation of workplace arsenic poisoning? Am J Ind Med 15:1–5
Navas-Acien A, Sharrett AR, Silbergeld EK, Schwartz BS, Nachman KE, Burke TA, Guallar E (2005) Arsenic exposure and cardiovascular disease: a systematic review of the epidemiologic evidence. Am J Epidemiol 162(11):1037–1049
Nevens F, Fevery J, Van Steenbergen W, Sciot R, Desmet V, De-Groot J (1990) Arsenic and non-cirrhotic portal hypertension: a report of 8 cases. J Hepatol 1:80–85

Nevens F, Staessen D, Sciot R (1994) Clinical aspects of incomplete septal cirrhosis in comparison with macronodular cirrhosis. Gastroenterology 106:459–463
Nie JS, Pei QL, Han G, Xu JX, Mu JJ (2006) Semen quality decreased by inorganic arsenic. J Environ Occup Med 23:189–190
Pant N, Kumar R, Murthy RC, Srivastava SP (2001) Male reproductive effect of arsenic in mice. Biometals 14:113–117
Pant N, Murthy RC, Srivastava SP (2004) Male reproductive toxicity of sodium arsenite in mice. Hum Exp Toxicol 23:399–403
Pershagen G (1981) The carcinogenicity of arsenic. Environ Health Perspect 40:93–100
Pinto SS, Enterline PE, Henderson V (1977) Mortality experience in relation to a measured arsenic trioxide exposure. Environ Health Perspect 19:127–130
Poklis A, Saady JJ (1990) Arsenic poisoning: acute or chronic? Suicide or murder? Am J Forensic Med Pathol 11:226–232
Quatrehomme G, Ricq O, Lapalus P (1992) Acute arsenic intoxication: forensic and toxicologic aspects (an observation). J Forensic Sci 37:1163–1171
Rahman M, Tondel M, Ahmad SA (1999) Hypertension and arsenic exposure in Bangladesh. Hypertension 33:74–78
Rahman M, Tondel M, Ahmad SA, Axelson O (1998) Diabetes mellitus associated with arsenic exposure in Bangladesh. Am J Epidemiol 148(2):198–203
Ratnaike RN (2003) Acute and chronic arsenic toxicity. Postgrad Med J 79(933):391–396
Radabaugh TR, Aposhian HV (2000) Enzymatic reduction of arsenic compounds in mammalian systems: reduction of arsenate to arsenite by human liver arsenate reductase. Chem Res Toxicol 1:26–30
Rodrıguez VM, Jiménez-Capdeville ME, Giordano M (2003) The effects of arsenic exposure on the nervous system. Toxicol Lett 145(1):1–8
Roggenbeck BA, Banerjee M, Leslie EM (2016) Cellular arsenic transport pathways in mammals. J Environ Sci 49:38–58
Rossman TG, Uddin AN, Burns FJ (2004) Evidence that arsenite acts as a cocarcinogen in skin cancer. Toxicol Appl Pharmacol 198(3):394–404
Saady JJ, Blanke RV, Poklis A (1989) Estimation of the body burden of arsenic in a child fatally poisoned by arsenite weedkiller. J Anal Toxicol 13:310–312
Santra A, Das-Gupta J, De BK (1999) Hepatic manifestations in chronic arsenic toxicity. Indian J Gastroenterol 18:152–155
Schenk VW, Stolk PJ (1967) Psychosis following arsenic (possibly thalium) poisoning. Psychiatr Neurol Neurochir 70:31–37
Schwartz RA (1997) Arsenic and the skin. Int J Dermatol 36(4):241–250
Shen H, Xu W, Zhang J, Chen M, Martin FL, Xia Y, Liu L, Dong S, Zhu YG (2013) Urinary metabolic biomarkers link oxidative stress indicators associated with general arsenic exposure to male infertility in a Han Chinese population. Environ Sci Technol 47:8843–8851
Sijko M, Kozłowska L (2021) Influence of dietary compounds on arsenic metabolism and toxicity. Part II—human studies. Toxics 9(10):259
Simeonova PP, Luster MI (2004) Arsenic and atherosclerosis. Toxicol Appl Pharmacol 198:444–449
Smith AH, Arroyo AP, Mazumdar DN (2000) Arsenic-induced skin lesions among Atacameno people in northern Chile despite good nutrition and centuries of exposure. Environ Health Perspect 108:617–620
Soderland P, Lovekar S, Weiner DE, Brooks DR, Kaufman JS (2010) Chronic kidney disease associated with environmental toxins and exposures. Adv Chronic Kidney Dis 17:254–264
Sun HJ, Xiang P, Luo J, Hong H, Lin H, Li HB, Ma LQ (2016) Mechanisms of arsenic disruption on gonadal, adrenal and thyroid endocrine systems in humans: a review. Environ Int 95:61–68
Tabocova S, Hunter ES, Gladen BC (1996) Developmental toxicity of inorganic arsenic in whole embryo: culture oxidation state, dose, time, and gestational age dependence. Toxicol Appl Pharmacol 138:298–307

Tchounwou PB, Patlolla AK, Centeno JA (2003) Carcinogenic and systemic health effects associated with arsenic exposure: a critical review. Toxicol Pathol 31(6):575–588

Thomas DJ, Styblo M, Lin S (2001) The cellular metabolism and systemic toxicity of arsenic. Toxicol Appl Pharmacol 176:127–144

Tsai SM, Wang TN, Ko YC (1999) Mortality for certain diseases in areas with high levels of arsenic in drinking water. Arch Environ Health 54:186–193

Tsai SY, Chou HY, The HW, Chen CM, Chen CJ (2003) The effects of chronic arsenic exposure from drinking water on the neurobehavioral development in adolescence. Neurotoxicology 24(4–5):747–753

Tseng CH, Huang YK, Huang YL, Chung CJ, Yang MH, Chen CJ et al (2005) Arsenic exposure, urinary arsenic speciation, and peripheral vascular disease in blackfoot disease-hyperendemic villages in Taiwan. Toxicol Appl Pharmacol 206(3):299–308

Wasserman GA, Liu X, Parvez F, Ahsan H, Factor-Litvak P, Van Geen A et al (2004) Water arsenic exposure and children's intellectual function in Araihazar, Bangladesh. Environ Health Perspect 112(13):1329–1333

Watanabe T, Hirano S (2013) Metabolism of arsenic and its toxicological relevance. Arch Toxicol 87(6):969–979

Wanibuchi H, Salim EI, Kinoshita A, Shen J, Wei M, Morimura K et al (2004) Understanding arsenic carcinogenicity by the use of animal models. Toxicol Appl Pharmacol 198(3):366–376

Yang CY, Chang CC, Tsai SS, Chuang HY, Ho CK, Wu TN (2003) Arsenic in drinking water and adverse pregnancy outcome in an arseniasis-endemic area in northeastern Taiwan. Environ Res 91:29–34

Zheng L, Kuo CC, Fadrowski J, Agnew J, Weaver VM, Navas-Acien A (2014) Arsenic and chronic kidney disease: a systematic review. Curr Environ Health Rep 1(3):192–207

Zheng LY, Umans JG, Tellez-Plaza M (2013) Urine arsenic and prevalent albuminuria: evidence from a population-based study. Am J Kidney Dis 61:385–394

Zhang TL, Gao YX, Lu JF, Wang K (2000) Arsenite, arsenate and vanadate affect human erythrocyte membrane. J Inorg Biochem 79:195–203

# Chapter 4
# Modulation of Different Signaling Pathways in Liver Cancer by Arsenic Trioxide


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**Abstract** The greatest health concern facing the globe today is still cancer. In order to defeat various malignancies, researchers are now racing to develop effective anticancer tactics to stop this global tidal wave of cancer in both its extremely early and advanced stages. However, very few specific treatments or medications have so far been proven to be effective. An old medication called arsenic trioxide ($As_2O_3$) has recently gained resurgence as a treatment for several cancers. Arsenic is generally recognized as a naturally hazardous material that can cause a wide range of harmful adverse reactions. Despite its present image as a poison, arsenic is one of the world's oldest medicines and has been used for ages to treat conditions ranging from cancer to infections. Due to its treatable antitumor impact in acute promyelocyticleukaemia (APL) patients, it attracted a lot of attention from people worldwide. The anticancer medication most frequently used among the arsenicals is (ATO) arsenic trioxide. Numerous studies have been carried out to comprehend the molecular pathways through which ATO induces or facilitates the apoptotic signalling pathway in cancer cells. The treatment of Hepatocellular Carcinoma (HCC) and other cancers with novel, currently available arsenic-based therapeutics is discussed here. We also discussed the novel molecular mechanism that underlies the combined therapy' induction of apoptosis.

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**Keywords** Arsenic trioxide (ATO) · Hepatocellular carcinoma (HCC) · Cellular signaling pathways · Apoptosis

## 4.1 Introduction

Numerous cancer-related fatalities globally are caused by hepatocellular carcinoma (HCC) (Tunissiolli et al. 2017). The total burden of liver cancer is rising globally over time, in contrast to the declining disease burden and effect of many other serious malignancies. Between 2005 and 2015, liver cancer, which had an increase of 4.6% in absolute years of life lost, was the second-leading cause of cancer-related death globally (Bray et al. 2018; McGlynn et al. 2021). Hepatocellular carcinoma (HCC) incidence has increased during the past few years. Liver cancer is predicted to be the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide in 2018. When compared to other cancers, a total of 841,000 (4.7%) new liver cancers are estimated to have occurred in 2018 in addition to 782,000 (8.2%) deaths (Bray et al. 2018). The rise in hepatitis B and C virus infections, metabolic syndrome, and alcohol-induced liver disorders have all been linked to this increase (Malek et al. 2014). Liver cancer incidence and mortality are 2–3 times higher among men in the majority of geographical regions. In transitioning nations, men experience two times the incidence rates of women (Rawla et al. 2018). Since the late 1990s, ageing and population expansion have caused age-standardized incidence rates (ASIRs) of liver cancer to progressively decline globally, although the overall number of cases has been rising (Global Burden of Disease Cancer Collaboration 2017; Crissien and Frenette 2014). Males were more likely than females to acquire HCC (2.4:1), and more instances were discovered in Melanesia, Micronesia, and Polynesia than in Eastern and Southern Asia, Middle and Western Africa (Crissien and Frenette 2014; Ferlay et al. 2010; Altekruse et al. 2009).Importantly, the prevalence of obesity, non-alcoholic steatohepatitis (NASH), and hepatitis C would all increase, along with the risk of HCC. Although the expenses are now prohibitive, recent advancements in the treatment of HBV and HCV imply that a significant proportion of liver cancer cases could be averted (Rawla et al. 2018). Due to its significant anticancer potential, arsenic, one of the traditional medicines, is being employed as a medicinal agent throughout the world. In the nineteenth century, chronic myelogenous leukaemia (CML) was first treated with arsenic trioxide (ATO), a trivalent arsenite (AsIII) (Paul et al. 2022). By encouraging differentiation in acute promyelocytic leukaemia (APL) cells, ATO easily triggers apoptosis and is thus used as a therapeutic medication in the clinical setting (Zhou et al. 2007; Sonneveld 2017). As a result, mounting data suggests that ATO and/or other arsenicals are effective cancer treatments. An increasing body of research suggests that, in addition to ATO monotherapy, ATO may be a beneficial medicine when paired with recently developed molecularly targeted therapies as well as traditional anticancer therapeutics like radiation and chemotherapy. As an illustration, it has been demonstrated clinically that the combination of ATO and all-trans retinoic acid (ATRA) results in less toxicity

and better outcome than the combination of ATRA and chemotherapy when treating patients with APL (Hu et al. 2020; Bayat et al. 2017; Jambrovics et al. 2020).The anticancer action of ATO-based therapy in various forms of solid cancer and haematological malignancies is summarized in this chapter. In addition, the pro-apoptotic effect of these combination therapies on cancer cells and their molecular basis are summarized. As millions of people are at risk, the link between arsenic and cancer has become a much bigger issue over time. Arsenic, a naturally occurring substance, has earned a place in history as both a toxin that should be avoided and a miraculous cure (Paul et al. 2022). The cytotoxic capabilities of arsenic and its methylated compounds in the eradication of cancer are quite poorly understood. The increased awareness of arsenic's toxicity and carcinogenicity, as well as its use in chemotherapy, must be characterized with caution given our limited understanding of the several channels via which arsenic exerts its detrimental effects (Khairul et al. 2017). In this chapter, we demonstrate that arsenical chemicals promote cancer cell death when paired with other anticancer medicines, such as chemotherapies, radiation and molecularly targeted medications, in order to provide a fuller knowledge of the restorative role of arsenic in cancer treatment. Arsenic has been shown to have anticancer properties in numerous studies, and these studies have also discussed the potential targets of ATO in cancerous cells. Arsenic mediated synergistic anticancer benefits with various anticancer therapies are still unknown to have underlying molecular mechanisms, nonetheless (Kamps et al. 2017). This shows that it would be able to target particular substances, signalling systems, or even individual cancer cells, which could lead to the emergence of a new population of cancer cells that are more aggressive and may eventually become resistant to treatment. Therefore, new treatment drugs and/or approaches are needed to combat medication resistance and enhance the prognosis and quality life of tumor patients. The selectivity of cancer treatments may be improved with further knowledge of the connection between the triggering of genetic/epigenetic alterations as well as apoptosis induction in cancer cells. To create a novel combination therapy for cancer, more research is needed to demonstrate the synergistic anticancer activity of ATO-based combination medicines. However, it is still unclear exactly what changes in metabolism arsenic and its constituents cause. The use of this metalloid again to treat APL is a novel development in the field of cancer treatment. Based on these facts, arsenic may be a possible target in several cancer types, and these tactics may provide insight into valuable uses of arsenicals as cancer treatments in the near future. In this review, we concentrated on the targeted pathways that would be useful in illuminating the area's actual significance in relation to toxicity as well as in possible drugs. In order to affect different cellular responses, such as stimulation of apoptosis, growth restriction, angiogenesis inhibition, and many others, arsenic and its related chemicals use many anticancer mechanisms listed in Table 4.1.

**Table 4.1** List of typical ATO-based combination cancer therapeutics

| S. No. | Arsenic in combination | Types of cancer | Mechanism of action | Refs. |
|---|---|---|---|---|
| 1 | ATO + ATRA (All-trans-retinoic acid) | Acute promyelocyticleukemia (APL) | Differentially promote PML-RAR proteasomal degradation by ATO and APL | de Thé and Chen (2010) |
| | | Acute myeloid leukemia (AML) | FLT3 signalling pathways are both inhibited | Liu et al. (2020) |
| | | AML/NPM1-mutated | Decrease in nucleophosmin quality (NPM1) | El Hajj et al. (2015a, b) |
| | | Adult T-cell leukemia | HTLV-I transactivator protein (Tax) degradation | Ji et al. (2014) |
| | | Ovarian cancer | Depletion of GSH, increased production of ROS within cells, and activation of a pathway linked to oxidative stress | Griffith (1982) |
| | | Lung cancer | GSH depletion | Han et al. (2008) |
| | | Glioma | GSH depletion | Klauser et al. (2014) |
| 2 | ATO + Cisplatin (CDDP) | Ovarian cancer | Down regulation of HIF1A, IGF1R, MET, and AR and up regulation of BAX and TP53 (effects by only ATO) | Zhang et al. (2009) |
| | | Lung cancer | Bax levels rise whereas Bcl-2 and clustering levels fall | Li et al. (2009) |
| | | Cervical cancer | Caspase-3 is activated jointly | Byun et al. (2013a, b) |
| | | Glioma | Suppressing the characteristics of cancer stem cells (CSCs) | Fang and Zhang (2020) |
| | | Hepatoma | Lower GSH level | Lin et al. (2005) |

(continued)

**Table 4.1** (continued)

| S. No. | Arsenic in combination | Types of cancer | Mechanism of action | Refs. |
|---|---|---|---|---|
| | | Lung adenocarcinoma | Lower GSH level | |
| | | Breast cancer | Lower GSH level | |
| 3 | ATO + radiotherapy | Prostate cancer | Akt/mTOR signalling pathway inhibition | Wang et al. (2018) |
| | | Oral cancer | Reduction of tumour angiogenesis, proliferation, and metastasis | Kumar et al. (2008) |
| | | Cervical cancer | Deregulation of MMP-9 expression produced by radiation, activation of MAPKs induced by ROS production, and Bax translocation | Wei et al. (2005; Kang and Lee 2008) |
| | | Breast cancer | Bcl-2/Bax ratio | Liu et al. (2012a, b) |
| | | Glioma | Increased mitotic arrest and control over the ERK1/ERK2 and PI3K/Akt signalling pathways | Chiu et al. (2009) |
| | | Oral cancer | ROS production, a drop in Bcl-2 protein levels, and constitutive caspase-3 activation | Nakaoka et al. (2014) |
| 4 | ATO + buthioninesulfoximine (BSO) | AML | ROS-induced phosphorylation of JNK and $BIM_{EL}$ and induction of intrinsic apoptosis | Chen et al. (2006) |
| | | Lymphoma and leukemia | JNK is phosphorylated by ROS, and death receptor 5 is upregulated | Tanaka et al. (2014) |

(continued)

**Table 4.1** (continued)

| S. No. | Arsenic in combination | Types of cancer | Mechanism of action | Refs. |
|---|---|---|---|---|
| 5 | ATO + bortezomib (BOR | Multiple myeloma | ATO/BOR and p38 inhibitor (SB203580) had a synergistic effect on Bcl-2 down regulation and apoptosis in MM cell lines | Wen et al. (2010) |
| | | Mantle cell lymphoma | NF-B activity inhibition, cyclin D1 and Bcl-2 expression reductions, and reduced interaction of Mcl-1 with Bak | Zhao et al. (2015), El Eit et al. (2014) |
| | | Chronic myelogenous leukemia (CML) | Activation of CML leukemia-initiating cells to suppress | Bazarbachi et al. (1999) |
| 6 | ATO + interferon-α (IFN-α) | ATL | HTLV-I transactivator protein (Tax) degradation | El-Sabban et al. (2000), Abou-Merhi et al. (2007) |
| | | Primary effusion lymphoma | A reduction in NF-B activity | Abou-Merhi et al. (2007) |

## 4.2 Potential Targets of Arsenic

Aside from affecting diverse pathways, arsenic causes profound cellular changes, such as the induction of apoptosis, a slowing of the rate of cell division, a suppression of angiogenesis, and a stimulation of differentiation (Miller Jr et al. 2002; Antman 2001). Arsenic may interact with closely spaced cysteine moieties on essential cell proteins to cause its biological effects. Arsenic is well known anticancer agent, particularly in the treatment of APL. The protein mentioned above aids in blocking the gene that controls myeloid differentiation. The cysteine-rich region of the PML gene aids with the interaction with arsenic, according to the gene sequences. The nuclear body located inside the nucleus is where this PML protein is typically found (Antman 2001; Davison et al. 2002).When PML and RARretinoic acid receptor alpha gene (RARA) interact in leukaemia, nuclear bodies are disrupted, which causes the PML proteins to be broken up into smaller pieces. In addition to blocking myeloid differentiation, RA treatment also prevents the PML-RARA fusion used in ATRA therapy for APL (Antman 2001). Arsenic was demonstrated as a unique approach for the treatment of ATR as it demonstrates total abrogation in both RA-resistant and RA-sensitive APL patients. Arsenic also causes the breakdown of PML-RARA

fusion protein (Alimoghaddam 2014; Jing 2004). A nuclear protein named Daxx that co localizes with PML in nuclear bodies and inhibits transcription is promoted by arsenic trioxide (Jing 2004). In Fas-induced apoptosis, Daxx plays a significant role in modulating the transcription of genes associated to death (Zhang et al. 2001; Lallemand-Breitenbach and de Thé 2010). As a result, even a little rise in arsenic concentration has an impact on PML within nuclear bodies and is sufficient to cause Daxx-dependent apoptosis. The covalent modification of PML by the ubiquitin-like protein SUMO-1, which is affected by arsenic and related compounds, results in an increase in PML-containing nuclear bodies and is a key factor in the pro-apoptotic signal pathway (Lallemand-Breitenbach and de Thé 2010). As a result, an increasing dose of arsenic causes apoptosis via increasing the SUMO-1 modification of PML-RARA.

## 4.3 Response of Arsenic on Cellular Signaling Pathways

Arsenic has been implicated in pro-apoptotic pathways in a number of cancer cell lines that may be dependent on PML and P53, according to researchers. In MBC-1, a B-cell lymphoma gastric cancer cell, arsenic trioxide increases P53 expression, which causes apoptosis followed by caspase activation (Bernardi and Pandolfi 2007; Percherancier et al. 2009; Kang et al. 2019). Infected cells with human T-cell lymphotropic virus type 1 experience G1 phase arrest, an accumulation of P53, Cip1/p21 and p27KIP1, along with dephosphorylation of retinoblastoma protein, which triggers death (Ma et al. 2014; Zhong et al. 2018). Arsenite causes double strand breaks in human fibroblast cells, which also phosphorylates or upregulates P53, helping to boost the production of P53's downstream proteins (P21 and others) (Yih and Lee 2000; John et al. 2000). According to reports, an arsenic treatment to some extent demands on P53 accumulation, mostly because of the participation of proteins associated to phosphatidylinositol-3-kinase in antaxia-telangiectasia mutant pathways (Ishitsuka et al. 2000; Williams and Schumacher 2016; Yu et al. 2014; Levine 1997; Carr and Jones, 2016). In APL patients, arsenic downregulates Bcl-2 while upregulating p53, other growth arrest-related genes, and apoptosis. The modulation of arsenic-mediated apoptosis is significantly influenced by Bcl-2 (Yu et al. 2014; Shiloh 2003; Zannini et al. 2014). Arsenic changes the nuclear body binding of PML-containing cells, Bax, and p27KIP1, which together with interferons cause cell death (Zheng et al. 2010; Kumar et al. 2018; Zhou et al. 2007).

## 4.4 Effects of Arsenic on Signalling Pathways

As a result of the increased activity of mitogenic components like c-Fos and c-Jun caused by sodium arsenite, because this sodium arsenite increases the DNA binding activity of transcription factor AP-1 (activator protein-1). This AP-1 also

activates the JNKs, which are crucial for the phosphorylation of numerous transcription factors and increase the production of early-stage genes (Liu et al. 2016; Lam et al. 2014). The principal way that arsenic activates the JNK pathway is by obstructing the constitutive JNK phosphatase. When arsenic compounds are present, they activate MEKK3 and MEKK4 in human embryonic kidney cells, however when arsenic is not, MEKK2 must also be activated in order to activate the JNK pathway (Porter et al. 1999). Additionally, arsenic affects various signalling pathways (briefly summarized in Fig. 4.1) which leads to elevated oxidative stress and stimulates apoptosis in tumor cells. Members of the MAP kinase family, which controls extracellular signalling pathways, are activated in bronchial epithelial cells as a result of arsenic exposure (Wu et al. 1999; Chen et al. 2000). Additionally, according to the literature, the introduction of arsenite to epidermal cell lines causes the activation of three PKC family isozymes, which in turn arbitrates signal transmission (Koulet al. 2013). Since various PKC isoforms are involved in mediating signal transduction and are translocated from the cytosol to the plasma membrane by arsenic chemicals, these enzymes may serve as an excellent target for limiting the biological consequences of arsenic therapies. More studies with targeted inhibitors are required, and the dominant-negative mutant model aids in determining which MAP kinase proteins play a significant role in the arsenic-mediated activity in a given cell type. Tyrosine phosphatase: Because these enzymes have vicinal thiols, they may be a target for substances related to arsenic. According to a paper, tyrosine phosphatase is a molecular target of arsenic's activity (Li et al. 2018). According to certain investigations, although the amount of posphotyrosine rises as a result of arsenic exposure, there are no changes in the activity of the enzyme.

## 4.5 Role of Arsenic in Apoptosis

Recent investigations on myeloma cells shows that arsenic trioxides induces apoptosis by activating caspases-3 in both myeloid leukaemia and neuroblastoma cell lines, however dexamethasone alone does not significantly activate caspases-9 in arsenic-mediated apoptosis. Telomerase activity inhibition may be the primary mechanism by which arsenic induces apoptosis (Cosentino-Gomes et al. 2012; Shen et al. 2013). Arsenic trioxides caused the telomerase gene and its activity to be downregulated in NB4 cells (Hayashi et al. 2002; Ishitsuka et al. 1999). This could be as a result of the direct effects of arsenic-trioxide on Sp1 and Myc transcription factors.

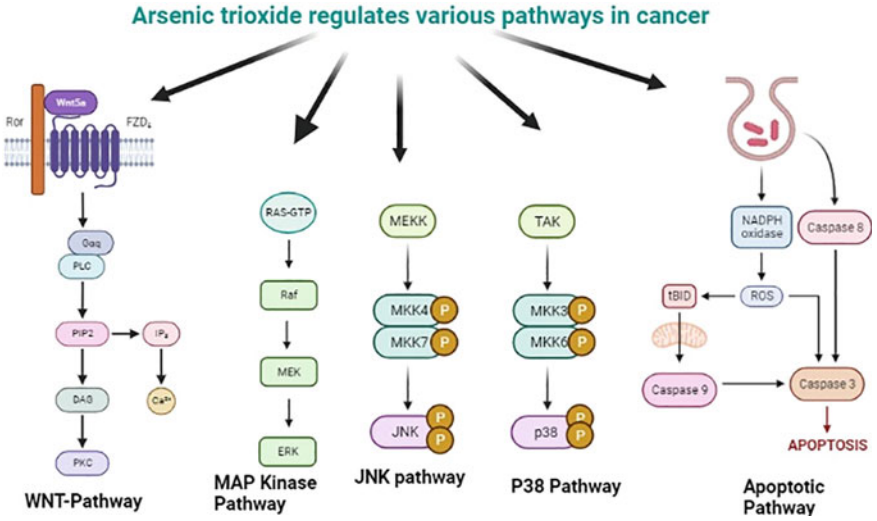


**Fig. 4.1** The primary signalling pathways that ATO controls to fight cancer. ATO induced ROS as well as WNT/JNK/P38/MAPK phosphorylation to trigger apoptosis in tumor microenvironment. These ATO induced phosphorylation and several anticancer therapeutic may cooperatively induce anticancer effect

## 4.6 Reactive Oxygen Species (ROS) and Arsenic

By controlling several pathways involved in numerous redox interactions with local oxidants and other cellular antioxidant systems, arsenic and its related chemicals alter the oxidation as well as oxidative reduction balance. Since arsenic has a significant affinity for thiol groups, proteins with disulphide oxidation potentials may be redox sensitive. Redox control undoubtedly mediates important cell activities. Arsenic targets redox-sensitive proteins and enzymes to provide both therapeutic and harmful effects (Zheng et al. 2010). The effects of arsenic on a number of redox sensitive signalling molecules, including AP-1, P52, P21, and S-nitrosthiols, which result in the deregulation of diverse cell signalling and gene expression, according to studies, ironically share many aspects of tumor promoters (Xu et al. 2014; Chou et al. 2001). Endogenous glutathione and thioredoxin are essential for controlling redox signalling and shielding cells from arsenic's harmful effects.

## 4.7 Other Arsenic Cellular Targets

According to several findings, glucocorticoid receptor ligand binding is blocked when arsenic concentrations below10 micro molar are present (Chen et al. 1998). This is because the area in question contains a dithiol that is essential for optimal ligand

binding. Additionally, the oestrogen receptor is activated by arsenic, which increases the estrogen-related genes. Studies have also shown that arsenic may function as an environmental oestrogen because it triggers apoptosis in numerous cell types, including MCF-7 (Pace et al. 2017; Telford and Fraker 1997; Stoica et al. 2000). It hinders angiogenesis, which has a detrimental effect on the proliferation of tumor cells. According to reports, arsenic could potentially target the tubulin cytoskeleton because of its high sulfhydryl content (Roboz et al. 2000). Pyruvate dehydrogenase has previously been identified as one of arsenic trioxide's key molecular targets. This molecular target is responsible for hypoglycemia and reduced gluconeogenesis. In vitro, pyruvate dehydrogenase activity is directly inhibited by a concentration of 5 micromolar arsenic trioxide compound.

## 4.8 Synergist Effects of Arsenic with Other Natural Compounds in Cancer Protection

### *4.8.1 Hepatocellular Carcinoma*

Hepatocellular carcinoma (HCC) is the 5th most common and most frequent primary liver cancer Worldwide. Activating Akt or its downstream signaling factors, such as mTOR, ribosomal protein S6 kinase, glycogen synthase kinase-3beta and eukaryotic translation initiation factors (4E) binding protein, increases the survival rate of patients with high metastatic HCC when sorafenib (mutikinase inhibitors) and ATO are combined (Lew et al. 1999; Sadaf et al. 2018; Zhai et al. 2015; Guilbert et al. 2013; Chaudhary et al. 2022). The anticancer effects of metformin, also enhanced by ATO in HCC cells (Kasukabe et al. 2015). Similarly various molecular mechanisms affected by arsenic to induce its anticancer potential are shown in Fig. 4.2. When combined with quercetin and aloe emodin, arsenic trioxide reduced the viability of cancerous cells in comparison to healthy cells by inducing apoptosis, suppressing telomerase, up regulating the expression of Bax, down regulating Bcl-2 (an anti-apoptotic protein), and decreasing the expression of Bcl-2 (a pro-apoptotic protein). Due to the synergistic effects of quercetin and aloe-emodin on liver tumor cells, ATO significantly reduced the risk of cancer (Chaudhary et al. 2022). These results demonstrate that a combination of ATO and tried-and-true herbal medications can successfully slow the growth of liver tumors by inhibiting telomerase activity.

### *4.8.2 Colon Cancer*

Arsenic trioxide, an inorganic form of arsenic, prevents rapamycin from being activated: Nuclear factor kappa is a protein complex that regulates DNA transcription, cytokine generation, and cell survival. When these functions are inhibited, IkB-alpha

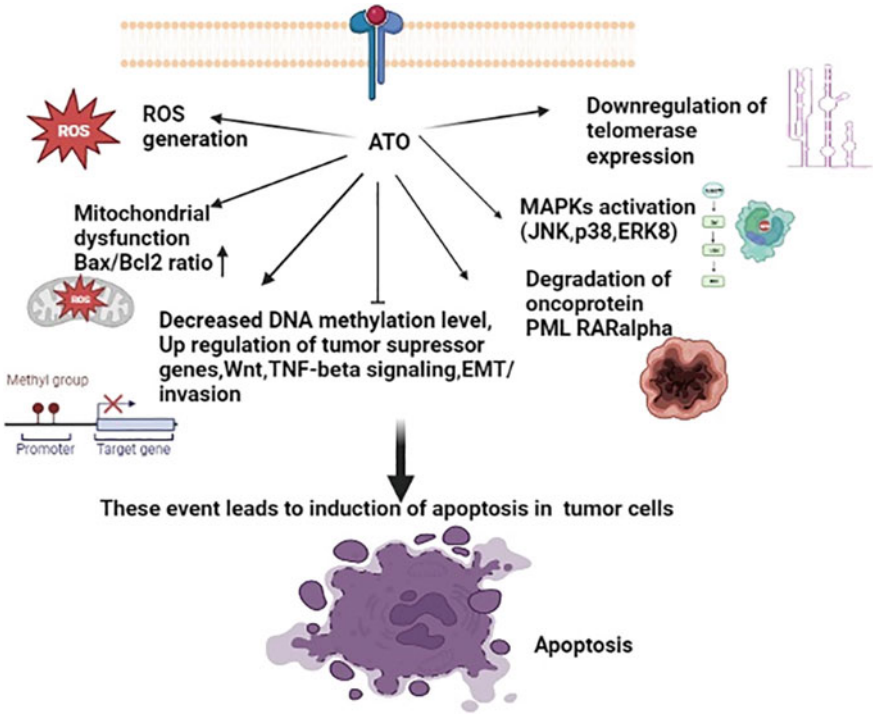


**Fig. 4.2** The molecular mechanism via which ATO works in concert with other treatments to combat cancer. ATO produces intracellular ROS in the majority of cancer cells, which may cause the apoptotic signalling pathway to be activated. By increasing its metabolite S-adenosyl-l-homocysteine (SAH) and decreasing methyl donors (S-adenosylmethionine (SAM)), ATO may impede the DNA methyltransferase activity of DNMT. Apoptosis in cancer cells may be induced by the demethylation impact of ATO and other anticancer therapies in combination. ATO binds to PML while ATRA binds to RAR in APL cells. Therefore, combined ATO-ATRA therapy causes differentiation, proteasomal degradation of the onco-protein PML-RARA, and subsequently apoptosis. ATO causes liver cancer cells to undergo apoptosis, which inhibits the telomerase enzyme

is not phosphorylated and is not degraded in HCT-116 cells (Chen et al. 2011).This inhibited phosphorylation of IkB-alpha caused by arsenic induces apoptosis in colon cancer and hence plays a therapeutic or anticancer role. In addition to this, numerous studies have shown that arsenic in combination with the PI3K inhibitor (LY294002) significantly reduces tumors in colon cancer cell lines (Huang et al. 2016).

### *4.8.3 Prostate Cancer*

Arsenic essentially blocks the intracellular Akt/mTOR signalling pathway, which is crucial for controlling the cell cycle (Felix et al. 2005). Inhibiting PC-3 growth

by downregulating the Hh (full form) signalling pathway is directly related to its anticancer strategy, and the antitumor impact was further increased by cyclopamine, a traditional inhibitor of Hh pathway. Researchers combined the ATO-mTOR inhibitor RAD001, which exhibits enhanced autophagy and death rates in prostate cancer cells to create a synergistic therapy (Cai et al. 2015). Beclin 1 mRNA stability was essentially connected to the onset of autophagy-mediated cell death (Chen and Costa 2018; Tai et al. 2017). Therefore, compared to monotherapy with no improvement in weight reduction, ATO-RAD001 combination therapy has a significantly more substantial role in the inhibition of cancer and the proliferation of tumors.

### *4.8.4 Oral Cancer*

The most prevalent head and neck cancer has a poor prognosis despite the wide range of therapeutic options that are currently available. The most effective treatments for oral cancer are the platinum-based anti-tumor medication cisplatin (CDDP) and radiotherapy which include arsenic trioxide as a drug additive (Kang et al. 2011; Menon and Dhamija 2018). ATO + dithithreitol (DTT) has been shown in numerous studies to raise the pro-appoptotic molecules Bak and Bax while simultaneously reducing Bcl-2 and p53 (Menon and Dhamija 2018), which results in the substantial reduction in oral cancer cell proliferation rate.

### *4.8.5 Ovarian Cancer*

Ovarian cancer has the highest mortality rate when compared to all other malignant tumours of the female genital organs. ATO has been shown to be substantially more effective when combined with CDDP (Cisplatin, a chemotherapeutic drug used to treat a variety of malignancies), and also multiplies the cytotoxic effect of CDDP by itself (Dasari and Tchounwou 2014). Numerous studies have also indicated that buthioninesulfoximine and ascorbic acid might increase the efficiency of ATO by modulating oxidative stress-related pathways and GSH depletion in antitumor induction (Zhang et al. 2009).

### *4.8.6 Cervical Cancer*

One of the most common cancers in women globally is cervical cancer, which is typically treated through radiotherapy and a combination therapy that also includes chemotherapeutics such platinum-based medications. Matrix metallopeptidase 9 (MMP-9), which is mainly involved in the breakdown of extracellular matrix, is suppressed by ATO, and as a result, radiation-accelerated lung metastases are reduced

(Liu et al. 2012a, b). Various in vitro and in vivo data indicate that radiation treatment along with ATO has a more positive impact on cervical cancer than was anticipated in terms of its anticancer effects. Apart from this, ATO also promotes Bcl-2 phosphorylation and the translocation of the Bax protein, which regulates apoptosis (Ong et al. 2011). This, in turn, activates the JNK and MAPK pathways. In ATO-radiation-induced apoptosis, ROS play a significant role (Wei et al. 2005). Tetra arsenic oxide, in addition to ATO, has been shown to have an anticancer effect on cervical cancer cells. The highest tumor growth is reduced when these arsenic oxides are combined with CDDP, especially in cases of cervical cancer (Kang and Lee 2008). Additionally, this therapy significantly increases the amount of apoptotic cells, giving it a novel anticancer function.

### *4.8.7 Breast Cancer*

One of the main causes of cancer-related fatalities in women around the world is this particular type of cancer are breast cancer. It has been demonstrated in numerous studies that ATO causes a decrease in DNA methyltransferase-1 expression while increasing oestrogen receptor alpha expression, which has been shown to improve overall prognosis and enhance disease-free survival (Kim et al. 2012). Surprisingly, ATO combined antiestrogen therapy with tamoxifen (TAM) successfully inhibits tumor growth in the MDA-MB-435 S (human breast cancer cell line) (Byun et al. 2013a, b). Numerous studies have shown that ATO increases rapamycin's anticancer properties and the in vivo apoptosis that is generated by the combination of ATO and melatonin (Zhang et al. 2011). When used after co-incubation with ATO, several plant growth regulators, likecotylenin A(CN–A), have outstanding anticancer efficacy against breast cancer cells in vitro (Chaudhary et al. 2022). ATO is not as harmful to breast cancer as other forms of arsenic, such as monomethylarsenic acid (MMaIII) and dimethylarsenic acid (DMA III).

### *4.8.8 Lung Cancer*

It is well known that lung cancer is the most prevalent type of cancer globally. Lung cell lines are induced to undergo apoptosis when treated with ATO and a non-steroidal anti-inflammatory medication of the arylalkanoic acid class such sulindic (Zhai et al. 2015). Sulindic and ATO work together to promote apoptosis in lung cancer cell lines by primarily targeting the mitochondrial route, the NF-kB pathways, and also mediating p53-induced down regulation of surviving (Chen et al. 2011). Additionally, research has shown that ATO-sulindac combination therapy increases cytotoxicity in lung cancer cell lines (A549) by inducing ROS-mediated MAPK phosphorylation (Huang et al. 2016). Along with this additional structural analogue of sulindaci, it has also been shown that nonselective cyclooxygenase inhibitors like indomethacin can

increase the effects of arsenic on Akt, Src, c-Raf, and Erk via facilitating proteasomal degradation (Jiang et al. 2004). When ATO and resveratrol combine, it causes ROS-mediated ER stress, mitochondrial malfunction (Jiang et al. 2004), and ultimately death in A549 cells.

### *4.8.9 Gastric Cancer and Pancreatic Cancer*

When combined with ATO, anti-apoptotic drugs like ABT-737, which block Bcl-2 and Bcl-Xl, significantly reduce the growth rate of human gastric cancer cell lines (Jin et al. 2006; Han et al. 2008). According to studies, the sesquiterpene lactone parthenolide from the remedy feverfew promotes caspase activation and subsequent ROS production, which in turn promotes apoptosis in the pancreatic cancer cell lines (such as PANC-1and BxPC-3) (Zhang et al. 2011). In the PANC-1 cell line, ATO and parthenolide greatly slow tumour proliferation. Because of its significant cellular ROS scavenging capacity, studies have shown that ATO alone has a limited effect on cytotoxicity of pancreatic ductal adenocarcinoma (Lam et al. 2016; Sun et al. 2012).

### *4.8.10 Glioblastoma*

In human glioma cell lines, arsenic trioxide stimulates the expression of DR5 (death receptor 5), a death receptor of the TRAIL (tumour necrosis factor-related apoptosis inducing ligand) family. Glioma cell survival is decreased by the synergistic interaction of ATO and TRAIL. Radiation therapy enhances mitotic arrest and modifies the ERK1/2 and PI3K/Akt signalling pathways, which in turn positively affects the effects of autophagy in U118-MG cells when combined with ATO (Cang et al. 2015; Wang et al. 2009). ATO with Docosahexaenoic acid (DHA), a polyunsaturated fatty acid, significantly increases the amount of apoptosis in ATO-resistant solid tumor cell lines, including those that are resistant to the drug in cases of cervical, breast, ovarian, colon, prostate and pancreatic cancer, with no toxic side effects on normal skin fibroblasts, human microvascular endothelial and peripheral blood mononuclear cells (Cang et al. 2015).

### *4.8.11 Promyelocyticleukemia (APL)*

Arsenic trioxide, usually known as Trisenox or ATO, is a chemotherapeutic medication. It is a treatment for acute promyelocyticleukemia, a subtype of acute myeloid leukemia (APL). It is also being studied as a potential treatment for other cancers. According to a number of investigations, arsenic trioxide combined with all trans retinoic acid inhibits cell growth and promotes in vitro apoptosis in a variety of

cell types, including lung, hepatoma, breast cancer cells (Lang et al. 2016; Kim et al. 2008). In addition, Kryeziu et al. demonstrated that erlotinib, a selective EGFR inhibitor, when used in combination with ATO prevents DNA damage from being repaired when double-strand breaks occur in mesothelioma, hepato-cellular carcinoma, colon cancer, thyroid cancer, and cervix cancer in vitro (Kryeziu et al. 2013; Chiu et al. 2010).

## 4.9 Hematological Malignancies

### *4.9.1 Acute Promyelocyticleukemia (APL)*

Numerous studies have shown that As4S4 and As3 + combined therapy cause PML/RAR oncoproteins to degrade and subsequently trigger apoptosis (Ravandi et al. 2009). Other investigations noted that by triggering the Src family kinase inhibitor PP2, the addition of ATRA-ATO causes an increase in the rate of differentiation of APL cells (Abaza et al. 2017). ATO exhibits anti-leukemic activity, and this characteristic of ATO is enhanced by the combination therapy that includes granulocyte-monocyte colony stimulating factor, a noncalcemic vitamin D analogue (19-Nor-125(OH)2D2), a selective EGFR inhibitor (Gefitinib), and high-dose vitamin C (ascorbic acid) (Kryeziu et al. 2013; Lo-Coco et al. 2013; Tarkanyi et al. 2005).

### *4.9.2 Acute Myeloid Leukemia (AML)*

Acute myeloid leukemia, a cancer of the bone marrow, is characterized by the over-abundance of juvenile leukocytes at an early stage of differentiation. Reports have suggested that FLT3 mutations in AML patients have shorter internal tandem duplication (FLT3-ITTD), which promotes disease-free survival (Ravandi et al. 2009). Additionally, studies have demonstrated that FLT3-IT positive cells undergo apoptosis when ATO and the FLT3-specific inhibitor AG1296 are combined. The combination of ATRA + ATO produces synergistic cytotoxic effect against FLT3-ITD AML cells in many APL patients by simultaneously suppressing FLT3 signalling pathways (Rogers et al. 2014). By specifically targeting the nucleophosmin (NPMI) oncoprotein, which is mutated in 30% of cases of AML, this combination also causes apoptosis in NPM1-mutated AML cells (Muto et al. 2001). By lowering the production of ROS in AML cells, BSO with ATO also exhibits anticancer effects (Thiede et al. 2002), Dichloroacetate (Takahashi et al. 2006), Azacytidine (El Hajj et al. 2015a, b), Rapamycin (Tanaka et al. 2014) and Aclacinomycin A (Emadi et al. 2015) are other agents that cause apoptosis in AML cells in addition to BSO and ATO.

### 4.9.3 Multiple Myeloma (MM)

Relevant dosages of ascorbic acid reduce GSH levels in myeloma cell lines and increase ATO-induced cell death (Chau et al. 2015). One of the appealing alternatives for individuals with refractory MM is ATO + ascorbic acid + melphalan (Dembitz et al. 2015). The best effect on the survival rate of myeloma patients is provided by a combination of immune-modulatory medications including thalidomide, lenalidomide and pomalidomide as well as a number of proteasome inhibitors like bortezomib and carfilzomib (Jung et al. 2002; Ye et al. 2015). Reports have also hinted that increased STAT3 inhibition, JNK activation, over-expression of p21, Bim, p27, and p53 as well as decreased Bcl-2 expression are all linked to increased cytotoxicity of ATO-BOR (Grad et al. 2001).The sensitivity of MM cells is enhanced by the combination of ATO + vitamin E analogue Trolox (Berenson et al. 2006) a MEK inhibitor PD325901 (Stewart 2012) a natural quinoidditerpenecryptotanshinone, and a phytochemical sulforaphane (Wen et al. 2010; Jian et al. 2017). ATO also causes the up-regulation of cereblon, which is an antimyeloma target (Lo-Coco et al. 2013).

### 4.9.4 Lymphoma

Mantle cell lymphoma, an inoperable B-cell non-Hodgkin lymphoma, exhibits anticancer effects, according to research (Jung et al. 2012; Zhao et al. 2015). When combined with ATO, cucurbitacin B from Trichosantheskirilowiimaxim increases the rate of apoptosis in Burkitt's lymphoma cell lines both in vitro and in vivo via suppressing STAT3 phosphorylation) (Ding et al. 2017).

## 4.10 Conclusion

Here, we have demonstrated that arsenical compounds, either alone or in amalgamation with other anticancer therapies including radiation, chemotherapy, and molecularly targeted medicines, aid in triggering apoptosis in a variety of cancer cell types. Due to technological development and an abundance of anticancer therapies, it is now possible to target specific molecules, signalling pathways, and even single cellular biological processes, which may produce refractory cancer cells, many of them may develop drug resistance. Therefore, the development of novel treatment agents or alternatives is urgently needed to combat medication resistance and enhance the prognosis and quality of life of cancer patients. Numerous clinical trials investigating the therapeutic potential of arsenic are now being conducted on various forms of solid tumors and malignancies. As arsenic has been shown to have various promising therapeutic potential at low concentrations, which is already governed by APL, it is suggested that it may also have promise for preclinical models of other

cancers like HCC. Additionally, research is needed to comprehend the connection between arsenic-induced apoptosis and genetic changes in cancer cells, which could advance research on selectivity for cancer treatment. To create a novel combinatorial therapy for cancer, more research is needed to comprehend the synergistic anticancer impact of ATO-based combination therapies.

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## References

Abaza Y, Kantarjian H, Garcia-Manero G et al (2017) Longterm outcome of acute promyelocyticleukemia treated with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab. Blood 129:1275–1283

Abou-Merhi R, Khoriaty R, Arnoult D, El Hajj H, Dbouk H, Munier S, El-Sabban ME, Hermine O, Gessain A, de Thé H, Mahieux R, Bazarbachi A (2007) PS-341 or a combination of arsenic trioxide and interferon-alpha inhibit growth and induce caspase-dependent apoptosis in KSHV/HHV-8-infected primary effusion lymphoma cells. Leukemia 21(8):1792–801. https://doi.org/10.1038/sj.leu.2404797.PMID: 17568816

Alimoghaddam K (2014) A review of arsenic trioxide and acute promyelocyticleukemia. Int J Hematol Oncol Stem Cell Res 8(3):44–54

Altekruse SF, McGlynn KA, Reichman ME (2009) Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol: Official J Am Soc Clin Oncol 27(9):1485–1491. https://doi.org/10.1200/JCO.2008.20.7753

Antman KH (2001) Introduction: the history of arsenic trioxide in cancer therapy. Oncologist 6:1–2

Bayat RM, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, Yeger H (2017) Combination therapy in combating cancer. Oncotarget 8(23):38022–38043. https://doi.org/10.18632/oncotarget.16723

Bazarbachi A, El-Sabban ME, Nasr R, Quignon F, Awaraji C, Kersual J, Dianoux L, Zermati Y, Haidar JH, Hermine O, de Thé H (1999) Arsenic trioxide and interferon-alpha synergize to induce cell cycle arrest and apoptosis in human T-cell lymphotropic virus type I-transformed cells. Blood 93(1):278–83. PMID: 9864171

Berenson JR, Boccia R, Siegel D et al (2006) Efficacy and safety of melphalan, arsenic trioxide and ascorbic acid combination therapy in patients with relapsed or refractory multiple myeloma: A prospective, multicenter, phase II, single-arm study. Br J Haematol 135:174–183

Bernardi R, Pandolfi PP (2007) Structure, dynamics and functions of promyelocytic leukaemia nuclear bodies. Nat Rev Mol Cell Biol 8:1006–1016

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.CA: Cancer J Clin 68(6):394–424. https://doi.org/10.3322/caac.21492

Byun JM, Jeong DH, Lee DS, Kim JR, Park SG, Kang MS et al (2013a) Tetraarsenic oxide and cisplatin induce apoptotic synergism in cervical cancer. Oncol Rep 29:1540–1546

Byun JM, Jeong DH, Lee DS, Kim JR, Park SG, Kang MS, Kim YN, Lee KB, Sung MS, Kim KT (2013b) Tetraarsenic oxide and cisplatin induce apoptotic synergism in cervical cancer. Oncol Rep 29(4):1540–1546. https://doi.org/10.3892/or.2013.2243. Epub 2013 Jan 18 PMID: 23338680

Cai X, Yu K, Zhang L, Li Y, Li Q, Yang Z, Wang W (2015) Synergistic inhibition of colon carcinoma cell growth by Hedgehog-Gli1 inhibitor arsenic trioxide and phosphoinositide 3-kinase inhibitor LY294002. OncoTargets Ther 8:877–883. https://doi.org/10.2147/OTT.S71034

Cang S, Iragavarapu C, Savooji J, Song Y, Liu D (2015) ABT-199 (venetoclax) and BCL-2 inhibitors in clinical development. J Hematol Oncol 8:129

Carr MI, Jones SN (2016) Regulation of the Mdm2-p53 signaling axis in the DNA damage response and tumorigenesis. Transl Cancer Res 5(6):707–724. https://doi.org/10.21037/tcr.2016.11.75

Chau D, Ng K, Chan TS, Cheng YY, Fong B, Tam S et al (2015) Azacytidine sensitizes acute myeloid leukemia cells to arsenic trioxide by up-regulating the arsenic transporter aquaglyceroporin 9. J Hematol Oncol 8:46

Chaudhary A, Bhardwaj SK, Khan A, Srivastava A, Sinha KK, Ali M, Haque R (2022) Combinatorial effect of arsenic and herbal compounds in telomerase-mediated apoptosis induction in liver cancer. Biol Trace Elem Res. https://doi.org/10.1007/s12011-022-03430-0. Epub ahead of print. PMID: 36192614

Chen QY, Costa M (2018) PI3K/Akt/mTOR signaling pathway and the biphasic effect of arsenic in carcinogenesis. Mol Pharmacol 94(1):784–792. https://doi.org/10.1124/mol.118.112268

Chen YC, Lin-Shiau SY, Lin JK (1998) Involvement of reactive oxygen species and caspase 3 activation in arsenite-induced apoptosis. J Cell Physiol 177(2):324–333. https://doi.org/10.11002/(SICI)1097-4652(199811)177:2

Chen NY, Ma WY, Huang C, Ding M, Dong Z (2000) Activation of PKC is required for arsenite-induced signal transduction. J Environ Pathol Toxicol Oncol 19:297–305

Chen C, Zhang Y, Wang Y, Huang D, Xi Y, Qi Y (2011) Genistein potentiates the effect of arsenic trioxide against human hepatocellular carcinoma: role of Akt and nuclear factor-κB. Cancer Lett 301:75–84

Chen D, Chan R, Waxman S, Jing Y (2006) Buthioninesulfoximine enhancement of arsenic trioxide-induced apoptosis in leukemia and lymphoma cells is mediated via activation of c-Jun NH2-terminal kinase and up-regulation of death receptors. Cancer Res 66(23):11416–11423. https://doi.org/10.1158/0008-5472.CAN-06-0409. PMID: 17145888

Chiu HW, Lin JH, Chen YA, Ho SY, Wang YJ (2010) Combination treatment with arsenic trioxide and irradiation enhances cell-killing effects in human fibrosarcoma cells in vitro and in vivo through induction of both autophagy and apoptosis. Autophagy 6(3):353–365

Chiu HW, Ho SY, Guo HR, Wang YJ (2009) Combination treatment with arsenic trioxide and irradiation enhances autophagic effects in U118-MG cells through increased mitotic arrest and regulation of PI3K/Akt and ERK1/2 signaling pathways. Autophagy 5(4):472–483. https://doi.org/10.4161/auto.5.4.7759. PMID: 19242099

Chou WC, Hawkins AL, Barrett JF, Griffin CA, Dang CV (2001) Arsenic inhibition of telomerase transcription leads to genetic instability. J Clin Investig 108(10):1541–1547. https://doi.org/10.1172/JCI14064

Cosentino-Gomes D, Rocco-Machado N, Meyer-Fernandes JR (2012) Cell signaling through protein kinase C oxidation and activation. Int J Mol Sci 13(9):10697–10721. https://doi.org/10.3390/ijms130910697

Crissien AM, Frenette C (2014) Current management of hepatocellular carcinoma. Gastroenterol Hepatol 10(3):153–161

Dasari S, Tchounwou PB (2014) Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol 740:364–378. https://doi.org/10.1016/j.ejphar.2014.07.025

Davison K, Mann KK, Miller Jr WH (2002) Arsenic trioxide: mechanism of action. Semin Hematol 39(2):3–7

de Thé H, Chen Z (2010) Acute promyelocytic leukaemia: novel insights into the mechanisms of cure. Nat Rev Cancer 10:775–783

Dembitz V, Lalic H, Ostojic A, Vrhovac R, Banfic H, Visnjic D (2015) The mechanism of synergistic effects of arsenic trioxide and rapamycin in acute myeloid leukemia cell lines lacking typical t(15;17) translocation. Int J Hematol 102:12–24

Ding X, Chi J, Yang X, Hao J, Liu C, Zhu C et al (2017) Cucurbitacin B synergistically enhances the apoptosis-inducing effect of arsenic trioxide by inhibiting STAT3 phosphorylation in lymphoma Ramos cells. Leuk Lymphoma 58:2439–2451

El Eit RM, Iskandarani AN, Saliba JL, Jabbour MN, Mahfouz RA, Bitar NM, Ayoubi HR, Zaatari GS, Mahon FX, De Thé HB, Bazarbachi AA, Nasr RR (2014) Effective targeting of chronic myeloid leukemia initiating activity with the combination of arsenic trioxide and interferon alpha. Int J Cancer 134(4):988–996. https://doi.org/10.1002/ijc.28427. Epub 2013 Sep 10. PMID: 23934954

El Hajj H, Dassouki Z, Berthier C, Raffoux E, Ades L, Legrand O et al (2015a) Retinoic acid and arsenic trioxide trigger degradation of mutated NPM1, resulting in apoptosis of AML cells. Blood 125:3447–3454

El Hajj H, Dassouki Z, Berthier C, Raffoux E, Ades L, Legrand O, Hleihel R, Sahin U, Tawil N, Salameh A, Zibara K, Darwiche N, Mohty M, Dombret H, Fenaux P, de Thé H, Bazarbachi A (2015b) Retinoic acid and arsenic trioxide trigger degradation of mutated NPM1, resulting in apoptosis of AML cells. Blood 125(22):3447–3454. https://doi.org/10.1182/blood-2014-11-612416. Epub 2015b Mar 23. PMID: 25800051

El-Sabban ME, Nasr R, Dbaibo G, Hermine O, Abboushi N, Quignon F, Ameisen JC, Bex F, de Thé H, Bazarbachi A (2000) Arsenic-interferon-alpha-triggered apoptosis in HTLV-I transformed cells is associated with tax down-regulation and reversal of NF-kappa B activation. Blood 96(8):2849–2855. PMID: 11023521

Emadi A, Sadowska M, Carter-Cooper B, Bhatnagar V, van der Merwe I et al (2015) Perturbation of cellular oxidative state induced by dichloroacetate and arsenic trioxide for treatment of acute myeloid leukemia. Leuk Res 39:719–729

Fang Y, Zhang Z (2020) Arsenic trioxide as a novel anti-glioma drug: a review. Cell Mol Biol Lett 25:44. https://doi.org/10.1186/s11658-020-00236-7

Felix K, Manna SK, Wise K, Barr J, Ramesh GT (2005) Low levels of arsenite activates nuclear factor-kappaB and activator protein-1 in immortalized mesencephalic cells. J Biochem Mol Toxicol 19(2):67–77. https://doi.org/10.1002/jbt.20062

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int. J Cancer 127(12):2893–2917. https://doi.org/10.1002/ijc.25516

Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, Dicker DJ, Chimed-Orchir O, Dandona R, Dandona L, Fleming T, Forouzanfar MH, Hancock J, Hay RJ, Hunter-Merrill R, Huynh C, Hosgood HD, Johnson CO, Jonas JB, Naghavi M et al (2017) Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol 3(4):524–548. https://doi.org/10.1001/jamaoncol.2016.5688

Grad JM, Bahlis NJ, Reis I, Oshiro MM, Dalton WS, Boise LH (2001) Ascorbic acid enhances arsenic trioxide-induced cytotoxicity in multiple myeloma cells. Blood 98:805–913

Griffith OW (1982) Mechanism of action, metabolism, and toxicity of buthioninesulfoximine and its higher homologs, potent inhibitors of glutathione synthesis. J Biol Chem 257(22):13704–13712. PMID: 6128339

Guilbert C, Annis MG, Dong Z, Siegel PM, Miller WH Jr, Mann KK (2013) Arsenic trioxide overcomes rapamycin-induced feedback activation of AKT and ERK signaling to enhance the anti-tumor effects in breast cancer. PLoS One 8:e85995

Han YH, Kim SZ, Kim SH, Park WH (2008) Induction of apoptosis in arsenic trioxide-treated lung cancer A549 cells by buthioninesulfoximine. Mol Cells 26(2):158–164 Epub 2008 Jul 3 PMID: 18596414

Hayashi T, Hideshima T, Akiyama H, Richardson P, Schlossman RL, Chauhan D, Waxman S, Anderson KC (2002) Arsenic trioxide inhibits growth of human multiple myeloma cells in the bone marrow microenvironment. Mol Cancer Ther 1(10):851–860

Hu WC, Teo WH, Huang TF, Lee TC, Lo JF (2020) Combinatorial low dose arsenic trioxide and cisplatin exacerbates autophagy via AMPK/STAT3 signaling on targeting head and neck cancer initiating cells. Front Oncol 10:463. https://doi.org/10.3389/fonc.2020.00463

Huang A, Yue D, Liao D, Cheng L, Ma J, Wei Y et al (2016) SurvivinT34A increases the therapeutic efficacy of arsenic trioxide in mouse hepatocellular carcinoma models. Oncol Rep 36:3283–3290

Ishitsuka K, Ikeda R, Suzuki S, Ohno N, Utsunomiya A, Uozumi K, Hanada S, Arima T (1999) The inductive pathways of apoptosis and $G_1$ phase accumulation by arsenic trioxide in an adult T-cell leukemia cell line, MT-1. Blood 94(Suppl. 1):263b

Ishitsuka K, Hanada S, Uozumi K, Utsunomiya A, Arima T (2000) Arsenic trioxide and the growth of human T-cell leukemia virus type I infected T-cell lines. Leuk Lymphoma 37(5–6):649–655. https://doi.org/10.3109/10428190009058521

Jambrovics K, Uray IP, Keillor JW, Fésüs L, Balajthy Z (2020) Benefits of combined all-trans retinoic acid and arsenic trioxide treatment of acute promyelocyticleukemia cells and further enhancement by inhibition of atypically expressed transglutaminase 2. Cancers 12(3):648. https://doi.org/10.3390/cancers12030648

Ji H, Li Y, Jiang F, Wang X, Zhang J, Shen J, Yang X (2014) Inhibition of transforming growth factor beta/SMAD signal by MiR-155 is involved in arsenic trioxide-induced anti-angiogenesis in prostate cancer. Cancer Sci 105(12):1541–1549. https://doi.org/10.1111/cas.12548

Jian Y, Gao W, Geng C, Zhou H, Leng Y, Li Y et al (2017) Arsenic trioxide potentiates sensitivity of multiple myeloma cells to lenalidomide by upregulating cereblon expression levels. Oncol Lett 14:3243–3248

Jiang TT, Brown SL, Kim JH (2004) Combined effect of arsenic trioxide and sulindacsulfide in A549 human lung cancer cells in vitro. J Exp Clin Cancer Res 23(2):259–262

Jin HO, Yoon SI, Seo SK et al (2006) Synergistic induction of apoptosis by sulindac and arsenic trioxide in human lung cancer A549 cells via reactive oxygen species-dependent down-regulation of survivin. Biochem Pharmacol 72(10):1228–1236

Jing Y (2004) The PML-RARalpha fusion protein and targeted therapy for acute promyelocyticleukemia. Leuk Lymphoma 45(4):639–648

John L, Sauter E, Herlyn M, Litwin S, Adler-Storthz K (2000) Endogenous p53 gene status predicts the response of human squamous cell carcinomas to wild-type p53. Cancer Gene Ther 7(5):749–756. https://doi.org/10.1038/sj.cgt.7700166

Jung HJ, Chen Z, McCarty N (2012) Synergistic anticancer effects of arsenic trioxide with bortezomib in mantle cell lymphoma. Am J Hematol 87:1057–1064

Jung HJ, Chen Z, McCarty N (2002) Synergistic anticancer effects of arsenic trioxide with bortezomib in mantle cell lymphoma. Am J Hematol 87(12):1057–1064. https://doi.org/10.1002/ajh.23317. Epub 2012 Sep 11. PMID: 22965904; PMCID: PMC3894928

Kamps R, Brandão RD, Bosch BJ, Paulussen AD, Xanthoulea S, Blok MJ, Romano A (2017) Next-generation sequencing in oncology: genetic diagnosis, risk prediction and cancer classification. Int J Mol Sci 18(2):308. https://doi.org/10.3390/ijms18020308

Kang R, Zeh HJ, Lotze MT, Tang D (2011) The Beclin 1 network regulates autophagy and apoptosis. Cell Death Differ 18(4):571–580. https://doi.org/10.1038/cdd.2010.191

Kang T, Ge M, Wang R et al (2019) Arsenic sulfide induces RAG1-dependent DNA damage for cell killing by inhibiting NFATc3 in gastric cancer cells. J Exp Clin Cancer Res 38:487. https://doi.org/10.1186/s13046-019-1471-x

Kang YH, Lee SJ (2008) Role of p38 MAPK and JNK in enhanced cervical cancer cell killing by the combination of arsenic trioxide and ionizing radiation. Oncol Rep 20(3):637–643. PMID: 18695917

Kasukabe T, Okabe-Kado J, Kato N, Honma Y, Kumakura S (2015) Cotylenin A and arsenic trioxide cooperatively suppress cell proliferation and cell invasion activity in human breast cancer cells. Int J Oncol 46:841–848

Khairul I, Wang QQ, Jiang YH, Wang C, Naranmandura H (2017) Metabolism, toxicity and anticancer activities of arsenic compounds. Oncotarget 8(14):23905–23926. https://doi.org/10.18632/oncotarget.14733

Kim EH, Yoon MJ, Kim SU, Kwon TK, Sohn S, Choi KS (2008) Arsenic trioxide sensitizes human glioma cells, but not normal astrocytes, to TRAIL-induced apoptosis via CCAAT/enhancer-binding protein homologous protein-dependent DR5 up-regulation. Cancer Res 68:266–275

Kim YW, Bae SM, Battogtokh G, Bang HJ, Ahn WS (2012) Synergistic anti-tumor effects of combination of photodynamic therapy and arsenic compound in cervical cancer cells: in vivo and in vitro studies. PLoS One 7:e38583

Klauser E, Gülden M, Maser E, Seibert S, Seibert H (2014) Additivity, antagonism, and synergy in arsenic trioxide-induced growth inhibition of C6 glioma cells: effects of genistein, quercetin and buthionine-sulfoximine. Food ChemToxicol 67:212–221. https://doi.org/10.1016/j.fct.2014.02.039. Epub 2014 Mar 12 PMID: 24632069

Koul HK, Pal M, Koul S (2013) Role of p38 MAP kinase signal transduction in solid tumors. Genes Cancer 4(9–10):342–359. https://doi.org/10.1177/1947601913507951

Kryeziu K, Jungwirth U, Hoda MA et al (2013) Synergistic anticancer activity of arsenic trioxide with erlotinib is based on inhibition of EGFR-mediated DNA double-strand break repair. Mol Cancer Ther 12:1073–1084

Kumar P, Gao Q, Ning Y, Wang Z, Krebsbach PH, Polverini PJ (2008) Arsenic trioxide enhances the therapeutic efficacy of radiation treatment of oral squamous carcinoma while protecting bone. Mol Cancer Ther 7(7):2060–2069. https://doi.org/10.1158/1535-7163.MCT-08-0287. PMID: 18645016

Kumar S, Brown A, Tchounwou PB (2018) Trisenox disrupts MDM2-DAXX-HAUSP complex and activates p53, cell cycle regulation and apoptosis in acute leukemia cells. Oncotarget 9(69):33138–33148. https://doi.org/10.18632/oncotarget.26025

Lallemand-Breitenbach V, de Thé H (2010) PML nuclear bodies. Cold Spring Harb Perspect Biol 2(5):a000661. https://doi.org/10.1101/cshperspect.a000661

Lam S, Li Y, Zheng C, Leung LL, Ho JC (2014) E2F1 downregulation by arsenic trioxide in lung adenocarcinoma. Int J Oncol 45:2033–2043. https://doi.org/10.3892/ijo.2014.2609

Lam SK, Leung LL, Li YY, Zheng CY, Ho JC (2016) Combination effects of arsenic trioxide and fibroblast growth factor receptor inhibitor in squamous cell lung carcinoma. Lung Cancer 101:111–119

Lang M, Wang X, Wang H et al (2016) Arsenic trioxide plus PX-478 achieves effective treatment in pancreatic ductal adenocarcinoma. Cancer Lett 378:87–96

Levine AJ (1997) p53, the cellular gatekeeper for growth and division. Cell 88:323–331

Lew YS, Brown SL, Griffin RJ, Song CW, Kim JH (1999) Arsenic trioxide causes selective necrosis in solid murine tumors by vascular shutdown. Cancer Res 59:6033–6037

Li H, Zhu X, Zhang Y, Xiang J, Chen H (2009) Arsenic trioxide exerts synergistic effects with cisplatin on non-small cell lung cancer cells via apoptosis induction. J Exp Clin Cancer Res: CR 28(1):110. https://doi.org/10.1186/1756-9966-28-110

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 17(3):4422–4432. https://doi.org/10.3892/mmr.2018.8383

Lin LM, Li BX, Xiao JB, Lin DH, Yang BF (2005) Synergistic effect of all-trans-retinoic acid and arsenic trioxide on growth inhibition and apoptosis in human hepatoma, breast cancer, and lung cancer cells in vitro. World J Gastroenterol 11(36):5633–5637. https://doi.org/10.3748/wjg.v11.i36.5633

Liu H, Tao X, Ma F, Qiu J, Wu C, Wang M (2012a) Radiosensitizing effects of arsenic trioxide on MCF-7 human breast cancer cells exposed to 89 strontium chloride. Oncol Rep 28(5):1894–1902. https://doi.org/10.3892/or.2012.1979. PMID: 22922982

Liu N, Tai S, Ding B, Thor RK, Bhuta S, Sun Y et al (2012b) Arsenic trioxide synergizes with everolimus (Rad001) to induce cytotoxicity of ovarian cancer cells through increased autophagy and apoptosis. Endocr Relat Cancer 19:711–723

Liu L, Li Y, Xiong X, Qi K, Zhang C, Fang J, Guo H (2016) Low dose of arsenic trioxide inhibits multidrug resistant-related P-glycoprotein expression in human neuroblastoma cell line. Int J Oncol 49:2319–2330. https://doi.org/10.3892/ijo.2016.3756

Liu XJ, Wang LN, Zhang ZH, Liang C, Li Y, Luo JS, Peng CJ, Zhang XL, Ke ZY, Huang LB, Tang YL, Luo XQ (2020) Arsenic trioxide induces autophagic degradation of the FLT3-ITD mutated protein in FLT3-ITD acute myeloid leukemia cells. J Cancer 11(12):3476–3482. https://doi.org/10.7150/jca.29751

Lo-Coco F, Avvisati G, Vignetti M et al (2013) Retinoic acid and arsenic trioxide for acute promyelocyticleukemia. N Engl J Med 369:111–121

Ma ZB, Xu HY, Jiang M, Yang YL, Liu LX, Li YH (2014) Arsenic trioxide induces apoptosis of human gastrointestinal cancer cells. World J Gastroenterol 20(18):5505–5510. https://doi.org/10.3748/wjg.v20.i18.5505

Malek NP et al (2014) The diagnosis and treatment of hepatocellular carcinoma. DeutschesArzteblatt Int 111(7):101–106. https://doi.org/10.3238/arztebl.2014.0101

McGlynn KA, Petrick JL, El-Serag HB (2021) Epidemiology of hepatocellular carcinoma. Hepatology (Baltimore, Md.) 73(Suppl 1):4–13. https://doi.org/10.1002/hep.31288

Menon MB, Dhamija S (2018) Beclin 1 phosphorylation—at the center of autophagy regulation. Front Cell Dev Biol 6:137. https://doi.org/10.3389/fcell.2018.00137

Miller Jr WH, Schipper HM, Lee JS, Singer J, Waxman S (2002) Mechanism of action of arsenic trioxide. Cancer Res 62(14):3893–3903

Muto A, Kizaki M, Kawamura C et al (2001) A novel differentiation-inducing therapy for acute promyelocyticleukemia with a combination of arsenic trioxide and GM-CSF. Leukemia 15:1176–1184

Nakaoka T, Ota A, Ono T, Karnan S, Konishi H, Furuhashi A, Ohmura Y, Yamada Y, Hosokawa Y, Kazaoka Y (2014) Combined arsenic trioxide-cisplatin treatment enhances apoptosis in oral squamous cell carcinoma cells. Cell Oncol (Dordr) 37(2):119–129. https://doi.org/10.1007/s13402-014-0167-7. Epub 2014 Mar 6. PMID: 24599717

Ong PS, Chan SY, Ho PC (2011) Differential augmentative effects of buthioninesulfoximine and ascorbic acid in As2O3-induced ovarian cancer cell death: oxidative stress-independent and -dependent cytotoxic potentiation. Int J Oncol 38:1731–1739

Pace C, Dagda R, Angermann J (2017) Antioxidants protect against arsenic induced mitochondrial cardio-toxicity. Toxics 5(4):38. https://doi.org/10.3390/toxics5040038

Paul NP, Galván AE, Yoshinaga-Sakurai K, Rosen BP, Yoshinaga M (2022) Arsenic in medicine: past, present and future. Biometals: Int J Role Metal Ions Biol Biochem Med 1–19. Advance online publication. https://doi.org/10.1007/s10534-022-00371-y

Percherancier Y, Germain-Desprez D, Galisson F, Mascle XH, Dianoux L, Estephan P, Chelbi-Alix MK, Aubry M (2009) Role of SUMO in RNF4-mediated promyelocyticleukemia protein (PML) degradation: sumoylation of PML and phospho-switch control of its SUMO binding domain dissected in living cells. J Biol Chem 284(24):16595–16608. https://doi.org/10.1074/jbc.M109.006387

Porter AC, Fanger GR, Vaillancourt RR (1999) Signal transduction pathways regulated by arsenate and arsenite. Oncogene 18:7794–7802

Ravandi F, Estey E, Jones D et al (2009) Effective treatment of acute promyelocyticleukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumabozogamicin. J Clin Oncol 27:504–510

Rawla P, Sunkara T, Muralidharan P, Raj JP (2018) Update in global trends and aetiology of hepatocellular carcinoma. Contemp Oncol (poznan, Pol) 22(3):141–150. https://doi.org/10.5114/wo.2018.78941

Roboz GJ, Dias S, Lam G, Lane WJ, Soignet SL, Warrell RP, Rafii S (2000) Arsenic trioxide induces dose- and time-dependent apoptosis of endothelium and may exert an antileukemic effect via inhibition of angiogenesis. Blood 96:1525–1530

Rogers CS, Yedjou CG, Sutton DJ, Tchounwou PB (2014) Vitamin D3 potentiates the antitumorigenic effects of arsenic trioxide in human leukemia (HL-60) cells. Exp Hematol Oncol 3:9

Sadaf N, Kumar N, Ali M, Ali V, Bimal S, Haque R (2018) Arsenic trioxide induces apoptosis and inhibits the growth of human liver cancer cells. Life Sci 205:9–17. https://doi.org/10.1016/j.lfs.2018.05.006

Shen S, Li XF, Cullen WR, Weinfeld M, Le XC (2013) Arsenic binding to proteins. Chem Rev 113(10):7769–7792. https://doi.org/10.1021/cr300015c

Shiloh Y (2003) ATM and related protein kinases: safeguarding genome integrity. Nat Rev Cancer 3:155–168. https://doi.org/10.1038/nrc1011

Sonneveld P (2017) Management of multiple myeloma in the relapsed/refractory patient. Hematology 2017(1):508–517. American Society of Hematology. Education Program. https://doi.org/10.1182/asheducation-2017.1.508

Stewart AK (2012) Novel therapeutics in multiple myeloma. Hematology 17(Suppl 1):S105–S108

Stoica A, Pentecost E, Martin MB (2000) Effects of arsenite on estrogen receptor-α expression and activity in MCF-7 breast cancer cells. Endocrinology 141:3595–3602

Sun XP, Zhang X, He C, Qiao H, Jiang X, Jiang H et al (2012) ABT-737 synergizes with arsenic trioxide to induce apoptosis of gastric carcinoma cells in vitro and in vivo. J Int Med Res 40:1251–1264

Tai S, Xu L, Xu M, Zhang L, Zhang Y, Zhang K, Zhang L, Liang C (2017) Combination of Arsenic trioxide and Everolimus (Rad001) synergistically induces both autophagy and apoptosis in prostate cancer cells. Oncotarget 8(7):11206–11218. https://doi.org/10.18632/oncotarget.14493

Takahashi S, Harigae H, Yokoyama H et al (2006) Synergistic effect of arsenic trioxide and flt3 inhibition on cells with flt3 internal tandem duplication. Int J Hematol 84:256–261

Tanaka Y, Komatsu T, Shigemi H, Yamauchi T, Fujii Y (2014) BIMEL is a key effector molecule in oxidative stress-mediated apoptosis in acute myeloid leukemia cells when combined with arsenic trioxide and buthioninesulfoximine. BMC Cancer 14:27. https://doi.org/10.1186/1471-2407-14-27

Tarkanyi I, Dudognon C, Hillion J et al (2005) Retinoid/arsenic combination therapy of promyelocyticleukemia: Induction of telomerase-dependent cell death. Leukemia 19:1806–1811

Telford WG, Fraker PJ (1997) Zinc reversibly inhibits steroid binding to murine glucocorticoid receptor. Biochem Biophys Res Commun 238:86–89

Thiede C, Steudel C, Mohr B et al (2002) Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. Blood 99:4326–4335

Tunissiolli NM, Castanhole-Nunes M, Biselli-Chicote PM, Pavarino EC, da Silva RF, da Silva RC, Goloni-Bertollo EM (2017) Hepatocellular carcinoma: a comprehensive review of biomarkers, clinical aspects, and therapy. Asian Pac J Cancer Prev: APJCP 18(4):863–872. https://doi.org/10.22034/APJCP.2017.18.4.863

Wang W, Adachi M, Zhang R, Zhou J, Zhu D (2009) A novel combination therapy with arsenic trioxide and parthenolide against pancreatic cancer cells. Pancreas 38:e114–e123

Wang L, Min Z, Wang X, Hu M, Song D, Ren Z, Cheng Y, Wang Y (2018) Arsenic trioxide and sorafenib combination therapy for human hepatocellular carcinoma functions via up-regulation of TNF-related apoptosis-inducing ligand. Oncol Lett 16(3):3341–3350. https://doi.org/10.3892/ol.2018.8981

Wei LH, Lai KP, Chen CA, Cheng CH, Huang YJ, Chou CH, Kuo ML, Hsieh CY (2005) Arsenic trioxide prevents radiation-enhanced tumor invasiveness and inhibits matrix metalloproteinase-9 through downregulation of nuclear factor kappaB. Oncogene 24(3):390-398. https://doi.org/10.1038/sj.onc.1208192. PMID: 15531921

Wen J, Feng Y, Huang W, Chen H, Liao B, Rice L et al (2010) Enhanced antimyeloma cytotoxicity by the combination of arsenic trioxide and bortezomib is further potentiated by p38 MAPK inhibition. Leuk Res 34:85–92

Williams AB, Schumacher B (2016) p53 in the DNA-damage-repair process. Cold Spring Harb Perspect Med 6(5):a026070. https://doi.org/10.1101/cshperspect.a026070

Wu W, Graves LM, Jaspers I, Devlin RB, Reed W, Samet JM (1999) Activation of the EGF receptor signaling pathway in human airway epithelial cells exposed to metals. Am J Physiol 277:L924–L931

Xu W, Wang Y, Tong H, Qian W, Jin J (2014) Downregulation of hTERT: an important As2O3 induced mechanism of apoptosis in myelodysplastic syndrome. PLoS ONE 9(11):e113199. https://doi.org/10.1371/journal.pone.0113199

Ye Y, Xu X, Zhang M et al (2015) Low-dose arsenic trioxide combined with aclacinomycin a synergistically enhances the cytotoxic effect on human acute myelogenous leukemia cell lines by induction of apoptosis. Leuk Lymphoma 56:3159–3167

Yih LH, Lee T-C (2000) Arsenite induces p53 accumulation through an ATM-dependent pathway in human fibroblasts. Cancer Res 60:6346–6352

Yu Y, Zhang D, Huang H et al (2014) NF-κB1 p50 promotes p53 protein translation through miR-190 downregulation of PHLPP1. Oncogene 33:996–1005. https://doi.org/10.1038/onc.2013.8

Zannini L, Delia D, Buscemi G (2014) CHK2 kinase in the DNA damage response and beyond. J Mol Cell Biol 6(6):442–457

Zhai B, Jiang X, He C et al (2015) Arsenic trioxide potentiates the anticancer activities of sorafenib against hepatocellular carcinoma by inhibiting Akt activation. Tumour Biol 36:2323–2334

Zhang T, Chen G, Wang Z et al (2001) Arsenic trioxide, a therapeutic agent for APL. Oncogene 20:7146–7153. https://doi.org/10.1038/sj.onc.1204762

Zhang W, Wang L, Fan Q et al (2011) Arsenic trioxide re-sensitizes ERα-negative breast cancer cells to endocrine therapy by restoring ERα expression in vitro and in vivo. Oncol Rep 26(3):621–628

Zhang N, Wu Z-M, Mcgowan E, Shi J, Hong Z-B, Ding C-W, Xia P, Di W (2009) Arsenic trioxide and cisplatin synergism increase cytotoxicity in human ovarian cancer cells: therapeutic potential for ovarian cancer. Cancer Sci 100:2459–2464. https://doi.org/10.1111/j.1349-7006.2009.01340.x

Zhao LL, Liu YF, Peng LJ, Fei AM, Cui W, Miao SC et al (2015) Arsenic trioxide rewires mantle cell lymphoma response to bortezomib. Cancer Med 4:1754–1766

Zheng Y, Zhou M, Ye A, Li Q, Bai Y, Zhang Q (2010) The conformation change of Bcl-2 is involved in arsenic trioxide-induced apoptosis and inhibition of proliferation in SGC7901 human gastric cancer cells. World J Surg Oncol 8:31. https://doi.org/10.1186/1477-7819-8-31

Zhong L, Xu F, Chen F (2018) Arsenic trioxide induces the apoptosis and decreases NF-κB expression in lymphoma cell lines. Oncol Lett 16(5):6267–6274. https://doi.org/10.3892/ol.2018.9424

Zhou GB, Zhang J, Wang ZY, Chen SJ, Chen Z (2007) Treatment of acute promyelocytic leukaemia with all-trans retinoic acid and arsenic trioxide: a paradigm of synergistic molecular targeting therapy. Philos Trans Royal Soc Lond Ser B Biol Sci 362(1482):959–971. https://doi.org/10.1098/rstb.2007.2026

# Chapter 5
# Arsenic Induced Cancer: A Risk to Mental Health and Quality of Life


**Shishu Kesh Kumar and Das Ambika Bharti**

**Abstract** Environmental health hazard of arsenic contamination in groundwater causes cancer and thus is a serious human health concern worldwide. A cross-sectional correlational research was undertaken to assess mental health and quality of life of arsenic induced cancer (AIC) patients from arsenic contaminated Gangetic plain of Bihar. With purposive sampling technique 93 AIC patients were drawn from the arsenic endemic regions of Bihar state. Comparative 103 cancer patients and 76 healthy individuals were drawn from non-arsenic affected regions of Bihar. Mental health and quality of life (QoL) was assessed using the Mental Health Inventory and WHOQOL-BREF scale respectively. Patients of AIC reported poor QoL especially, in terms of immediate environment and poor mental health in terms of integration of personality and environmental mastery compared to the cancer patients and their healthy counterparts from non-arsenic endemic regions of Bihar. However, AIC patients have intact perception of reality than their counterparts from non-arsenic endemic regions of Bihar. Conclusively, AIC seems to be a risk for the quality of life and mental health of its patients in the arsenic endemic middle Gangetic plain of Bihar. Findings advocates for future research on the adverse psychological impact of groundwater arsenic contamination in general and AIC in particular. Timely psychological interventions for affected population are also warranted from the policy makers, NGOs and social work sectors.

**Keywords** Arsenic endemic · Arsenic induced cancer · Groundwater contamination · Mental health · Quality of life

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## 5.1 Introduction

In many aspects twenty-first century is the era of change, witnessing changes in from environment to psychology of people (Inauen et al. 2021). These changes, though progressive, are leading to many serious problems of public concern (Chan 2018). Serious environmental issues of the present century could potentially change the entire life trajectory on earth (Singer 2020). Immediate interventions/remediation are needed against alarming challenges of water and air pollution, increased toxic waste, ever harming global warming, acid rain, and increasingly shrinking energy supplies (Singh and Singh 2017). Substantial increases in human exposer to heavy metals are the givens of heavy industrial activities of past (Balali-Mood et al. 2021) and so are new diseases emerging at a historically unprecedented rate. Nervous system disorders, gastrointestinal/kidney and immune system dysfunction, skin lesions, birth defects, vascular damage, and cancer are the frequent complications caused by toxic exposure to heavy metals such as Arsenic, mercury etc. (Balali-Mood et al. 2021).

Arsenic, especially, has emerged as a great health hazard to human (Madhav et al. 2020). High Arsenic exposure could be induced from arsenic contaminated groundwater used for several purposes such as drinking, irrigation, household activities etc. (Madhav et al. 2020). With nearly 180 countries facing arsenic contamination it is impacting at mass level with approx. 230 million people facing this arsenic menace (Shaji et al. 2021). WHO recommend 10 ppb as a permissible level for drinking groundwater but many countries have reported exceeded level (WHO 2011) in which Asian region are the most affected. Countries in southern Asia like India, Pakistan, Bangladesh, Nepal, China, Vietnam, Burma, Cambodia and Thailand are showing remarkable increase in groundwater arsenic contamination (Shaji et al. 2021). In India more than 20 states and 4 union territories are affected by arsenic contamination (Chakraborti et al. 2018; CGWB 2018). Over past five years arsenic contamination has increased 145% across India (Times of India 2021). Groundwater arsenic contamination in the Ganga River Basin (GRB) is up to 4730 μg/L (Chakraborti et al. 2018). In an estimate the most arsenic affected states in India are: West Bengal (28 million), Bihar (21 million), Uttar Pradesh (15 million), Assam (8.6 million) and Punjab (6 million) (Mukherjee et al. 2021). In Bihar, 22 out of 38 states are affected with arsenic groundwater contamination. The total population at risk is around 9 million (Thakur and Gupta 2019) and this number is increasing day by day (Mishra et al. 2016).

Studies report that consuming groundwater with arsenic above permissible limit may result in several dangerous health issues such as, arsenicosis, skin, cancer of lung, kidney and bladder, coronary heart disease, myocardial damage, hyperkeratosis, diabetes, hyperpigmentation of palm and sole, liver damage hypertension and Bowens disease (Lalwani et al. 2004; Steinmaus et al. 2014; Chakraborti et al. 2018; Kumar and Bharti 2021a; Mukherjee et al. 2021; Shaji et al. 2021). Recently, Kumar et al. (2022) reported pronounced anaemia, skin manifestations, loss of appetite, constipation, diarrhoea, high blood pressure, breathlessness, diabetes,

mental impairments, lumps in the body and cancer incidences among the exposed population.

Apart from the well documented adverse physical effects, arsenic contamination has adverse psychological effects too (Brinkel et al. 2009; Kumar and Bharti 2021b) but only scantly explored and reported in literature (Havenaar and Van den Brink 1997). Although Syed et al. (2012) highlighted serious issues related to mental health among arsenicosis patients from developing countries. Two Indian studies from West Bengal have reported possible significant association between ones' psychological health and prolonged arsenic exposure (Majumdar and Mazumder 2012; Sen and Biswas 2012). Prolonged arsenic exposure in the arsenic endemic regions is also associated with low quality of life and poor mental health (Syed et al. 2012; Chowdhury et al. 2016); depressions, anxiety, stress (Kumar and Bharti, 2021b), social injustice, discrimination and prejudice (Nasreen 2003; Keya 2004; Chowdhury et al. 2006). Arsenic contamination not only affects the victims but their family too causing psychological trauma and harassment (Chowdhury et al. 2006; Khan et al. 2007; Singh and Vedwan 2015).

According to WHOQOL Group (1998), quality of life (QOL) is "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment" (WHOQOL GROUP 1998). Long term arsenic exposure affects QOL of the victim (Laskar et al. 2010). Most of the arsenic affected area is rural as well as most of the sufferers comes from lower SES or poor households (Thakur and Gupta 2019). In addition, poor patients are greatly vulnerable to social and economic problems. (Ahmad et al. 2007). They find it difficult to bear travel and medical cost (Ahmad et al. 2007).

As victim suffers from physical health issue as well as psychological and social issues their personal and familial life get hampered (Brinkel et al. 2009). They lose job, as a result economic crisis are common for them, and in addition, the treatment expenses aggravate the situations (Brinkel et al. 2009). Family support plays significant role in psychological distress but victim residing in arsenic affected area may also bear criticism from their family (Lincoln et al. 2003; Horwitz et al. 2015) as such the adverse consequences of chronic arsenic exposure may affect physical, social and mental spheres of human life (Keya 2004). The socio-cultural issues like isolation, instability, social stigma, societal refusal, discrimination, marital problems (divorce, separation) and several economic losses like less payment or loss of employment (Rahman et al. 2018) makes the patients an economic, social and psychological burden for their families.

## 5.2 Rationale

Environmental issues are health issues in the twenty-first century (Inauen et al. 2021). Arsenic is an environmental health hazard and because of adverse health consequences, groundwater arsenic contamination is a major public health concern (UNICEF 1998; WHO 2011). India is seriously affected by ground water arsenic contamination (Shaji et al. 2021) and situation is worst in Bihar (Mishra et al. 2016). Adverse consequences of chronic exposure to arsenic on physical health are widely studied in global as well as Indian context. Moreover, the physiological consequences of cancer from arsenic endemic Indian Gangetic plain are also extensively studied. Research pursuits to study the psychological dimensions/aftermaths of arsenic induced cancer (AIC) are scantly reported in literature from the Asian countries and that from India particularly. Hence, this study was conducted in the arsenic endemic middle Gangetic plain of Bihar, India to assess the understudied psychological aspects (particularly mental health and quality of life) of AIC.

## 5.3 Methods

### *5.3.1 Hypotheses*

**Hypothesis 1(a)**: Patients of AIC from the arsenic endemic GPB, India would significantly differ on their psychological well-being (mental health and quality of life) from their comparative counterparts from the non-arsenic endemic regions of the state.

**Hypothesis 1(b)**: Patients of AIC from the arsenic endemic GPB, India would significantly differ on their psychological well-being (mental health and quality of life) from their comparative healthy counterparts from non-arsenic endemic regions of Bihar**.**

### *5.3.2 Research Design*

A cross-sectional correlational research was conducted in the arsenic endemic middle Gangetic plain of Bihar, India.

### *5.3.3 Sample*

Through purposive sampling method a total of 272 (N = 272) sample/participant was drawn from Bihar, India. Mean age of the participants was 50.72 (range = 32–60 years). The total sample was subdivided into three treatment conditions. In treatment condition-I, there was 93 arsenic induced cancer patients ($n_1 = 93$, mean age = 52.60 years) drawn from MCSRC, Patna, Bihar. The researchers/clinicians at MCSRC made the differential diagnosis for AIC after due consideration to their respective clinical history for arsenicosis and absence of clinical co-morbidity. The prominent biomarkers like arsenic in drinking water source, arsenic in hair, arsenic in blood and arsenic in nail were the basis of the differential diagnosis. The participants lived for more than 10 years in the arsenic affected (such as Buxar, Patna, Bhagalpur, Bhojpur, Khagaria, Vaishali, and Samastipur) middle Gangetic plain of Bihar. There were 103 cancer patients ($n_2 = 103$, mean age = 50.13) in Treatment condition II from non-arsenic affected regions of Bihar, India. These participants were also drawn from MCSRC, Patna, Bihar. There were 76 healthy participants in control group from non-arsenic affected regions of Bihar, India.

### *5.3.4 Tools*

Following psychometrically sound tools were used to gather relevant information from the participants of the present study.

#### 5.3.4.1 Socio-demographic and Clinical Data Sheet

It was a structured format created to collected relevant participants information such as gender, age, residential area and education status, duration of stay in the study area. It also included information about previous clinical history of the participants.

#### 5.3.4.2 Mental Health Inventory (Jagdish and Srivastava 1983)

This is an inventory of 56 items; rated on a four-point Likert scale (ranging from "always" to "never"). It is used to assess mental health along with its six dimensions namely perception of reality, integration of personality, positive self-evaluation, environmental mastery, group-oriented attitude and autonomy. The split-half reliability of this inventory was 0.726 and ranged from 0.75 to 0.79 for their six dimensions.

#### 5.3.4.3 The WHOQOL-BREF (WHOQOL Group 1998)

It is a 26-items scale; item are rated on 5-point ordinal scale. It is used to assess quality of life along with its four dimensions namely psychological health, environmental health, social relationships and physical health. It has good psychometric properties and is cross culturally sensitive (WHOQOL Group 1998).

### *5.3.5 Ethical Approval*

The ethical approval committee of MCSRC, Patna (India) had given its approval to draw the sample from its esteemed institution to collect relevant data from them. The authors also took ethical approval from the Departmental Research Degree Committee (DRDC) of their respective University department to conduct the study.

### *5.3.6 Procedure*

A test booklet was prepared by compiling all three questionnaires in a specific sequence. Through purposive sampling method, study sample was drawn and data was collected in three phases. The test booklet was administered to each participant one on one basis. In the first phase data was collected from the participants of treatment condition-I (AIC cases). In the second phase data was collected from the participants of treatment condition-II (Cancer cases from non-arsenic affected regions of Bihar). The participants of the two treatment conditions were diagnosed and referred by the clinicians/researchers of MCSRC, Patna, Bihar (India). In the last phase data was collected from a comparative group of healthy counterparts from the non-arsenic endemic regions of middle Gangetic plain of Bihar. Rapport was established with all the participants and purpose of the study was explained. After explaining the voluntary nature of participation, informed consent for voluntary participation was taken. Instructions related to each scale were given clearly and their queries or confusions (if any) were resolved before administering the tests.

Approximately each participant took 20–25 min to complete the questionnaires. Throughout the process, ethical guidelines laid down by the American Psychological Association (APA 2010) were adhered to. Statistical package for social sciences (SPSS) version-25 was used for data handling and required statistical analysis.

## 5.4 Results

Table 5.1 reveals that AIC patients scored lower on overall QOL (M = 88.903, SD = 22.785) including its three dimensions namely environmental (M = 27.107, SD = 8.961), social relationship (M = 11.215, SD = 2.746) and physical health (M = 22.312, SD = 7.127) when compared to cancer cases from non-arsenic endemic regions with scores on overall QOL (M = 92.747, SD = 18.027), environmental (M = 30.048, SD = 5.517), social relationship (M = 11.573, SD = 2.075) and physical health (M = 23.466, SD = 5.818). Healthy counterparts scored higher on overall QOL (M = 120.171, SD = 5.730), environmental (M = 36.487, SD = 3.189), social relationship (M = 13.724, SD = 1.271) and physical health (M = 32.921, SD = 1.917) as compare to AIC patients.

**Table 5.1** Descriptive statistics (mean and SD) of three treatment condition (namely AIC patients, cancer patients from non-arsenic endemic regions and healthy participants) with respect to QOL

| | Sample | N | Mean | SD |
|---|---|---|---|---|
| Physical health | Cancer patients from non-arsenic endemic regions | 103 | 23.466 | 5.818 |
| | AIC patients | 93 | 22.312 | 7.127 |
| | Healthy participants | 76 | 32.921 | 1.917 |
| Psychological health | Cancer patients from non-arsenic affected regions | 103 | 21.272 | 4.716 |
| | AIC patients | 93 | 21.785 | 4.641 |
| | Healthy participants | 76 | 28.000 | 1.641 |
| Social relationship | Cancer patients from non-arsenic affected regions | 103 | 11.573 | 2.075 |
| | AIC patients | 93 | 11.215 | 2.746 |
| | Healthy participants | 76 | 13.724 | 1.271 |
| Environmental | Cancer patients from non-arsenic affected regions | 103 | 30.048 | 5.517 |
| | AIC patients | 93 | 27.107 | 8.961 |
| | Healthy participants | 76 | 36.487 | 3.189 |
| QOL | Cancer patients from non-arsenic affected regions | 103 | 92.747 | 18.027 |
| | AIC patients | 93 | 88.903 | 22.785 |
| | Healthy participants | 76 | 120.171 | 5.730 |

Cancer patients from non-arsenic affected regions scored lower on psychological health (M = 21.272, SD = 4.716) than healthy counterparts (M = 28.000, SD = 1.641) and AIC patients (M = 21.785, SD = 4.641).

Table 5.2 shows that three treatment groups were significantly different from each other on overall QOL ($F = 76.739$, $p < 0.001$) as well as on its three dimensions: environmental ($F = 45.215$, $p < 0.001$), social relationship ($F = 32.301$, $p < 0.001$), physical health ($F = 88.745$, $p < 0.001$) and psychological health ($F = 69.961$, $p < 0.001$).

Post-hoc test was further applied on the data to ascertain the groups which differed significantly on QOL and its dimensions.

Table 5.3 and Fig. 5.4 clearly shows that AIC patients differ significantly on only one dimension of QOL i.e., environmental ($MD = 2.941$, $p < 0.005$) as compared with cancer patients from non-arsenic endemic regions. AIC patients have poor environmental QOL as compared with cancer patients from non-arsenic affected regions of Bihar (Table 5.1).

Table 5.3, Figs. 5.1, 5.2, 5.3, 5.4, and 5.5 clearly shows that AIC patients and healthy participants significantly differ on overall QOL ($MD = 31.268$, $p < 0.001$) as well as on all dimensions of QOL namely environment ($MD = 9.379$, $p < 0.001$), social relationship ($MD = 2.508$, $p < 0.001$), physical health ($MD = 10.609$, $p < 0.001$) and psychological health ($MD = 6.215$, $p < 0.001$). AIC patients were found to have poor overall QOL along with its all dimensions as compared with healthy counterparts (can be seen in Table 5.1).

**Table 5.2** ANOVA table comparing the three treatment conditions (namely AIC patients, cancer patients from non-arsenic affected regions and healthy participants) on overall QOL and its four dimensions

| | | Sum of squares | Df | Mean squares | F | Sig. |
|---|---|---|---|---|---|---|
| Physical health | Between group | 5544.518 | 2 | 2772.259 | 88.745 | 0.001 |
| | Within group | 8403.114 | 269 | 31.238 | | |
| | Total | 13,947.632 | 271 | | | |
| Psychological health | Between group | 2315.791 | 2 | 1157.896 | 69.961 | 0.001 |
| | Within group | 4452.087 | 269 | 16.551 | | |
| | Total | 6767.879 | 271 | | | |
| Social relationship | Between group | 301.179 | 2 | 150.590 | 32.301 | 0.001 |
| | Within group | 1254.100 | 269 | 4.662 | | |
| | Total | 1555.279 | 271 | | | |
| Environmental | Between group | 3783.533 | 2 | 1891.767 | 45.215 | 0.001 |
| | Within group | 11,254.669 | 269 | 41.839 | | |
| | Total | 15,038.202 | 271 | | | |
| QOL | Between group | 47,569.172 | 2 | 23,784.586 | 76.739 | 0.001 |
| | Within group | 83,374.342 | 269 | 309.942 | | |
| | Total | 130,943.515 | 271 | | | |

**Table 5.3** Post-hoc test of Tukey for multiple comparisons on overall QOL among three treatment conditions (AIC patients, cancer patients from non-arsenic endemic regions and healthy participants)

| Coping strategies | Comparing sample | | Mean Differences | Sig. |
|---|---|---|---|---|
| Physical health | Cancer patients from non-arsenic endemic regions | Healthy participants | 9.455 | 0.001 |
| | AIC patients | Cancer patients from non-arsenic affected regions | 1.154 | 0.320 |
| | Healthy participants | AIC patients | 10.609 | 0.001 |
| Psychological health | Cancer patients from non-arsenic endemic regions | Healthy participants | 6.728 | 0.001 |
| | AIC patients | Cancer patients from non-arsenic endemic regions | 0.513 | 0.652 |
| | Healthy participants | AIC patients | 6.215 | 0.001 |
| Social relationship | Cancer patients from non-arsenic endemic regions | Healthy participants | 2.151 | 0.001 |
| | AIC patients | Cancer patients from non-arsenic endemic regions | 0.358 | 0.479 |
| | Healthy participants | AIC patients | 2.508 | 0.001 |
| Environmental | Cancer patients from non-arsenic endemic regions | Healthy participants | 6.438 | 0.001 |
| | AIC patients | Cancer patients from non-arsenic endemic regions | 2.941 | 0.005 |
| | Healthy participants | AIC patients | 9.379 | 0.001 |
| QOL | Cancer patients from non-arsenic endemic regions | Healthy participants | 27.424 | 0.001 |
| | AIC patients | Cancer patients from non-arsenic endemic regions | 3.844 | 0.280 |
| | Healthy participants | AIC patients | 31.268 | 0.001 |

Table 5.4 reveals that AIC patients scored lower on mental health (M = 157.602, SD = 15.599) along with its four dimensions namely, environmental mastery (M = 26.226, SD = 3.828), group-oriented attitude (M = 29.376, SD = 2.896), integration of personality (M = 29.537, SD = 5.266) and positive self-evaluation (M = 30.989, SD = 5.218) as compared to cancer cases from non-arsenic endemic regions with scores on mental health (M = 160.175, SD = 15.389) along with its four dimensions

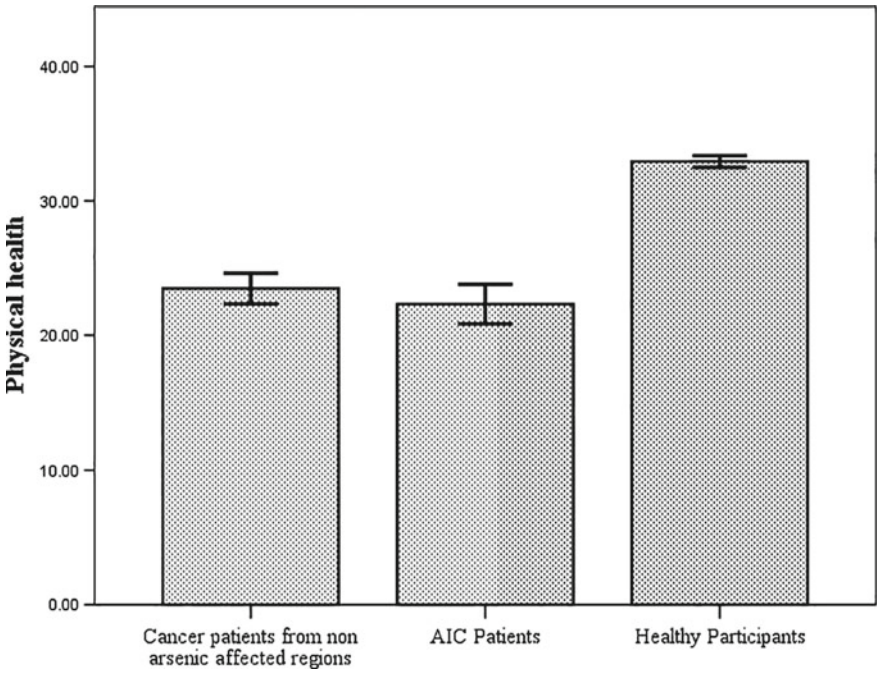


**Fig. 5.1** Comparison (Mean and SD) of the three treatment groups with respect to the physical health dimension of QoL

namely environmental mastery (M = 27.641, SD = 2.704), group-oriented attitude (M = 29.476, SD = 3.343), integration of personality (M = 31.718, SD = 6.589) and positive self-evaluation (M = 32.349, SD = 3.859). AIC patients significantly differed from their healthy counterparts on mental health (M = 184.329, SD = 9.809) along with its four dimensions namely environmental mastery (M = 31.039, SD = 2.700), group-oriented attitude (M = 32.671, SD = 2.783), integration of personality (M = 38.684, SD = 3.303) and positive self-evaluation (M = 36.711, SD = 2.586).

From Table 5.4 it may be clearly seen that AIC patients scored high on two dimensions of mental health i.e., perception of reality (M = 24.849, SD = 5.287) and autonomy (M = 16.548, SD = 2.238) as compared with cancer cases from non-arsenic endemic regions of Bihar with lower score on perception of reality (M = 22.699, SD = 2.873) and autonomy (M = 16.311, SD = 2.254).

Table 5.5 clearly demonstrate that all three treatment groups significantly differed from each other on mental health ($F = 89.027$, $p < 0.001$) along with its all seven dimensions namely environmental mastery ($F = 51.188$, $p < 0.001$), integration of personality ($F = 65.783$, $p < 0.001$), perception of reality ($F = 17.931$, $p < 0.001$), group-oriented attitude ($F = 31.099$, $p < 0.001$), autonomy ($F = 44.063$, $p < 0.001$) and positive self-evaluation ($F = 43.478$, $p < 0.001$).

Further**,** Post-hoc test was applied on the data to ascertain the groups which differed significantly on mental health and its dimensions.

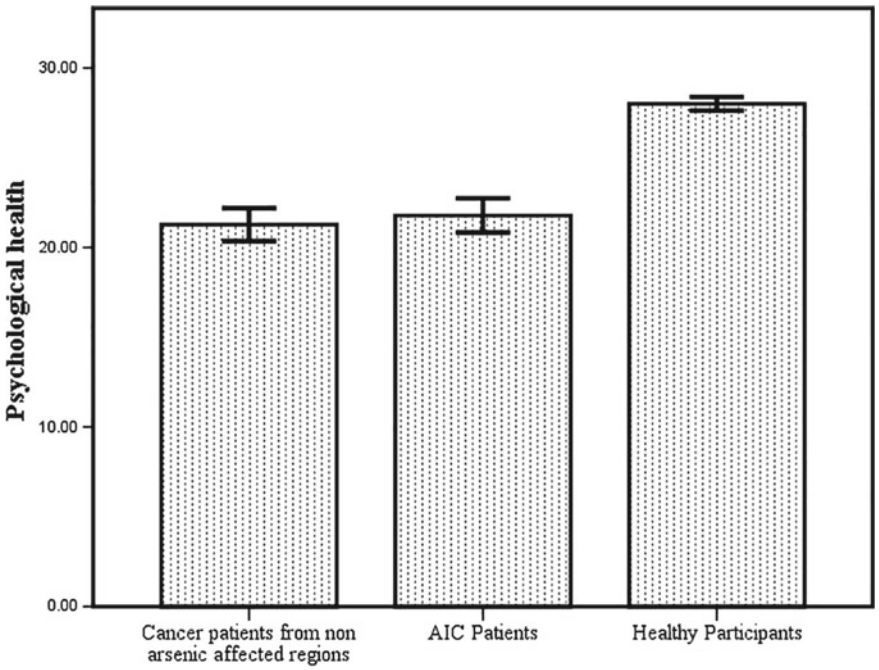


**Fig. 5.2** Comparison (Mean and SD) of the three treatment groups with respect to QoL in the dimension of psychological health

Table 5.6 and Figs. 5.6, 5.7, 5.8 and 5.9 shows that AIC patients and cancer cases from non-arsenic endemic regions significantly differ on mental health in term of its three dimensions (environmental mastery (MD = 1.415, $p < 0.005$), integration of personality (MD = 2.181, $p < 0.013$) and perception of reality (MD = 2.150, $p < 0.001$)). AIC victims are found to have poor mental health in terms of its two dimensions namely environmental mastery and integration of personality. However, AIC patients reported better mental health on its one dimension i.e., perception of reality as compared with cancer patients from non-arsenic regions of Bihar (can be seen Table 5.4).

Table 5.6 also evident that AIC patients differ significantly on mental health (MD = 26.727, $p < 0.001$) along with its all dimensions namely group-oriented attitude (MD = 3.295, $p < 0.001$), autonomy (MD = 2.636, $p < 0.001$), environmental mastery (MD = 4.814, $p < 0.001$), integration of personality (MD = 9.146, $p < 0.001$) and positive self-evaluation (MD = 5.721, $p < 0.001$) except perception of reality (MD = 1.190, $p = 0.109$) as compared with their healthy counterparts.

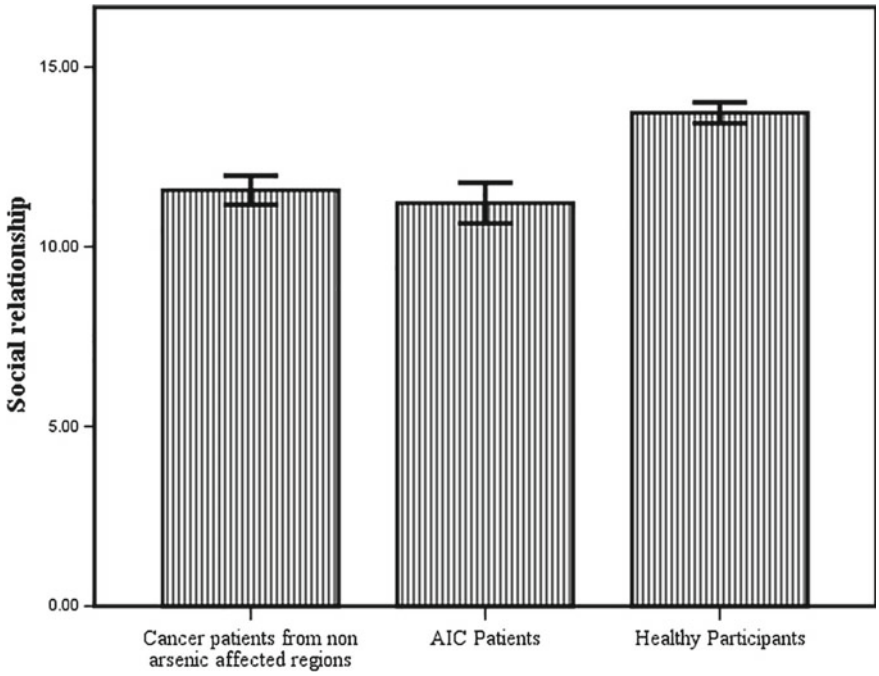


**Fig. 5.3** Comparison (Mean and SD) of the three treatment groups on QoL in the dimension of social relationship

## 5.5 Discussion

In the changing world and environment, arsenic has emerged as one of the most pervasive environmental health hazards and it is affecting people's physical as well as psychological health all over the world (Inauen et al. 2021). It is carcinogenic in nature and studies have reported high prevalence of cancer in the arsenic endemic Gangetic plain of Bihar (Singh et al. 2015; Chakraborti et al. 2018; Kumar et al. 2021, 2022). Environment has important impact on our physical health which in turn determines directly as well as indirectly our psychological well-being (Peek et al. 2009; Chen et al. 2013). The mass level impact of groundwater arsenic contamination warrants the understanding of the possible linkage between the environmental health hazard, the physiological underpinnings and the psychological health condition. In the paucity of sufficient research exploring the psychological aspects of groundwater arsenic contamination, the present study was undertaken to assess the mental health and quality of life of AIC patients from the arsenic endemic Gangetic plain of Bihar state.

The finding suggests that AIC patients have poor environmental quality of life when compared to cancer cases taken from non-arsenic endemic regions in the Gangetic plain of Bihar. Poor environmental quality of life means that AIC patients

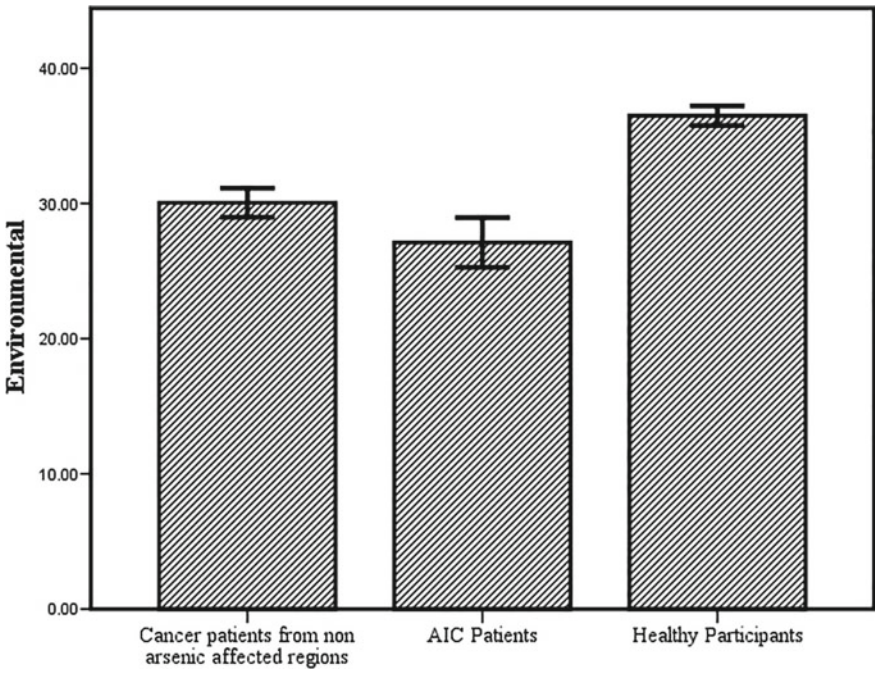


**Fig. 5.4** Comparison (Mean and SD) of the three treatment groups on its QoL in the environment dimension

have limited opportunities to learn, perform new skills, avails limited financial resources, health facilities, and low level of social activities in their neighbourhood because people boycott them and hesitate to talk or interact with them as they think that disease is contagious in nature so it can spread by touching (Lincoln et al. 2003; Tsutsumi et al. 2004; Chowdhury et al. 2006). People treat its patients as neglectful (Chowdhury et al. 2006). These belief systems create difficulties for the AIC patients in their mundane reality of life. Chronic illness are always found to affect activities of daily living, that adversely impacts their quality of life, their subjective well-being and mental health (Keya 2004). These patients are refused enough support from friends, family, relatives etc. (Horwitz et al. 2015; Rahman et al. 2018). Earlier studies have also reported that arsenic toxicity may affect physical, social and mental spheres of human life (Keya 2004). Family does not support victim due to fear of community discrimination (Keya 2004; Brinkel et al. 2009).

Most of the chronic arsenic contaminated area are far away from densely populated city and mostly belongs to rural regions of Bihar near Gangetic plains (Kumar and Ghosh 2021). In these interior regions, there are very few medical facilities available (Mishra 2009; Singh and Taylor 2019). Even in case of emergency the person residing in this area will not get-well equipped ambulance or medical facilities on time (Vail et al. 2018). The conditions are so bad that even clean water and food

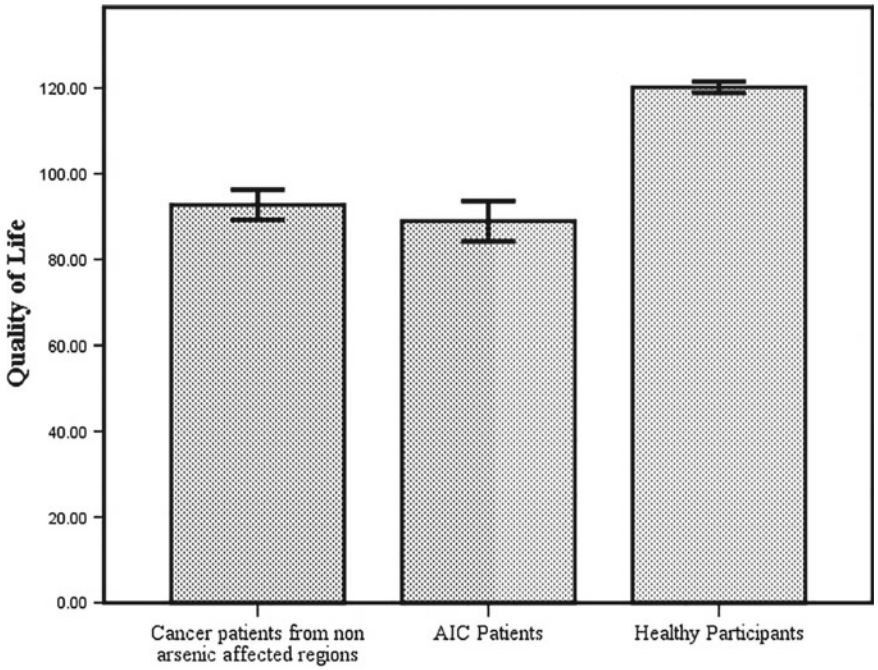


**Fig. 5.5** Comparison (Mean and SD) of the three treatment groups on overall QoL

are not available to the people residing here (Kumar and Ghosh 2021). Social dejection, discrimination and poor immediate environment may enhance the feelings of dissatisfaction, loneliness and anxiety in AIC patients. A study (Ernst et al. 2017) also revealed that due to social discrimination cancer patients may have poor QOL. The difficulties so caused indirectly pave a way to poor social relations as well when compared to their counterparts from the non-arsenic affected regions.

Findings of this study also reveal that AIC patients have lower mental health especially, in terms of its two dimensions namely environmental mastery and integration of personality compared to the cancer cases drawn from non-arsenic endemic regions of Bihar. However, it is also evident that AIC patients have clear perception of reality compared to their counterparts from non-arsenic endemic regions of Bihar. Individuals with symptoms of arsenicosis often succumb to fatalism and give up hope of recovery (Sarker and Mohiuddin 2002). Things get worse when they know that the cancer was caused not by their cancer-causing behaviour/life-style but by their mere exposure to arsenic-contaminated groundwater and food. Victims of chronic arsenic exposure may also face prejudices, humiliation and discrimination from their social setting (Fujino et al. 2004; Chowdhury et al. 2006). This results in many emotional and mental health problems like feeling of hopelessness, fear, anger etc. (Phelan et al. 2013; Fujisawa and Hagiwara 2015; Ernst et al. 2017). A person with arsenicosis symptoms also reports poor mental health (Syed et al. 2012) and the common

**Table 5.4** Descriptive statistics (Mean and SD) of three treatment condition (namely AIC patients, cancer patients from non-arsenic endemic regions and healthy participants) with respect to mental health (MH)

| | Sample | N | Mean | SD |
|---|---|---|---|---|
| Positive self-evaluation | Cancer patients from non-arsenic endemic regions | 103 | 32.349 | 3.859 |
| | AIC patients | 93 | 30.989 | 5.218 |
| | Healthy participants | 76 | 36.711 | 2.586 |
| Perception of reality | Cancer patients from non-arsenic endemic regions | 103 | 22.699 | 2.873 |
| | AIC patients | 93 | 24.849 | 5.287 |
| | Healthy participants | 76 | 26.039 | 2.564 |
| Integration of personality | Cancer patients from non-arsenic endemic regions | 103 | 31.718 | 5.266 |
| | AIC patients | 93 | 29.537 | 6.589 |
| | Healthy participants | 76 | 38.684 | 3.303 |
| Autonomy | Cancer patients from non-arsenic endemic regions | 103 | 16.311 | 2.254 |
| | AIC patients | 93 | 16.548 | 2.238 |
| | Healthy participants | 76 | 19.184 | 2.011 |
| Group-oriented attitude | Cancer patients from non-arsenic endemic regions | 103 | 29.476 | 3.343 |
| | AIC patients | 93 | 29.376 | 2.896 |
| | Healthy participants | 76 | 32.671 | 2.783 |
| Environmental mastery | Cancer patients from non-arsenic endemic regions | 103 | 27.641 | 2.704 |
| | AIC patients | 93 | 26.226 | 3.828 |
| | Healthy participants | 76 | 31.039 | 2.700 |
| Mental health | Cancer patients from non-arsenic endemic regions | 103 | 160.175 | 15.389 |
| | AIC patients | 93 | 157.602 | 15.599 |
| | Healthy participants | 76 | 184.329 | 9.809 |

**Table 5.5** ANOVA table comparing the three treatment conditions (namely AIC patients, cancer patients from non-arsenic endemic regions and healthy participants) on Mental Health (MH) and its dimensions

| | | Sum of squares | df | Mean squares | F | Sig. |
|---|---|---|---|---|---|---|
| Positive self-evaluation | Between group | 1463.079 | 2 | 731.540 | 43.478 | 0.001 |
| | Within group | 4526.038 | 269 | 16.825 | | |
| | Total | 5989.118 | 271 | | | |
| Perception of reality | Between group | 520.791 | 2 | 260.396 | 17.931 | 0.001 |
| | Within group | 3906.444 | 269 | 14.522 | | |
| | Total | 4427.235 | 271 | | | |
| Integration of personality | Between group | 3737.846 | 2 | 1868.923 | 65.783 | 0.001 |
| | Within group | 7642.374 | 269 | 28.410 | | |
| | Total | 11,380.221 | 271 | | | |
| Autonomy | Between group | 420.161 | 2 | 210.081 | 44.063 | 0.001 |
| | Within group | 1282.512 | 269 | 4.768 | | |
| | Total | 1702.673 | 271 | | | |
| Group-oriented attitude | Between group | 576.262 | 2 | 288.131 | 31.099 | 0.001 |
| | Within group | 2492.294 | 269 | 9.265 | | |
| | Total | 3068.555 | 271 | | | |
| Environmental mastery | Between group | 1005.060 | 2 | 502.530 | 51.188 | 0.001 |
| | Within group | 2640.848 | 269 | 9.817 | | |
| | Total | 3645.908 | 271 | | | |
| Mental health | Between group | 35,585.560 | 2 | 17,792.780 | 89.027 | 0.001 |
| | Within group | 53,761.910 | 269 | 199.858 | | |
| | Total | 89,347.471 | 271 | | | |

complains included sleep disturbances, fatigue and poor appetite (Mazumder et al. 1998; Rahman et al. 2001).

Perception of reality is found to be intact in AIC patients as they very well know and accept the root cause of their sufferings. They are well aware of the bitter truth that prolonged exposure to arsenic poisoning through water and food is the reason for their current disease condition. They could neither undo the cancerous nature of arsenic nor relocate to places with safer drinking water and environment.

This study also reveals that healthy participants have better mental health and quality of life when compared with AIC patients residing in arsenic endemic middle Gangetic plain of Bihar. A study (McCorkle et al. 2011) shows that diagnosis of cancer itself causes traumatic situation in victims' life. Moreover, cancer related stigma is also seen in many studies responsible for depression, anxiety and stress (Major and O'Brien 2005; Phelan et al. 2013; Brown Johnson et al. 2014; Fujisawa and Hagiwara 2015; Ernst et al. 2017). Prejudice, stereotypes and discrimination are common for cancer patients in general (Yıldız and Koç, 2021). Having symptoms of keratosis, melanosis in sole and palm victims face social dejection (Brinkel

**Table 5.6** Post-hoc test of Tukey for multiple comparisons on MH among three treatment conditions (AIC patients, cancer patients from non-arsenic endemic regions and healthy participants)

| Coping strategies | Comparing sample | | Mean Differences | Sig. |
|---|---|---|---|---|
| Positive self-evaluation | Cancer patients from non-arsenic endemic regions | Healthy participants | 4.361 | 0.001 |
| | AIC patients | Cancer patients from non-arsenic endemic regions | 1.360 | 0.055 |
| | Healthy participants | AIC patients | 5.721 | 0.001 |
| Perception of reality | Cancer patients from non-arsenic endemic regions | Healthy participants | 3.340 | 0.001 |
| | AIC patients | Cancer patients from non-arsenic endemic regions | 2.150 | 0.001 |
| | Healthy participants | AIC patients | 1.190 | 0.109 |
| Integration of personality | Cancer patients from non-arsenic endemic regions | Healthy participants | 6.966 | 0.001 |
| | AIC patients | Cancer patients from non-arsenic endemic regions | 2.181 | 0.013 |
| | Healthy participants | AIC patients | 9.146 | 0.001 |
| Autonomy | Cancer patients from non-arsenic endemic regions | Healthy participants | 2.874 | 0.001 |
| | AIC patients | Cancer patients from non-arsenic endemic regions | 0.237 | 0.727 |
| | Healthy participants | AIC patients | 2.636 | 0.001 |
| Group-oriented attitude | Cancer patients from non-arsenic endemic regions | Healthy participants | 3.195 | 0.001 |
| | AIC patients | Cancer patients from non-arsenic endemic regions | 0.099 | 0.972 |
| | Healthy participants | AIC patients | 3.295 | 0.001 |
| Environmental mastery | Cancer patients from non-arsenic endemic regions | Healthy participants | 3.398 | 0.001 |
| | AIC patients | Cancer patients from non-arsenic endemic regions | 1.415 | 0.005 |
| | Healthy participants | AIC patients | 4.814 | 0.001 |

(continued)

**Table 5.6** (continued)

| Coping strategies | Comparing sample | | Mean Differences | Sig. |
|---|---|---|---|---|
| Mental health | Cancer patients from non-arsenic endemic regions | Healthy participants | 24.154 | 0.001 |
| | AIC patients | Cancer patients from non-arsenic endemic regions | 2.573 | 0.412 |
| | Healthy participants | AIC patients | 26.727 | 0.001 |

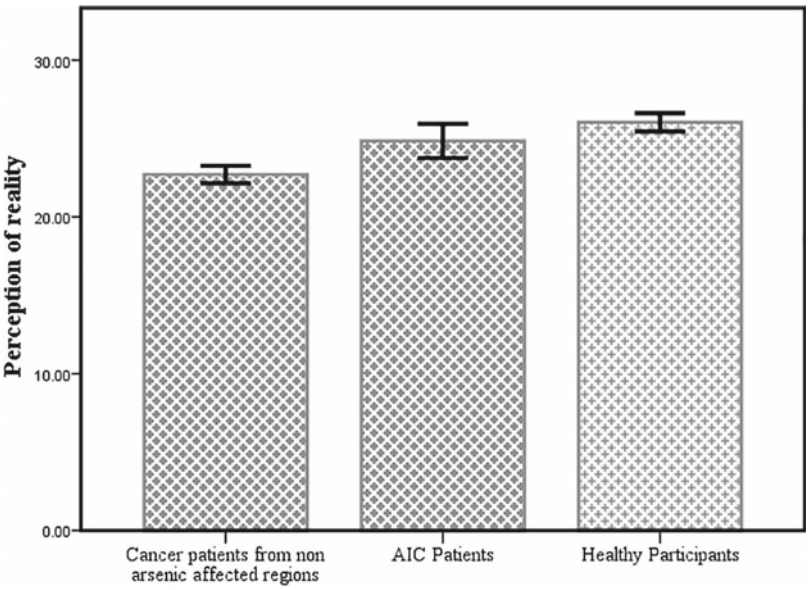


**Fig. 5.6** Comparison (Mean and SD) of the three treatment groups with respect to perception of reality

et al. 2009). They also face marriage related problems like divorce, separation etc. and social problem like dejection, discrimination, isolation etc. (Lincoln et al. 2003; Brinkel et al. 2009; Horwitz et al. 2015). Such factors play key role in having poor mental health and QOL by the AIC patients as compared with their healthy counterparts. In accordance with the present finding a study (Kumar and Bharti 2021b) also reviles that AIC patients face depression anxiety and stress as compare to their healthy counterparts. The AIC for its physiological and social underpinnings thus could be a risk to psychological wellbeing well reflected as mental health and quality of life in the arsenic affected regions.

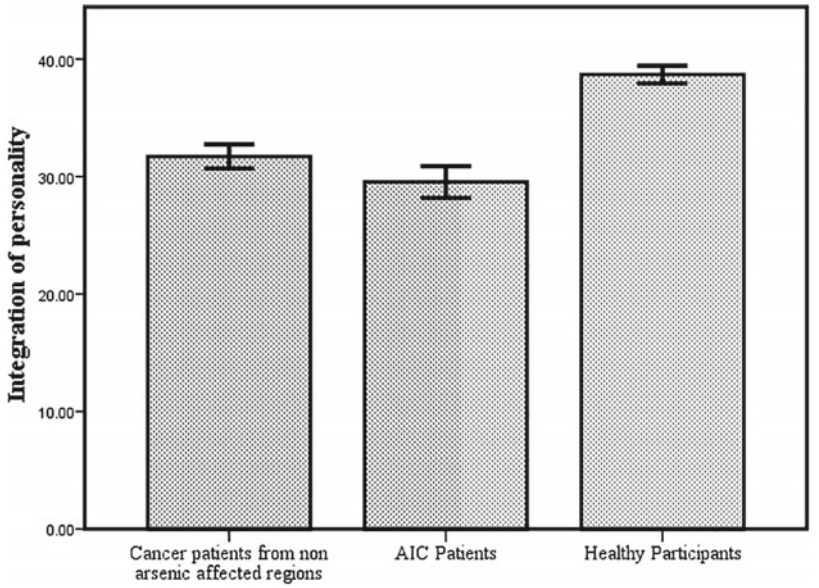


**Fig. 5.7** Comparison (Mean and SD) of the three treatment groups with respect to integration of personality

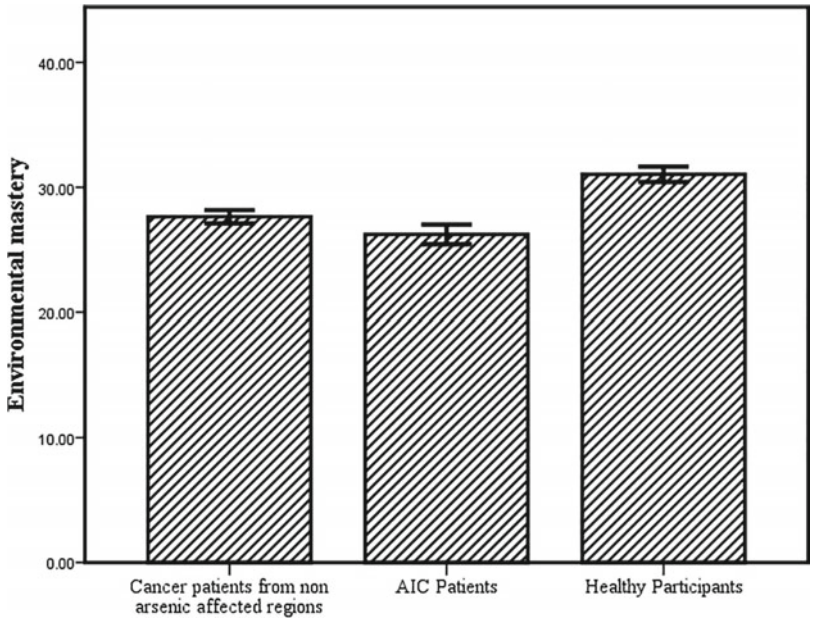


**Fig. 5.8** Comparison (Mean and SD) of the three treatment groups with respect to environmental mastery

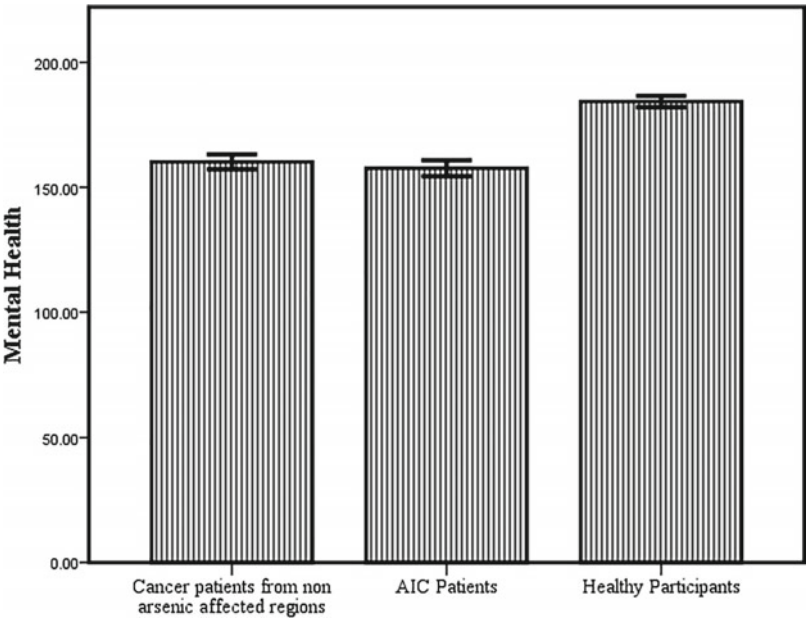


**Fig. 5.9** Comparison (Mean and SD) of the three treatment groups with respect to mental health

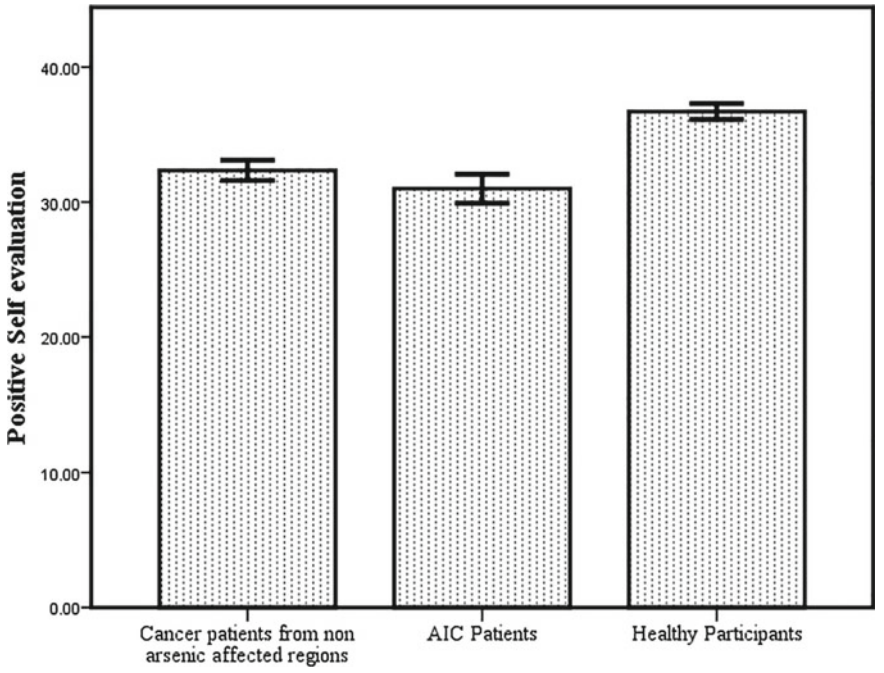


**Fig. 5.10** Comparison (Mean and SD) of the three treatment groups with respect to positive self-evaluation

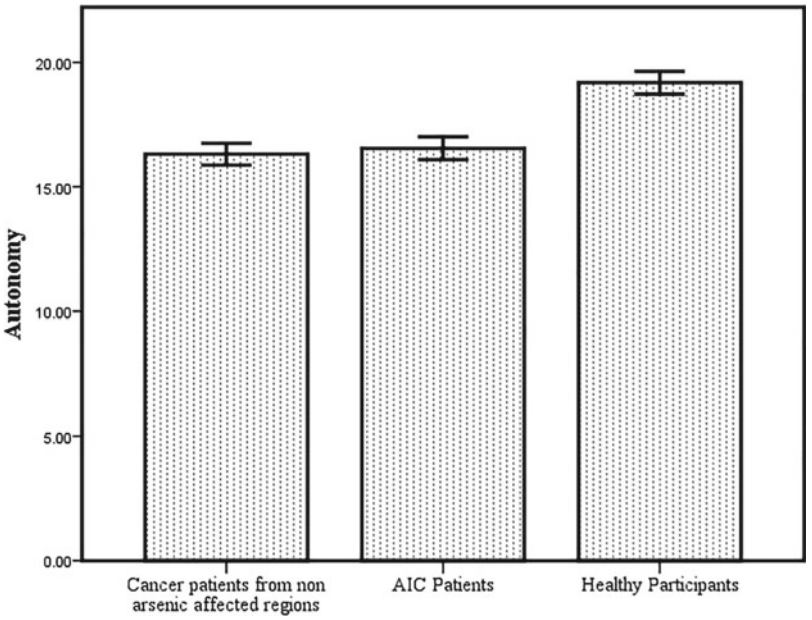


**Fig. 5.11** Comparison (Mean and SD) of the three treatment groups with respect to autonomy

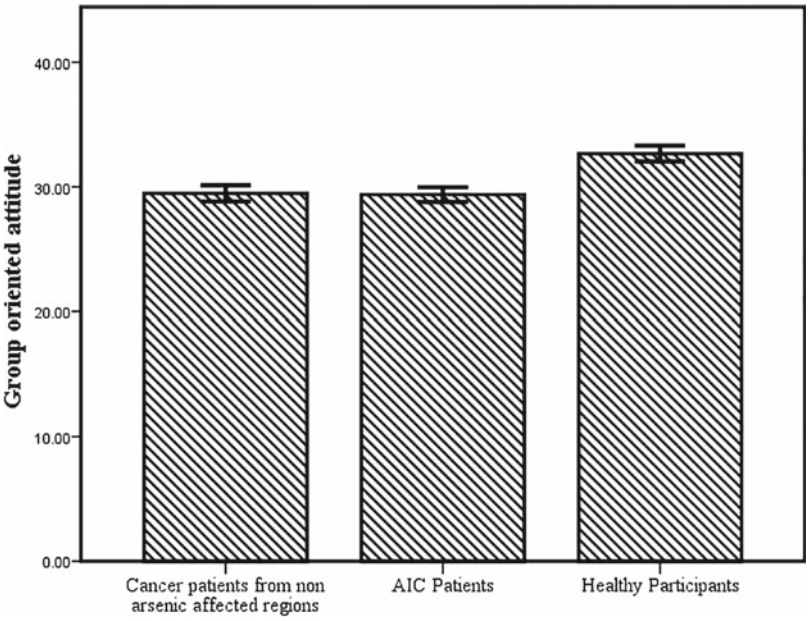


**Fig. 5.12** Comparison (Mean and SD) of the three treatment groups with respect to group-oriented attitude

## 5.6 Conclusion

The psychological aspects of AIC are equally significant to be investigated and understood for possible rehabilitation of the economically, physically, socially and psychologically burdened population residing in the arsenic endemic regions. Arsenic induced cancer (AIC) emerged as a key risk factor for the healthy mental health and better quality of life of its patients residing in the arsenic endemic Gangetic plain of Bihar. Arsenic contamination of the groundwater is not just an environmental health hazard but also the major deterring factor for enhanced mental health and quality of life. Psychological aspects of AIC thus warrants further investigations to gain complete understanding of the linkage between environment, physical health and psychological health. Moreover, timely psychological interventions for affected population are also warranted from the policy makers, NGOs and social work sectors.

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## References

Ahmad SA, Sayed MH, Khan MH, Karim MN, Haque MA, Bhuiyan MS, Rahman MS, Faruquee MH (2007) Sociocultural aspects of arsenicosis in Bangladesh: community perspective. J Environ Sci Heal A 42(12):1945–1958

American Psychological Association (2010) Ethical principles of psychologists and code of conduct. Retrieved from https://www.apa.org/ethics/code/principles.pdf

Balali-Mood M, Naseri K, Tahergorabi Z, Khazdair MR, Sadeghi M (2021) Toxic mechanisms of five heavy metals: mercury, lead, chromium, cadmium, and arsenic. Front Pharmacol 12:643972. https://doi.org/10.3389/fphar.2021.643972

Brinkel J, Khan MH, Kraemer A (2009) A systematic review of arsenic exposure and its social and mental health effects with special reference to Bangladesh. Int J Environ Res Pub Health 6(5):1609–1619

Brown Johnson CG, Brodsky JL, Cataldo JK (2014) Lung cancer stigma, anxiety, depression, and quality of life. J Psychosoc Oncol 32(1):59–73

CGWB F (2018) Ground water quality in shallow aquifers in India. CGWB, Ministry of water resources RD and GR, Government of India

Chakraborti D, Singh SK, Rahman MM, Dutta RN, Mukherjee SC, Pati S, Kar PB (2018) Groundwater arsenic contamination in the Ganga River Basin: a future health danger. Int J Environ Res Pub Health 15(2):180. https://doi.org/10.3390/ijerph15020180

Chan M (2018) Ten years in public health 2007–2017: report by Dr. Margaret Chan Director-general World Health Organization. World Health Organization. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/255355/9789241512442-eng.pdf

Chen J, Chen S, Landry PF (2013) Migration environmental hazards and health outcomes in China. Soc Sci Med 80:85–95

Chowdhury MAI, Uddin MT, Ahmed MF, Ali MA, Rasul SMA, Hoque MA, Alam R, Sharmin R, Uddin SM, Islam MS (2006) Collapse of socio-economic base of Bangladesh by arsenic contamination in groundwater? Appl Sci 6:1275–1286

Chowdhury S, Krause-Pilatus A, Zimmermann KF (2016) Arsenic contamination of drinking water and mental health. DEF-Discussion papers on Development Policy (222)https://doi.org/10.2139/ssrn.2811583

Ernst J, Mehnert A, Dietz A, Hornemann B, Esser P (2017) Perceived stigmatization and its impact on quality of life-results from a large register-based study including breast, colon, prostate and lung cancer patients. BMC Cancer 17(1):1–8

Fujino Y, Guo X, Liu J, You L, Miyatake M, Yoshimura T (2004) Mental health burden amongst inhabitants of an arsenic-affected area in Inner Mongolia, China. Soc Sci Med 59(9):1969–1973. Japan Inner Mongolia arsenic pollution (JIAMP) Study Group

Fujisawa D, Hagiwara N (2015) Cancer stigma and its health consequences. Curr Breast Cancer Rep 7(3):143–150

Havenaar JM, Van den Brink W (1997) Psychological factors affecting health after toxicological disasters. Clin Psychol Rev 17(4):359–374

Horwitz BN, Reynolds CA, Charles ST (2015) Understanding associations among family support, friend support, and psychological distress. Pers Relat 22(1):79–91

Inauen J, Contzen N, Frick V, Kadel P, Keller J, Kollmann J, Mata J, van Valkengoed AM (2021) Environmental issues are health issues: making a case and setting an agenda for environmental health psychology. Eur Psychol 26(3):219–229

Jagdish S, Srivastava AK (1983) Mental health inventory. Varanasi, Manovaigyanik parikshan sansthan. Varanasi, India

Keya MK (2004) Mental health of arsenic victims in Bangladesh. S Afr Anthropol 4:215–223

Khan MMH, Aklimunnessa K, Kabir M, Mori M (2007) Determinants of drinking arsenic-contaminated tubewell water in Bangladesh. Health Policy Plann 22(5):335–343

Kumar A, Ali M, Kumar R, Kumar M, Sagar P, Pandey RK, Akhouri V, Kumar V, Anand G, Niraj PK, Rani R (2021) Arsenic exposure in Indo Gangetic plains of Bihar causing increased cancer risk. Sci Rep-UK 11(1):1–16

Kumar A, Rahman M, Ali M, Salaun P, Gourain A, Kumar S, Kumar R, Niraj PK, Kumar M, Kumar D, Bishwapriya A (2022) Assessment of disease burden in the arsenic exposed population of Chapar village of Samastipur district, Bihar, India, and related mitigation initiative. Environ Sci Pollut Res 29(18):27443–27459

Kumar SK, Bharti DA (2021a) Arsenic exposure: sources, Menace, and Risk Management. In: Chitra VS, Balamurali RS (eds) Rejuvenating environmental studies: a multidisciplinary approach. Upanayan Publications, New Delhi, pp 92–96

Kumar SK, Bharti DA (2021b) Depression, anxiety and stress among arsenic-induced cancer patients in Indo-Gangetic plains of Bihar: role of proactive coping. Int Q Commun Health Educ. https://doi.org/10.1177/0272684X211033460

Kumar A, Ghosh AK (2021) Assessment of arsenic contamination in groundwater and affected population of Bihar. In: Arsenic toxicity: challenges and solutions. Springer, Singapore, pp 165–191

Lalwani S, Dogra TD, Bhardwaj DN, Sharma RK, Murty OP, Vij A (2004) Study on arsenic level in ground water of Delhi using hydride generator accessory coupled with atomic absorption spectrophotometer. Indian J Clin Biochem 19(2):135–140

Laskar MS, Rahaman MM, Akhter A, Sayed MU, Khan MH, Ahmad SA, Harada N (2010) Quality of life of arsenicosis patients in an arsenic-affected rural area in Bangladesh. Arch Environ Occup Health 65(2):70–76

Lincoln KD, Chatters LM, Taylor RJ (2003) Psychological distress among black and white Americans: differential effects of social support, negative interaction and personal control. J Health Soc Behav 44(3):390–407

Madhav S, Ahamad A, Singh AK, Kushawaha J, Chauhan JS, Sharma S, Singh P (2020) Water pollutants: sources and impact on the environment and human health. In: Pooja D, Kumar

P, Singh P, Patil S (eds) Sensors in water pollutants monitoring: role of material. Singapore, Springer, pp 43–62
Major B, O'brien, L.T. (2005) The social psychology of stigma. Ann Rev Psychol 56(1):393–421
Majumdar KK, Mazumder DG (2012) Effect of drinking arsenic-contaminated water in children. Indian J Publ Health 56(3):223–226
Mazumder DNG, Haque R, Ghosh N, De BK, Santra A, Chakraborty D, Smith AH (1998) Arsenic levels in drinking water and the prevalence of skin lesions in West Bengal. India Int J Epidemiol 27(5):871–877
McCorkle R, Ercolano E, Lazenby M, Schulman-Green D, Schilling LS, Lorig K, Wagner EH (2011) Self-management: enabling and empowering patients living with cancer as a chronic illness. CA Cancer J Clin 61(1):50–62
Mishra DS (2009) Safe drinking water status in the state of Bihar, India: challenges ahead. In: 34th WEDC international conference, Addis Ababa, Ethiopia
Mishra S, Dwivedi S, Kumar A, Chauhan R, Awasthi S, Mattusch J, Tripathi RD (2016) Current status of ground water arsenic contamination in India and recent advancements in removal techniques from drinking water. Int J Plant Environ 2(1 and 2):01–15
Mukherjee A, Sarkar S, Chakraborty M, Duttagupta S, Bhattacharya A, Saha D, Bhattacharya P, Mitra A, Gupta S (2021) Occurrence, predictors and hazards of elevated groundwater arsenic across India through field observations and regional-scale AI-based modeling. Sci Total Environ 759:143511. https://doi.org/10.1016/j.scitotenv.2020.143511
Nasreen M (2003) Social impacts of arsenicosis. In: Ahmed MF (eds) Arsenic contamination: Bangladesh perspective. ITN-Bangladesh, Dhaka, pp 340–353
Peek MK, Cutchin MP, Freeman D, Stowe RP, Goodwin JS (2009) Environmental hazards and stress: evidence from the Texas City stress and health study. J Epidemiol Commun Health 63(10):792–798
Phelan SM, Griffin JM, Jackson GL, Zafar SY, Hellerstedt W, Stahre M, Nelson D, Zullig LL, Burgess DJ, Van Ryn M (2013) Stigma, perceived blame, self-blame, and depressive symptoms in men with colorectal cancer. Psychol Oncol 22(1):65–73
Rahman MM, Chowdhury UK, Mukherjee SC, Mondal BK, Paul K, Lodh D, Biswas BK, Chanda CR, Basu GK, Saha KC, Roy S (2001) Chronic arsenic toxicity in Bangladesh and West Bengal, India—a review and commentary. J Toxicol Clin Toxicol 39(7):683–700
Rahman MA, Rahman A, Khan MZK, Renzaho AM (2018) Human health risks and socio-economic perspectives of arsenic exposure in Bangladesh: a scoping review. Ecotoxicol Environ Saf 150:335–343
Sarker PC, Mohiuddin M (2002) Arsenic poisoning and its impact on the socio economic and cultural life of the people of Bangladesh. S Asian Anthropol 2(2):97–102
Sen D, Biswas PS (2012) Arsenicosis: is it a protective or predisposing factor for mental illness? Iran J Psychiatry 7(4):180–183
Shaji E, Santosh M, Sarath KV, Prakash P, Deepchand V, Divya BV (2021) Arsenic contamination of groundwater: a global synopsis with focus on the Indian Peninsula. Geosci Front 12(3):101079. https://doi.org/10.1016/j.gsf.2020.08.015
Singer M (2020) Ecosyndemics: global warming and the coming plagues of the twenty-first century. In: Herring DA, Swedlund AC (eds) Plagues and epidemics: infected spaces past and present. Routledge, pp 21–37
Singh SK (2015) Groundwater arsenic contamination in the Middle-Gangetic Plain, Bihar (India): the danger arrived. Int J Environ Sci 4(2):70–76
Singh SK, Taylor RW (2019) Assessing the role of risk perception in ensuring sustainable arsenic mitigation. Groundwater Sustain Dev 9:100241. https://doi.org/10.1016/j.gsd.2019.100241
Singh SK, Vedwan N (2015) Mapping composite vulnerability to groundwater arsenic contamination: an analytical framework and a case study in India. Nat Hazard 75(2):1883–1908
Singh RL, Singh PK (2017) Global environmental problems. In: Singh RL (ed) Principles and applications of environmental biotechnology for a sustainable future. Springer, Singapore, pp 13–41

Steinmaus C, Ferreccio C, Acevedo J, Yuan Y, Liaw J, Durán V, Cuevas S, García J, Meza R, Valdés R, Valdés G (2014) Increased lung and bladder cancer incidence in adults after in utero and early life arsenic exposure. Cancer Epidemiol Biomark Prev 23(8):1529–1538

Syed EH, Poudel KC, Sakisaka K, Yasuoka J, Ahsan H, Jimba M (2012) Quality of life and mental health status of arsenic-affected patients in a Bangladeshi population. J Health Popul Nutr 30(3):262–269

Thakur BK, Gupta V (2019) Valuing health damages due to groundwater arsenic contamination in Bihar, India. Econ Hum Biol 35:123–132

Times of India (2021) Retrieved from https://www.google.com/amp/s/amp.theguardian.com/global-development/2021/jun/24/water-of-death-how-arsenic-is-poisoning-rural-communities-in-india

Tsutsumi A, Izutsu T, Islam MA, Amed JU, Nakahara S, Takagi F, Wakai S (2004) Depressive status of leprosy patients in Bangladesh: association with self perception of stigma. Leprosy Rev 75(1):57–66

UNICEF (1998) Plan of action to combat situation arising out of arsenic contamination in drinking water: plan to assist government of West Bengal report. United Nations Children's Fund, New York

Vail B, Morgan MC, Dyer J, Christmas A, Cohen SR, Joshi M, Gore A, Mahapatra T, Walker DM (2018) Logistical, cultural, and structural barriers to immediate neonatal care and neonatal resuscitation in Bihar, India. BMC Pregnancy Childb 18(1):1–10

WHO (2011) Guidelines for drinking-water quality. WHO Chronicle 38(4):104–108

WHOQOL Group (1998) Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med 28(3):551–558

Yıldız K, Koç Z (2021) Stigmatization, discrimination and illness perception among oncology patients: a cross-sectional and correlational study. Eur J Oncol Nurs 54:102000. https://doi.org/10.1016/j.ejon.2021.102000

# Chapter 6
# Health Effects of Long Term Exposure to Arsenic—A Pathological and Genotoxic Approach


**P. Vijaya and Anjali Singh Gill**

**Abstract** Pollution is increasing day by day in the environment due to variations in natural and anthropogenic activities that contaminates and infects all terrestrial as well as aquatic ecosystems with metals, non-metals, organic and inorganic compounds. Metals are dispended everywhere in the soils and waters of the earth's floor and exert damaging effects on life in the environment and even on human fitness. Arsenic is ubiquitous and its toxic effects in humans were focused mainly on somatic cells. Chronic arsenic exposure to inorganic arsenic can result skin cancer and also affect lungs, bladder, and liver. Several chemical forms of arsenic exhibits with different toxicity; thus, inorganic forms of this metalloid (arsenite and arsenate) are more toxic. Humans can be come in contact with arsenic via many sources like intake of air, food and water. Arsenic enhanced the peroxidation of lipids and decreased the concentrations of most of the antioxidant molecules (SOD, CAT, and GST). The reactive oxygen species (ROS) are accountable for the major cellular harm, peroxidation of lipids and loss of membrane bound enzymes. The arsenic compounds restrain DNA restore and stimulate chromosomal alterations, micronuclei formation and reduce mitotic index.

**Keywords** Arsenic (As) · Oxidative stress · Antioxidants · Chromosomal aberrations (CA) · Mitotic index (MI) · Micronuclei (MN)

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## 6.1 Introduction

Arsenic is a ubiquitous, global toxic metal that infects the food chain and enters in to the body via various routes and causes damage to many organs as it gets accumulated in them and finally may result in different types of cancers (Gabel 2000). It is mostly used as one of the ingredients in the production of insecticides, pesticides, paints and other products. Frank Capra' film on arsenic as well as old lace is highly acclaimed novel in which arsenic was depicted as a murder weapon. There are two types of arsenic i.e. inorganic and organic existing in trivalent and pentavalent state. Trivalent arsenic is more toxic than pentavalent state. Many international locations over the world are confronted with the aid of groundwater arsenic infection (Sarkar et al. 2008). The aquatic environment of Asian countries such as Bangladesh, India, China and Nepal has the maximum drastic prevalence of arsenic in groundwater (Shaji et al. 2021).

The mechanism of arsenic toxicity is the induction of sturdy oxidative pressure with manufacturing of unfastened radicals in cells (Flora et al. 2007). The elevation in the formation of reactive oxygen species (ROS) plays a crucial part in arsenic toxicity. The populations which are chronically exposed to arsenic generate significant oxidative stress that induce DNA damage (Basu et al. 2005) along with peroxidation and decrease glutathione level. The ROS production has been connected with converting the signaling pathways within the cells and management of transcription elements (Tapio and Grosche 2006). According to the recent study the chronic exposure of arsenic in low levels to humans induces oxidative DNA damage in polymorphonuclear cells of peripheral blood which in turn enhances and accelerates apoptosis of these cells (Pei et al. 2013).

The biotransformation of inorganic arsenic produces intermediate and final metabolites that are highly toxic and reactive compared to original ingested inorganic arsenic (iAs) (Vahter and Concha 2001). Arsenic upsets the natural oxidants and decreases equillibria with the aid of diverse mechanisms which might be involved in redox processes with endogenous oxidants and cellular antioxidant systems.

Arsenic enters the human frame via numerous routes like ingestion, inhalation or skin absorption. From the different forms of arsenic i.e. inorganic and organic forms, the inorganic shape is commonly located in the environment i.e. arsenate and arsenite. The pentavalent arsenate is commonly present on the upper surface of water and the trivalent arsenite is found in the deep water or ground water and by different human activities, this metal enters into the human life and also in environment. 95% of absorption takes place in gastrointestinal tract after the ingestion of arsenic. After that large amount of absorption occurs in liver, lungs, nephrons and integument (Hunter et al. 1942). About 90–95% of arsenic is positioned in the erythrocytes, wherein it binds to the globin gets transported to the opposite parts of body and almost 70% of arsenic is excreted out through urine after the methylation process.

Arsenic alters the various enzymatic reactions and influences almost all organs of the frame inflicting diabetes, skin diseases, neurotoxicity, hepatotoxicity, cytotoxicity and genotoxicity along with spleen and cardiovascular system. Thus, the oxidative

stress induced by arsenic affects the cellular enzymatic, respiratory and mitotic equipment and inhibit the DNA repair mechanism (Henkler et al. 2010). The opposite in all likelihood mechanism of arsenic toxicity entails DNA damage, sister chromatid change (SCE), gene amplification, aneuploidy, modification of expressions of genes and cellular proliferation. Arsenic is widely known effective clastogen, co-mutagen and co-carcinogen (Tchounwou et al. 2003).

As arsenic is one of the most excessive rating environmental pollutant and is ubiquitous in nature. The present work was designed to explore the long term effects of arsenic triggered cytotoxicity and genotoxicity in Swiss albino mice along with pathological approach.

## 6.2 Materials and Methodology

### *6.2.1 Subjects*

**Animals** (Swiss albino mice) having weight 20–25 g were taken and maintained in in hygiene and translucent cages. They were randomized into different groups. All the animals were kept under 12/12 h natural cycle with controlled heat and humidity. Mice were given standard mice feed in the form of pellets along with free access to R.O. water. The overall research procedure was revised and conducted by following the guidelines of Institutional Animal Ethical Committee (Reg No. 107/99/CPCSEA/2013-03).

### *6.2.2 Procurement of the Chemical*

Arsenic was obtained from Qualikems fine Chemical Pvt. Ltd., New Delhi. Arsenic trioxide ($As_2O_3$) is an inorganic compound and white colored powder having an atomic number 33 and its atomic weight is 75. The solution of toxic metal was obtained by mixing 1.32 g of $As_2O_3$ in distilled water and was given orally to mice.

### *6.2.3 Design of the Study*

Animals were categorized into 3 major sets of 6 animals each, for the conduct of the experiment (Fig. 6.1).

**Group I**—Control animals, **Group II**—Mice were administered arsenic (As), orally at an acute dose of 5 mg/kg bw for 15 days. **Group III**—Mice were administered an acute dose of 5 mg/kg bw of arsenic (As) orally for 45 days.

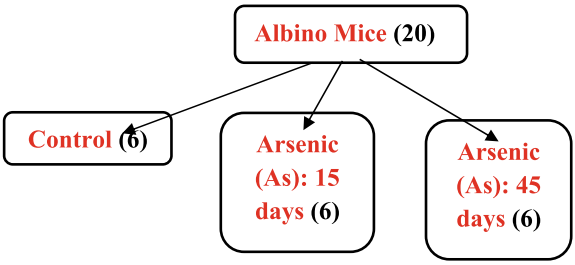


**Fig. 6.1** Grouping of animals between different categories for the study

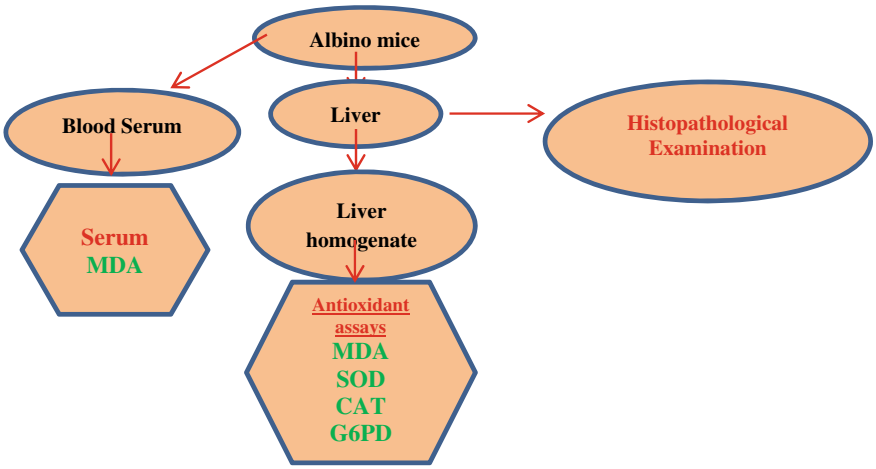


**Fig. 6.2** Graphical representation of biochemical methodology

### *6.2.4 Tissue Collection*

Autopsies were done after the completion of the experiment. Both the control and treated animals were weighted. Liver and bone marrow were extracted. Further, the liver was cleaned and washed with saline water and dried properly. It was further used for various biochemical, antioxidant and histological examination (Fig. 6.2). Bone marrow was used for the cytological studies.

### *6.2.5 Blood Sample Collection*

Approximately, 1 ml of blood was collected from each mouse on the day of autopsy. It was kept in separate eppendorf tubes followed by centrifugation to drain out serum in clean tubes which was then utilized for estimation of lipid peroxidation.

## 6.3 Biochemical Estimations

### *6.3.1 Preparation of Tissue Homogenates*

Liver was separated from all the groups, weighted and homogenized in a tissue homogenizer in 3 ml of phosphate buffer. The tissue homogenate was centrifuged at 12,000 rpm for 20 min in cold centrifuge, and the supernatant was collected for estimation of lipid peroxidation (MDA conc.), superoxide dismutase (SOD), catalase (CAT) and Glucose-6 phosphate dehydrogenase (G6PD) as shown in Fig. 6.2.

### *6.3.2 Measurement of Malondialdehyde (MDA)*

The thiobarbituric acid assay (TBARS) check was employed to evaluate the extent of lipid peroxidation (LPO) using malondialdehyde, a byproduct of LPO and is generated because of the breakdown of polyunsaturated fatty acids, which is taken as an index of oxidative pressure. It isn't viable to measure the real attention of the loose radicals within the blood/tissue homogenates because they remain there for most effective fraction of seconds. For that reason, the byproducts fashioned due to the production of loose radicals was measured to get a relative idea of the awareness of free radicals produced according to Wilbur et al. (1949). TBARS test is the maximum commonplace and clean approach to monitor lipid peroxidation in an individual.

The homogenized liver fractions had been treated with 1.15% KCl at 4 °C. The supernatant was aliquoted and used for the assay of lipid peroxidation. 2.5 ml of HCl containing TCA (12.5%) was introduced to the homogenate aggregate after which it was incubated at 90 °C accompanied by way of centrifugation. To the supernatant amassed, 1 ml of TBA (1.23%) was added and this was further incubated for 15 min at 90 °C. On Cooling, a red color was evolved within the solution. The optical density of the solution was determined at 530 nm against a blank. The molar extinction coefficient ($1.56 \times 105$ $cm^{-2}$ $mol^{-1}$) was used to calculate the amount of MDA which was changed and was expressed via millimoles of MDA in line with gram moist tissue.

### *6.3.3 Measurement of Superoxide Dismutase (SOD)*

It was measured by the most sensitive method of Das et al. (2000) which involves the generation of superoxide radical by photoreduction of riboflavin.

Liver tissue extract was homogenized in 10 ml of 0.25 M sucrose solution and centrifuged at 2500 rpm for 10 min at 4–20 °C. The supernatant become accumulated and SOD reagent (1.40 ml) was added accompanied by riboflavin solution. Then the

samples were incubated in inside the SOD box for 10 min. The tubes had been cooled after which 1 ml of Greiss reagent was added. The absorbance of the samples was examined at 543 nm against the blank using spectrophotometric technique.

### 6.3.4 Measurement of Catalase (CAT)

Catalase is an enzyme that catalyzes the breakdown of hydrogen peroxide to $H_2O$ and $O_2$. The quantity of catalase inside the tissue extracts become envisioned by way of the technique of Aebi (1983).

Liver tissue extract was homogenized in 0.1 M phosphate buffer (pH 7.0) and centrifuged at 1500 rpm for 10 min. The supernatant turned was used for the assay by the addition of hydrogen peroxide. Then the absorbance was studied at 240 nm in opposition to the clean tube having same aggregate besides the tissue homogenate. The quantity of catalase was calculated with the aid of molar extinction coefficient (71 $M^{-1}$ $cm^{-1}$) and was finally expressed in mmoles/g wet tissue.

### 6.3.5 Measurement of Glucose-6 Phosphate Dehydrogenase (G6PD)

The enzyme Glucose-6-Phosphate Dehydrogenase present in tissue extract was extracted by lysing the extract. The extracted enzyme oxidizes Glucose-6-Phosphate to 6-Phosphogluconate and simultaneously reduces co-enzyme NADP to NADPH giving growth in its absorbance at 340 nm.

### 6.3.6 Estimation of Lipid Peroxidation from Blood Serum (sMDA)

This was estimated using the method of Satoh (1978). Lipid peroxidation was performed on the blood samples to assess the total levels of lipid peroxidation in the blood. The thiobarbituric acid assay (TBARS) test was employed to assess the level of lipid peroxidation using malondialdehyde, by product of lipid peroxidation formed by the breakdown of polyunsaturated fatty acids (PUFAs) and taken as index of lipid peroxidation. TBARS test is most simple and easy method so, it is commonly and widely used test to assess the damage done by free radicals. The running precept at the back of this test was that malondialdehyde reacts with thiobarbituric acid to present a pink colour complex that was read at 535 nm.

In this method trichloroacetic acid and thiobarbituric acid are added to serum and the mixture was heated in boiling water bath. The ensuing chromogen if extracted

with n-butyl alcohol and the absorbance of the organic phase was decided at the wavelength of 530 nm. The molar extinction coefficient of free MDA has been given by Sinnhuber and Yu (1958) as $1.56 \times 10^5$ at 532 nm. The determined values are expressed as nmol/ml.

## 6.4 Cytogenetic Analysis

See Fig. 6.3.

### *6.4.1 Chromosomal Preparations*

The procedure was performed on bone-marrow cells according to the recommendations of Preston et al. (1987) (Fig. 6.3). Mice (control and treated) were given an intraperitoneal injection of colchicine at the rate of 1 mg/kg body weight, 2 h before autopsy. Bone-marrow was extracted from both femora by flushing with KCl. The collected cells underwent centrifuged at 2000 × g for 10 min, and were fixed in aceto-methanol solution. Centrifugation and fixation has been repeated five times with a time gap of 20 min. They were again resuspended in a small extent of fixative. The material was smeared on cool slides, were flame-dried followed by staining with freshly prepared Giemsa stain for 3–5 min. Finally the slides were cleared in distilled water to put off excess stain.

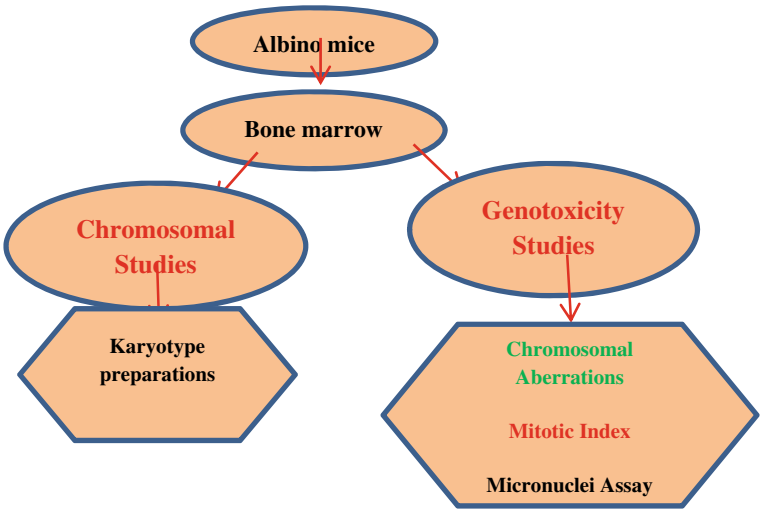


**Fig. 6.3** Graphical representation of cytological methodology

### 6.4.2 Mitotic Index (MI)

**It** was also determined from slides made for analysis of chromosomal aberration by the following method. Mitotic indices were obtained by counting the number of mitotic cells in 1000 cells/animal to a total of 5000 cells/treatment and control. The index was calculated by using the formula:

$$\textbf{Mitotic index (MI)} = \frac{\textbf{Number of dividing cells}}{\textbf{Total number of cells}} \times \textbf{100}$$

### 6.4.3 Micronuclei Assay

At the end of the trial, the animals from all the groups were taken and scoring of micronuclei from the bone marrow cells of mice was achieved by the approach of Agarwal and Chauhan (1993). Bone marrow cells have been flushed from both the femurs. Then the material was centrifuged at 1000 rpm for 10 min and washed in PBS twice and once again centrifuged at 1000 rpm for 10 min. After that the cells were fixed in methanol: acetic acid (3:1) in cold fixative. Slides were organised via dropping the proportions of pellets on the slides and they were dried at room temperature after which stained with Giemsa stain. The micronuclei cells were calculated by using the formula:

$$\textbf{MN}\ (\%) = \frac{\textbf{Number of observed cells with micronucleus}}{\textbf{Total number of observed cells}} \times \textbf{100}$$

### 6.4.4 Karyotype Preparations

Karyotype was prepared from well spread metaphase plate of the control mice. Individual chromosomes had been cut from metaphase plate and homologous chromosomes were paired on the idea of their length, arm ratio, morphology and then they were organised in descending order consistent with their sizes. The morphological classification of chromosomes proposed via Todehdehghan et al. (2011) has been accompanied to differentiate metacentric, submetacentric, subtelocentric and telocentric chromosomes.

### 6.4.5 *Genotoxicity Analysis*

Data of Chromosomal aberration test, micronucleus test and mitotic index was expressed as Mean ± S.E by applying two manner Anova test. Statistical analysis was performed by using software program called graph pad prism. $p < 0.01$ was considered to be the level of significance. Statistical importance in the frequencies of chromosomal aberrations, micronucleus check and mitotic index in-between the treated and control groups were evaluated.

## 6.5 Histopathological Study

Liver tissue of toxic and control mice were cleaned, washed and reduced into pieces and had been fixed with Bouin's fixative for 24 h. Then the tissues have been washed in 70% alcohol followed by dehydration in ascending grades of ethanol, wiped in xylene and embedded in paraffin wax (60 °C melting point) then sectioned at 5–6 μm. These sectioned were stretched on slides and were stained with hematoxylin and eosin staining technique (Drury and Wallington 1980) for histopathological research. These slides were discovered and scanned beneath microscope.

## 6.6 Statistical Analysis

The results were expressed as mean ± preferred error (SEM) from all the experiments accomplished using a standard number of animals ($n = 5$). Statistical significance was assessed via Scholar's t-test on GraphPad Prism software program. Intergroup comparisons were made through by the usage of Two-way analysis of variance (ANOVA). The significance level was localized as $p \leq 0.01$ and non-considerable levels were set as $p \geq 0.05$.

## 6.7 Results and Discussion

Swiss albino mice showed no mortality during acclimatization period. Body weights of all the mice were recorded during the acclimatization and experimental period. Mice of control group showed a gradual increase in body weight from 0 day to the end of experiment. Arsenic trioxide treated mice (group II and III) confirmed a significant decline in body weight (Figs. 6.4 and 6.5) at 15 and 45 days post treatment. Kaltreider et al. (2001) proposed that arsenic inhibited the capacity of glucocorticoid and its receptors to turn on the genes that are linked to weight loss. This decrease was in support to the study of Demerdash et al. (2009) who has worked on the sodium

arsenite and found similar trend of weight loss in rats. Nareda and Kumar (2021) also agreed with finding of our study and confirmed the reduction of body weight in arsenic treated animals. Arsenic is fantastically poisonous as well as corrosive to gastrointestinal tract resulting into partial anorexia and gastro-intestinal disturbances accompanied by lack of body weight in arsenic animals (Dwivedi et al. 2011).

A significant ($p < 0.01$) increase in the liver weight of arsenic treated mice (group II and III) was observed in comparison to control group at 15 and 45 days post treatment (Fig. 6.6). This remark is in confirmation with the study of Shiguang and Beynen (2000) who pronounced that liver weight extensively increased in male rats fed with 100 mg/kg arsenic diet for 2 weeks. Comparable consequences had been additionally reported by Jalaludeen et al. (2016) and Pineda et al. (2013). Demerdash et al. (2009) reported that accumulation of arsenic in the liver led to degeneration of hepatocytes that resulted in chronic inflammation leading to hepatomegaly. Further, Dwivedi and Gupta (2020) observed an increase in body and organ weight in rats intoxicated with the sodium arsenite and cadmium chloride for 30 and 60 days. Arsenic (at high doses) causes acute hepatic injury and hepatocellular necrosis that results in the leakage of hepatocellular enzymes into blood (Gora et al. 2014). They

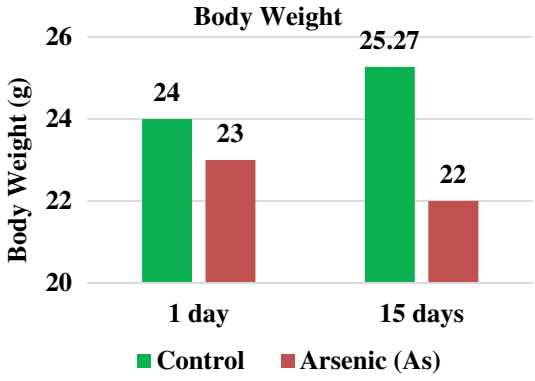


**Fig. 6.4** Weight of mice in both groups at 15 days

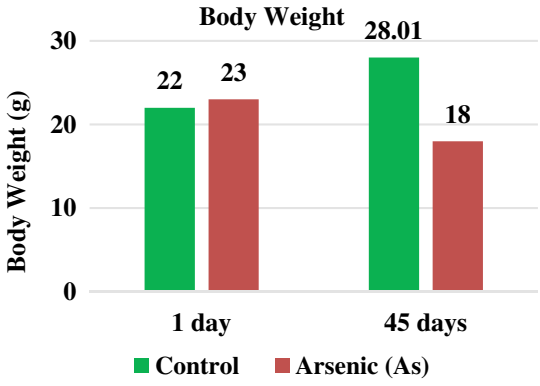


**Fig. 6.5** Weight of mice in both groups at 45 days

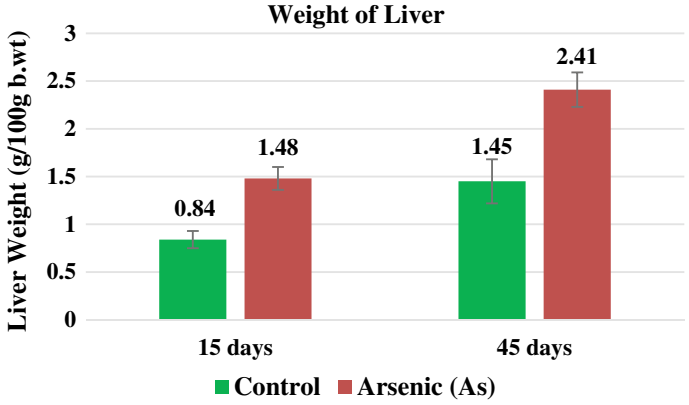


**Fig. 6.6** Weight of liver tissue in both groups

further, confirmed that this extent of damage to the hepatocytes has been commonly detected by the activity of antioxidant enzymes.

The MDA content in serum (Fig. 6.7) and liver tissue (Fig. 6.8) of arsenic treated mice (group II and III) showed extremely statistically significant ($p < 0.01$) elevation as compared to control value at both 15 and 45 days post-treatment. But there was a large ($p < 0.01$) decrease in SOD, CAT and G6PDH level (Figs. 6.9 and 6.10) of toxic group (group II and III) in comparison to control group. This can be because of the accumulation of arsenic in the liver tissue. These outcomes are in agreement with the findings of Nandi et al. (2008) and Suanarunsawat et al. (2011) who also reported comparable results within liver and heart of rats. The effects replicate that the administration of arsenic trioxide prompted oxidative strain in liver of mice. The lipid peroxidation which is a biomarker of oxidative stress was produced by the free radicals which participate in the pathogenesis of several diseases (Jariyawat et al. 2009; Suanarunsawat et al. 2010). Arsenic generates oxidative stress by initiating the manufacturing of free radicals and elevating the peroxidation of lipid membrane. The lipid peroxidation is a chain process involving initiation, propagation and termination reaction (Halliwell and Gutteridge 1999). The lipid peroxides are degraded into various products like alkanals, hydroxyl alkanals and ketone alkenes (Chen et al. 1998). In vitro studies, $NaAsO_2$ and $As_2O_3$ both affect the cell viability, genotoxicity, cytotoxicity, cell arrest apoptosis and caused oxidative injury in lungs of people (Jiang et al. 2013).

The cellular damage was the main mechanism of arsenic toxicity and was assessed by enhanced concentration of TBARS in experimental animals and humans exposed to arsenic (Das et al. 2010). The administration of sodium arsenite during lactation and gestation period increased the TBARS level in kidney and liver and decreased the level of antioxidant enzymes. The generation of ROS due to arsenic toxicity reduces natural antioxidants and mainly damage lipids which repair the cellular structure and function (Kitchin and Conolly 2010). Reddy et al. (2012) founded an increased TBARS level in hepatic tissue after arsenic administration because

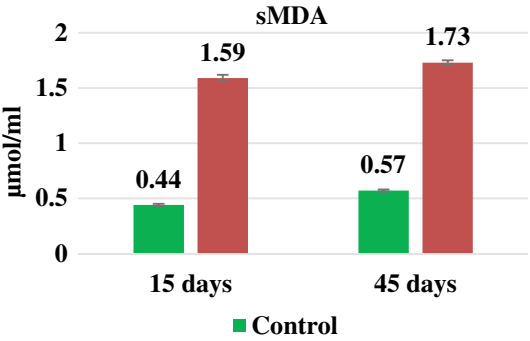


**Fig. 6.7** Concentration of sMDA in both groups

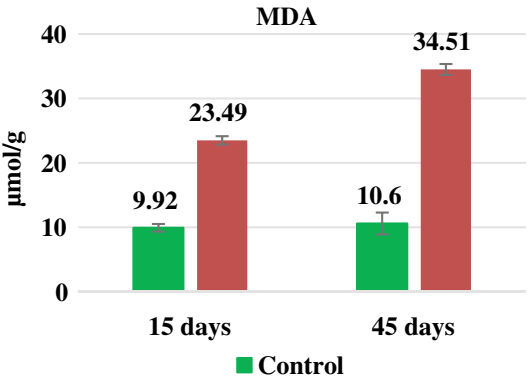


**Fig. 6.8** Concentration of tissue MDA in both groups

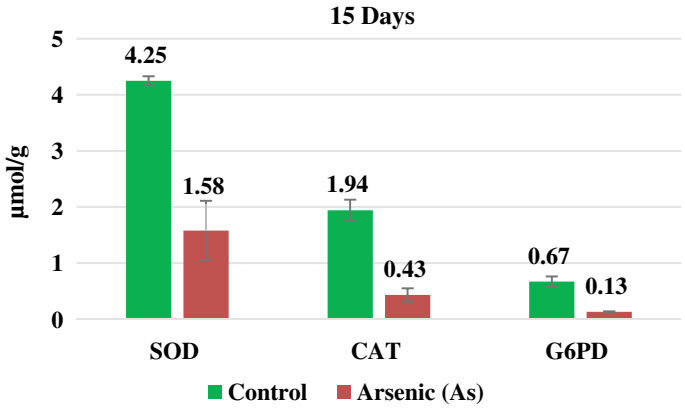


**Fig. 6.9** Concentration of tissue antioxidant enzymes in all groups at 15 days

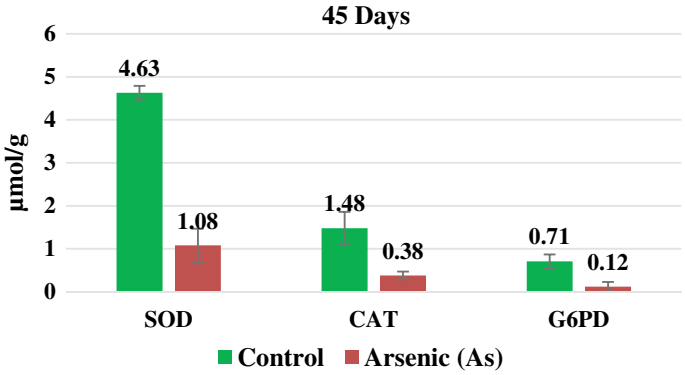


**Fig. 6.10** Concentration of tissue antioxidant enzymes in all groups at 45 days

of reduced degree of SH-groups and antioxidant enzymes. The production of huge number of ROS species as a result to arsenic toxicity weigh down the antioxidant protection mechanism and harm cellular elements which include lipids, proteins and DNA; which impair the cellular systems.

According to Prabhu and Sumedha (2014), arsenic-treated rats had higher levels of lipid oxidation, fatty acid hydroperoxides, protein carbonyl content and covalently linked dienes than control rats. Devi et al. (2000) also emphasized that arsenic, present in the biological system acts as a pro-oxidant that leads to oxidative stress which further causes lipid peroxidation and deterioration of liver cells. Abundance of ROS, causes cell death via apoptosis or necrosis, which is defined by degenerative changes and chromosome segregation (Conde de la Rosa et al. 2006).

Antioxidants protect the body from oxidative stress. In general, antioxidants excavate and inhibit the creation of ROS and lipid peroxidation (Ben Abdallah et al. 2009). Several enzymatic antioxidants, including SOD, CAT, GPx, GST, GR, and G6PDH, are the initial line of defence against arsenic-induced oxidative stress. SOD and CAT form the backbone of antioxidant system and immediately act against the free radicals produced during heavy metal exposure. The reduced activities of antioxidants due to the enhancement of arsenic toxicity and production of free radicals in the liver also tend to disturb antioxidant defense system and alter the structural stability of cell membrane and thus further affect the membrane-enclosed enzymes (Muthumani 2013). In addition, decreased SOD and CAT activity in arsenic-exposed rats raises the level of superoxide radical anions and lowers the level of NADPH required for CAT activation from its inactivated state (Yamanaka et al. 1991). Nandi et al. (2006) further observed sequential changes in lipid peroxides, SOD and CAT in erythrocytes, liver and renal tissue of arsenic treated rats.

The arsenic binds to sulfhydral groups of proteins along with various enzymes and intereferes with consumption of GSH that act as an important antioxidant molecule responsible for removing xenobiotics (Hultberg et al. 2001). Lee and Ho (1995) reported that SOD and CAT level were decreased in fibroblast cells of humans after treatment with sodium arsenite.

G6PD is an important antioxidant enzyme and helps RBC's to function in a proper manner. The decrease in the activity of G6PD in metal administered rats showed less production of NADPH which is needed for the generation of GSH from GSSH (Shila et al. 2005). Tang et al. (2015) observed that the normal RBCs and G6PD deficient RBCs differ in their response to oxidants because glutathione deficient cells are unable to produce required quantity of GSH pool as found in normal cells. Thus, ROS production was maximum in G6PD deficient group in comparison to normal group. The excessive ROS production induces tissue stress that increases DNA variations resulting in carcinogenesis (Lee and Yu 2016). The enhanced rate of apoptosis and arrested G2 cycle in G6PD deficient cells enhance the oxidative stress in K562 cell lines. Arsenic treated groups also showed hematopoietic toxicity and oxidative damage in G6PD deficient cells (Zhang et al. 2016).

Thus, genotoxicity studies have become very important and number of techniques are used to test alterations in DNA in the form of chromosomal aberrations, sister chromatid exchange, comet assay, mitotic index and micronucleus (Sanchez-Alarcon et al. 2021). The genotoxicants form strong covalent bonds with DNA that lead to the emergence of DNA adducts that results in mutations and prevents DNA replication (Yun et al. 2020). Genotoxicity bio monitoring is important in organisms due to various reasons. Firstly, it's an early detection and monitoring of the pollution in the environment and secondly, it can also help in preserving the ecological diversity in environment and prevent the pollution induced mutations. Further, it can help in assessing the health status of creatures. The DNA damage originally starts at the cellular level and finally manifests into various diseases.

The micronucleated cells in arsenic treated mice (group II and III) showed a statistically significant ($p < 0.01$) elevation in comparison to control group (Fig. 6.11). Arsenic trioxide was found to possess the genotoxic potential as revealed by significant ($p < 0.01$) increase in chromosomal aberrations at 15 and 45 days post-treatment in comparison to control mice (Figs. 6.13 and 6.14). Das et al. (2016) observed that the sodium arsenite, after long term exposure caused genotoxicity in the cells of mice along with increased oxidative stress in hepatic tissue, kidney and intestine of mice. It was supported by Picker and Fox (1996) who reflected that arsenic causes genotoxicity and other health effects. They further, detected that the chromosome abnormalities, nuclear aberrations and micronuclei were in the interphase stage of populations who were prone to arsenic (Fig. 6.12).

Chromosome aberrations are macro damage of the chromosomes and includes various types of structural and numerical alterations in chromosomes such as Aneuploidy, Polyploidy, Chromatid elongation, Centrometic fusion, Centromeric gap, Condensed chromosome, End to end joining, Fragmentation, Loss of definite walls, Pulverization, Ring formation, Stretching, Stickiness, Wooly appearance etc. that results due to the inhibition of DNA synthesis and DNA breakage (Grade et al. 2015). Au et al. (1991) found that the incidence of the chromosomal alterations was an important parameter to govern the correlation between the aberrations and occurrence of the various malignancies.

The proliferation status of the cells i.e. mitotic index was also calculated that showed a significant reduction in the proportion of the cells undergoing mitosis to

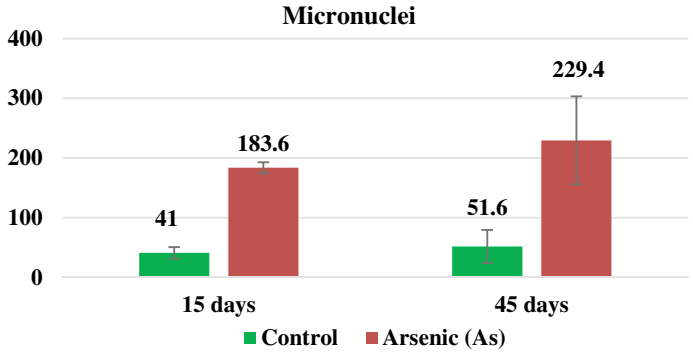


**Fig. 6.11** Micronucleated cells in both groups at 15 and 45 days

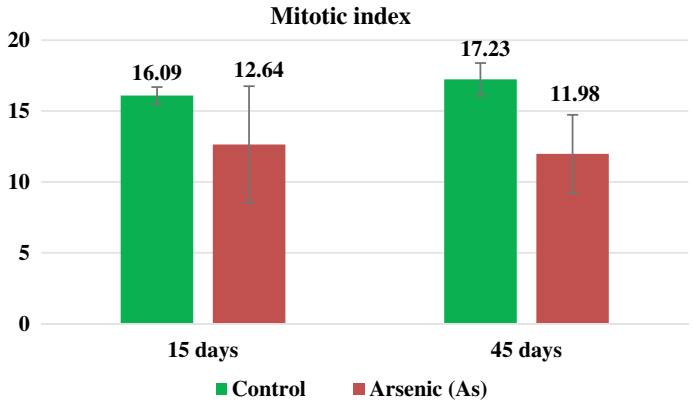


**Fig. 6.12** Mitotic index in both groups at 15 and 45 days

the number of cells not undergoing mitosis in the toxic group (group II and III) in accordance to control values (Fig. 6.12). Large number of in vitro and in vivo studies also supported our work and showed adverse genotoxic effects of inorganic arsenicals (Cohen et al. 2006). Rahman et al. (2008) reported an increase in pulverized chromosomes in those who were exposed to high level of arsenic in drinking water. Ochi et al. (2008) proposed that pulverized chromosome formation occurs due to cell blending, collapsing of cytokinesis followed by usual nuclear division. In present study, arsenic intoxicated mice showed centromeric attenuation and spindle fibre disruption that may cause centromeric destruction leading to chromatid depreciation. Similarly, the degeneration in centromere and serrated arms of chromosome were also observed by Kumar et al. (2016). Serration of the chromosomal structures show excessive heterochromatization which leads to the non-functioning of the active sites of chromosomes by highly effecting the gene regulation in mice.

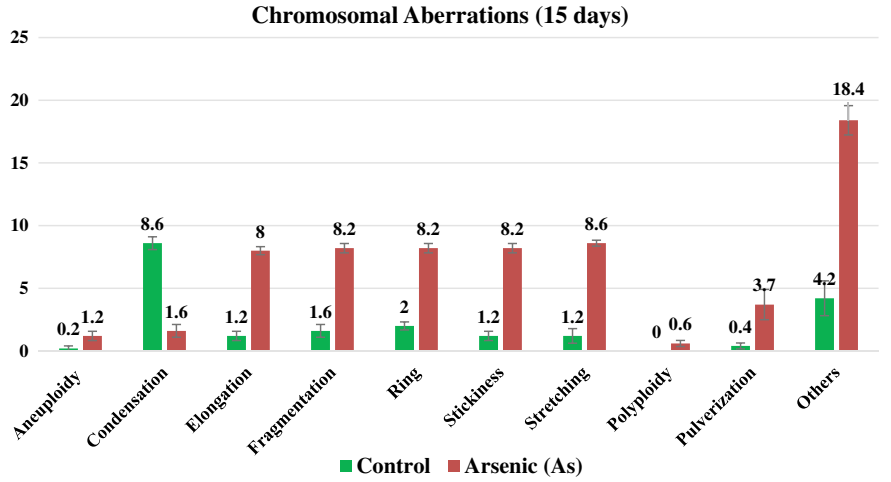


**Fig. 6.13** Chromosomal aberrations in both groups at 15 days

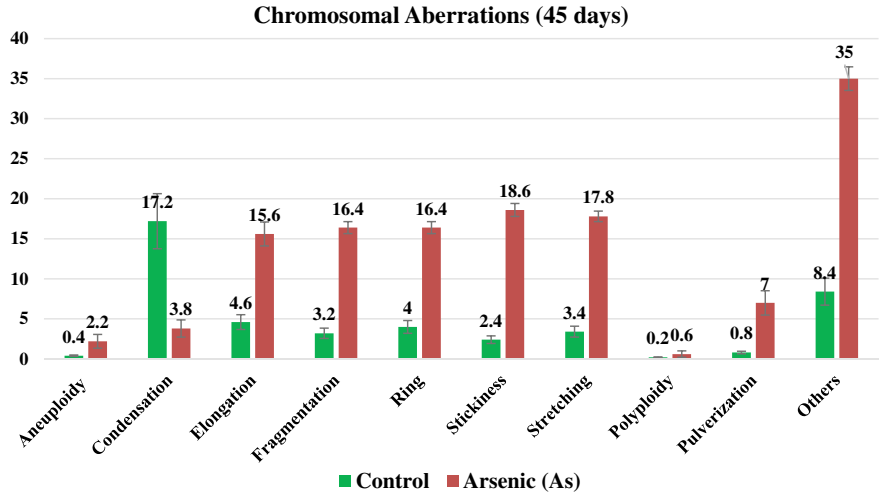


**Fig. 6.14** Chromosomal aberrations in both groups at 45 days

Saha et al. (2010) suggested that the chromosomal aberrations as well as the genotoxic effects enhances with increase in prolongation of exposure to arsenic and this was correlated with in our present study. The micronucleus (MN) assay is a valuable and sensitive process to elucidate the chromosomal mutations and their loss, which forms the basis for the development and up regulation of cancer (Sommer et al. 2020). There was a positive correlation between the lipid peroxidation and MN frequency as the free radicals generate oxidative stress which breakdown the antioxidant defenses, a positive factor to induce chromosomal breakage along with

MN formation (Mayer et al. 2000). It was also documented that females have a large number of MN frequency in comparison to male due to preferential loss of inactive X-chromosome (Nicoli et al. 2022). However, the life styles and dietetic habits were also important factors that influence the MN formation.

Micronuclei are the cytoplasmic chromatin containing bodies formed in bone marrow erythroblasts that further develops into a polychromatic erythrocyte, the nucleus undergoes extrusion resulting in micronuclei formation in enucleated cytoplasm that can be detected using specific staining processes (Luzhna et al. 2013). They further assessed chromosomal damage as well as damage to the mitotic spindle apparatus in polychromatic erythrocytes in bone marrow. The presence of MN indicate genetic damage as CA and MN are considered to be genotoxicity markers (Miller et al. 2002; Bonassi et al. 2000; Martinez et al. 2005; Salazar et al. 2009).

Chakraborthy and Madhusnata (2013) observed statistically significant elevation in the MN formation in tea drinkers and also in arsenic manifested people. Wu et al. (2001) reported that the genetic instability and cytogenetic alterations were associated with generation of ROS and decreased antioxidants by arsenic.

Arsenic is an environmental pollutant and humans are mostly exposed to metalloid through drinking water contaminated with industrial emissions. It gets absorbed into the gastrointestinal tract, lungs and blood stream when ingested in the body. Reactive nitrogen species (RNS) indirectly linked with ROS in causing oxidative injury in lipids, proteins along with DNA in cells exposed to arsenic. Further, Arsenic exposure caused various diseases and disrupts the functions of several important organs like liver, kidney and lung (Chowdhury et al. 2016) which was also proved by histological studies. Previously as well as recently scientists believe that oxidative injury and ROS generation are the considerable cause of heavy metal toxicity (Aflanie et al. 2015).

Liver has been the target organ for arsenic induced damage. Histological studies of liver tissue of control group (Fig. 6.15a) showed lobular organization, the lobules being incompletely separated from each other by connective tissue septa. Each lobule is made up of large number of polyhedral cells with prominent nucleus having one or more nucleoli. The cells in lobules are arranged in longitudinal cords around the central vein and are separated from each other by sinusoids that meet up between interlobular blood vessels with the central vein. The toxic group (II and III) showed high degree of oedema in case of liver tissue (Fig. 6.15b–d). Hyperaemia, hypertrophy and lymphocytic infiltrations were observed along with many pyknotic nuclei, binucleated and giant cells. These results were in support with the work of Noman et al. (2015). Even, Gora et al. (2014) disclosed that arsenic attributed hepatocytic damage was also characterized by vacuolar degradation along with necrosis in the liver cells of rats. Arsenic, in drinking water also caused increment in the plasma liver enzymes (Sarkar et al. 2014).

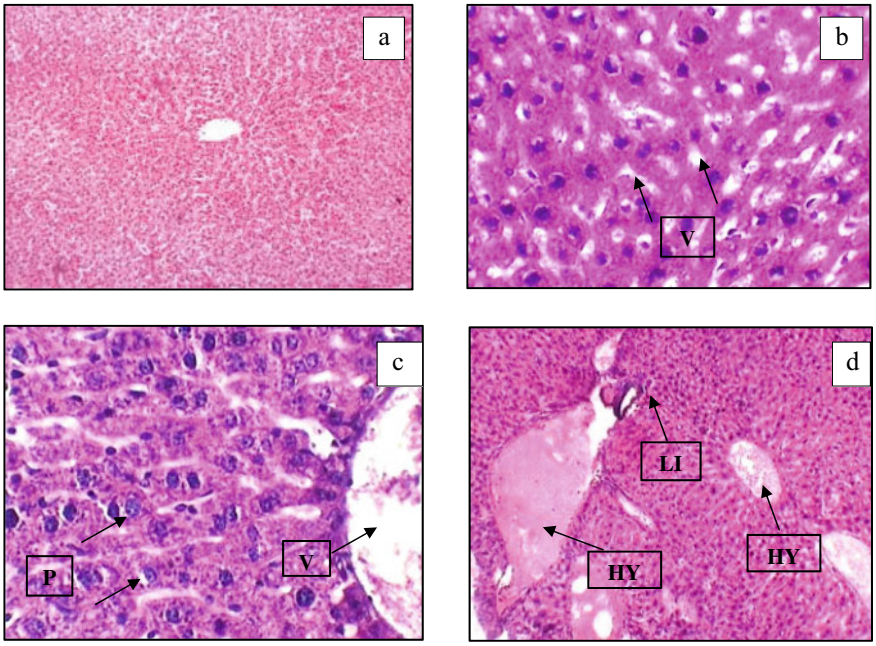


**Fig. 6.15** Photomicrographs of liver tissue of both the groups. **a** Control group, **b, c, d** Arsenic group (II and III) showing vacuolation (V), oedema, degranulation, hyperemia (HY) and formation of pyknotic (P) and multinucleated cells. Lymphocytic infiltration (LI) was also observed. X400 (H&E)

## 6.8 Conclusion

Arsenic (As) is a toxic metal and contaminates both terrestrial and aquatic environments affecting animals and even humans life. Arsenic induced oxidative stress which resulted in an elevation in MDA level in tissue and serum, decrease in antioxidant activities in hepatocytes of albino mice. The liver is the main organ affected by As exposure. Arsenic caused genotoxic and cytological effects in bone marrow of mice by decreasing the mitotic index value and enhancing the chromosomal aberrations and number of micronuclei.

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## References

Aebi HE (1983) Catalase. In: Bergmeyer HU (ed) Methods of enzymatic analysis, vol 3. Verlag Chemiew, Weinheim, pp 273–286

Aflanie I, Muhyi R, Suhartono E (2015) Effect of heavy metal on malondialdehyde and advanced oxidation protein products concentration: a focus on arsenic, cadmium, and mercury. J Med Bioeng 4(4):1–6

Agarwal DK, Chauhan LKS (1993) An improved chemical substitute for fetal calf serum for the micronucleus test. Biotechnol Histochem 68:187–188

Au WW, Ramanujam VMS, Ward JB, Legator MS (1991) Chromosome aberrations in lymphocytes of mice after sub-acute low level inhalation exposure to benzene. Mutat Res 260:219–224

Basu A, Som A, Ghoshal S, Mondal L, Chaubey RC, Bhilwade HN, Rahman MM, Giri AK (2005) Assessment of DNA damage in peripheral blood lymphocytes of individuals susceptible to arsenic induced toxicity in West Bengal, India. Toxicol Lett 159:100–112

Ben Abdallah F, Dammak I, Mallek Z, Attia H, Hentati B, Ammar-Keske L (2009) Effects of date seed oil on testicular antioxidant enzymes and epididymal sperm characteristics in male mice. Andrologia 41:229–334

Bonassi S, Hagmar L, Stromberg U, Montagud AH, Tinnerberg H, Forni A, Heikkila P, Wanders S, Wilhardt P, Hansteen IL, Knudsen LE, Norppa H (2000) Chromosomal aberrations in lymphocytes predict human cancer independently of exposure to carcinogens. Cancer Res 60:1619–1625

Chakraborthy T, Madhusnata D (2013) Study of the effect of tea in an arsenic exposed population using micronuclei as a biomarker. Int J Hum Genet 13(1):47–51

Chen YC, Lin-Shiau SY, Lin JK (1998) Involvement of reactive oxygen species and caspase3 activation induced apoptosis. J Cell Physiol 177:324–333

Chowdhury DUS, Islam S, Akter R, Khaleda L, Rahman Z, Al-Forkan M (2016) A study on the effect of arsenic on tissue histology and its deposition pattern in various organs of wistar albino rat. Eur J Pharm Med Res 3(1):580–587

Cohen SM, Arnold LL, Eldan M, Lewis AS, Beck BD (2006) Methylated arsenicals: the implications of metabolism and carcinogenicity studies in rodents to human risk assessment. Crit Rev Toxicol 36:99–133

Conde de la Rosa L, Schoemaker MH, Vrenken TE, BuistHoman M, Havinga R, Jansen PLM, Moshage H (2006) Superoxide anions and hydrogen peroxide induce hepatocyte death by different mechanisms: involvement of JNK and ERK MAP kinases. J Hepatol 44:918–929

Das K, Samamta L, Chainy GBN (2000) A modified spectrophotometric assay for superoxide dismutase using nitrite formation by superoxide radicals. Ind J Biochem Biophy 37:201–204

Das J, Ghosh J, Manna P, Sil PC (2010) Protective role of taurine against arsenic-induced mitochondria-dependent hepatic apoptosis via the inhibition of PKC delta- JNK pathway. PLoS ONE 5(9):2602

Das S, Upadhaya P, Giri S (2016) Arsenic and smokeless tobacco induce genotoxicity, sperm abnormality as well as oxidative stress in mice in vivo. Genes Environ 38(4):1–8

Demerdash FME, Yousef MI, Radwan FME (2009) Ameliorating effect of curcumin on sodium arsenite-induced oxidative damage and lipid peroxidation in different rat organs. Food Chem Toxicol 47:249–254

Devi UP, Ganasoundari A, Vrinda B, Srinivasan KK, Unnikrishnan MK (2000) Radiation protection by the *Ocimum* flavonoids orientin and vicenin: Mechanism of action. Radiat Res 154:455–460

Drury RA, Wallington EA (1980) Carleton's Histological Techniques, 5th edn, vol 1. Oxford University Press, London, pp 653–661

Dwivedi S, Gupta DK (2020) Concomitant influence of heavy metal intoxication on size of organs and body weight in albino rats. Int J Pharm Sci Res 11(3):1417–1424

Dwivedi VK, Arya A, Gupta H, Bhatnagar A, Kumar P, Chaudary M (2011) Chelating ability of sulbactomax drug in arsenic intoxication. Afr J Biochem Res 5:307–314

Flora SJS, Bhadauria S, Kannan GM, Singh N (2007) Arsenic induced oxidative stress and the role of antioxidant supplementation during chelation: a review. J Environ Biol 28(2):333–347
Gabel T (2000) Confounding variables in the environmental toxicology of arsenic. Toxicol 144:155–162
Gora RH, Baxia SL, Kerketta P, Patnail S, Roy BK (2014) Hepatoprotective activity of *Tephrosia purpurea* against arsenic induced toxicity in rats. Indian J Pharmacol 46:197–200
Grade M, Difilippantonio MJ, Camps J (2015) Patterns of chromosomal aberrations in Solid tumors. Recent Results Cancer Res 200:115–142
Halliwell B, Gutteridge JMC (1999) Free radicals in biology and medicine, 3rd edn. Oxford University Press, Midsomer
Henkler F, Brinkmann J, Luch A (2010) The role of oxidative stress in carcinogenesis induced by metals and xenobiotics. Cancers 2(2):376–396
Hultberg B, Andersson A, Isaksson A (2001) Interactions of metals and thiols in cell damage and glutathione distributions: potential of mercury toxicity by dithiothreitol. Toxicol 56:93–100
Hunter FT, Kip AF, Irvine W (1942) Radioactive tracer studies on arsenic injected as potassium arsenite. J Pharmacol Exp Ther 76:207
Jalaludeen AM, Ha WT, Lee R, Kim JH, Do JT, Park C, Heo YT, Lee WY, Song H, Biochanin A (2016) Ameliorates arsenic-induced hepato- and hematotoxicity in rats. Molecules 21(1):69
Jariyawat S, Kigpituck P, Suksen K, Chuncharunee A, Pivachaturawat P (2009) Protection against cisplatin-induced nephrotoxicity in mice by *Curcuma comosa* ethanol extract. J Nat Med 63(4):430–436
Jiang X, Chen C, Zhao W, Zhang Z (2013) Sodium arsenite and arsenic trioxide differently affect the oxidative stress, genotoxicity and apoptosis in A549 cells: An implication for the paradoxical mechanism. Environ Toxicol Pharmacol 36(3):891–902
Kaltreider RC, Davis AM, Lariviere JP, Hamilton JW (2001) Arsenic alters the function of the glucocorticoid receptor as a transcription factor. Environ Health Perspect 109:245–251
Kitchin KT, Conolly R (2010) Arsenic-induced carcinogenesis—oxidative stress as a possible mode of action and future research needs for more biologically based risk assessment. Chem Res Toxicol 23(2):327–335
Kumar R, Gahlot V, Ali M, Akhtar S, Kumar A (2016) Genotoxic effect of arsenic on chromosome structure of mice. Eur J Pharm Med Res 3(4):224–227
Lee TC, Ho IC (1995) Modulation of cellular antioxidants defense activities by sodium arsenite in human fibroblasts. Arch Toxicol 69:498–504
Lee CH, Yu HS (2016) Role of mitochondria ROS and DNA damage in arsenic induced carcinogenesis. Front Biosci 8(2):312–320
Luzhna L, Kathiria P, Kovalchuk O (2013) Micronuclei in genotoxicity assessment: from genetic to epigenetics and beyond. Front Genet 4:131
Martinez V, Creus A, Venegas W, Arroyo A, Beck JP, Gebel TW, Surralles J, Marcos R (2005) Micronuclei assessment in buccal cells of people environmentally exposed to arsenic in northern Chile. Toxicol Lett 155(2):319–327
Mayer C, Schmezer P, Freese R, Mutanen M, Hietanen E, Obe G, Basu S, Bartsch H (2000) Lipid peroxidation status, somatic mutations and micronuclei in peripheral lymphocytes: a case observation on a possible interrelationship. Cancer Lett 152:169–173
Miller WH Jr, Schipper HM, Lee JS, Singer J, Waxman S (2002) Mechanisms of action of arsenic Trioxide. Cancer Res 62(14):3893–3903
Muthumani M (2013) Tetrahydrocurcumin potentially attenuates arsenic induced oxidative hepatic dysfunction in Rats. J Clin Toxicol 3(4):1–10
Nandi D, Patra RC, Swarup D (2006) Oxidative stress indices and plasma biochemical parameters during oral exposure to arsenic in rats. Food Chem Toxicol 44:1579–1584
Nandi D, Patra RC, Ranjan R, Swarup D (2008) Role of co-administration of antioxidants in prevention of oxidative injury following sub-chronic exposure to arsenic in rats. Vet Arh 78(2):113–121

Nareda A, Kumar M (2021) Efficacy of *Triticum aestivum* (Wheat grass) against arsenic induced hepatic damages. Asain J Pharm Clin Res 14(2):77–82
Nicolì V, Tabano SM, Colapietro P, Maestri M, Ricciardi R, Stoccoro A, Fontana L, Guida M, Miozzo M, Coppedè F, Migliore L (2022) Preferential X chromosome inactivation as a mechanism to explain female preponderance in myasthenia gravis. Genes 13(4):696
Noman AS, Dilruba S, Mohanto NC, Rahman L, Khatun Z, Riad W, Al Mamun A, Alam S, Aktar S, Chowdhury S, Saud ZA, Rahman Z, Hossain K, Haque A (2015) Arsenic-induced histological alterations in various organs of mice. J Cytol Histol 6(3):323
Ochi T, Kita K, Suzuki T, Rumpler A, Goessler W, Francesconi K (2008) Cytotoxic, genotoxic and cell-cycle disruptive effects of thio-dimethylarseinate in cultured human cells and the role of glutathione. Toxicol Appl Pharmacol 228:59–67
Pei Q, Ma N, Zhang J, Xu W, Li Y, Ma Z, Li Y, Tian F, Zhang W, Mu J (2013) Oxidative DNA damage of peripheral blood polymorphonuclear leukocytes, selectively induced by chronic arsenic exposure, is associated with extent of arsenic-related skin lesions. Toxicol Appl Pharmacol 266:143–149
Picker JD, Fox DP (1996) Do curried foods produce micronuclei in buccal epithelial cells. Mutat Res 171:185–188
Pineda J, Herrera A, Antonio MT (2013) Comparison between hepatic and renal effects in rats treated with arsenic and/or antioxidants during gestation and lactation. J Trace Elem Med Biol 27:236–241
Prabu SM, Sumedha NC (2014) Ameliorative effect of diallyl trisulphide on arsenic-induced oxidative stress in rat erythrocytes and DNA damage in lymphocytes. J Basic Clin Physiol Pharmacol 25(2):181–197
Preston RJ, Dean BJ, Galloway S, Holden H, Mcfee AF, Shelby M (1987) Mammalian in vivo cytogenetic assays: analysis of chromosome aberrations in bone marrow cells. Mutat Res 189:157–165
Rahman MA, Hasegawa H, Rahman MM, Miah MAM, Tasmin A (2008) Straighthead disease of rice (*Oryza sativa L.)* induced by arsenic toxicity. Environ Exp Bot 62:54–59
Reddy MVB, Sasikala P, Karthik A, Sudheer SD, Murthy LN (2012) Protective role of curcumin against arsenic trioxide toxicity during gestation and lactational periods. Glob Vet 9(3):270–276
Saha JC, Dikshit AK, Bandyopadhyay M, Saha KC (2010) A review of arsenic poisoning and its effects on human health. Crit Rev Environ Sci Technol 29(3):281–313
Salazar AM, Sordo M, Ostrosky-Wegman P (2009) Relationship between micronuclei formation and p53 induction. Mutat Res 672(2):124–128
Sanchez-Alarcon J, Milic M, Bustamante-Montes LP, Isaac-Olive K, Valencia-Quintana R, Ramirez-Duran N (2021) Genotoxicity of mercury and its derivatives demonstrated in vitro and In vivo in human populations studies. Systematic review. Toxics 9(12):326
Sarkar S, Blaney L, Gupta A, Ghosh D, Sengupta A (2008) Arsenic removal from groundwater and its safe containment in a rural environment: validation of a sustainable approach. Environ Sci Technol 42:4268–4273
Sarkar S, Mukherjee S, Chattopadhyay A (2014) Low dose of arsenic trioxide triggers oxidative stress in zebrafish brain: expression of antioxidant genes. Ecotoxicol Environ Saf 107:1–8
Satoh KEI (1978) Serum lipid peroxide in cerebrovascular disorders determined by a new colorimetric method. Clin Chim Acta 90:37–43
Shaji E, Santosh M, Sarath KV, Prakash P, Deepchand V, Divya BA (2021) Arsenic contamination of ground water: a global synopsis with focus on the Indian Peninsula. Geosci Front 12:101079
Shiguang Y, Beynen AC (2000) High arsenic raises kidney copper and lows plasma copper concentrations in rats. Biol Trace Elem Res 81:63–70
Shila S, Kokilavani V, Subathra M, Panneerselvam C (2005) Brain regional responses in antioxidant system to alpha-lipoic acid in arsenic intoxicated rat. Toxicology 210:25–36
Sinnhuber RO, Yu T (1958) 2-Thiobarbituric acid method for measurement of rancidity in fishery products. 2II. The quantitative determination of malondialdehyde. Food Technol 12:9–12

Sommer S, Buraczewska I, Kruszewski M (2020) Micronucleus assay: the state of art, and future directions. Int J Mol Sci 21(4):1534

Suanarunsawat T, Ayutthaya WDN, Songsak T, Thirawarapan S, Poungshompoo S (2010) Antioxidant activity and lipid-lowering effect of essential oils extracted from *Ocimum sanctum* L. leaves in rats fed with a high cholesterol diet. J Clin Biochem Nutr 46:52–59

Suanarunsawat T, Ayutthaya WDN, Songsak T, Thirawarapan S, Poungshomp S (2011) Lipid-lowering and antioxidative activities of aqueous extracts of *Ocimum sanctum* L. leaves in rats fed with a high-cholesterol diet. Oxid Med Cell Longev 1–9

Tang HY, Ho HY, Wu PR, Chen SH, Kuypers FA, Cheng ML, Chiu DT (2015) Inability to maintain GSH pool in G6PH deficient red cells causes futile AMPK activation and irreversible metabolic disturbance. Antioxid Redox Signal 22(9):744–759

Tapio S, Grosche B (2006) Arsenic in the aetiology of cancer. Mutat Res 612:215–246

Tchounwou PB, Patlolla AK, Centeno JA (2003) Carcinogenic and systemic health effects associated with arsenic exposure a critical review. Toxicol Pathol 31:575–588

Todehdehghan F, Motedayen MH, Teimorzadeh SH, Shafaei K (2011) Karyotype of NIH, C57BL/6 and RAZI strain of laboratory mice (*Mus musculus*). Int J Vet Res 5(2):81–83

Vahter M, Concha G (2001) Role of metabolism in arsenic toxicity. Pharmacol Toxicol 89(1):1–5

Wilbur KM, Bernheim F, Shapiro OW (1949) The thiobarbituric acid reagent as a test for the oxidation of unsaturated fatty acid by various agents. Acta Biochem Biophys 24:305–313

Wu MM, Chiou HY, Wang TW, Hsueh YM, Wang IH, Chen CJ, Lee TC (2001) Association of blood arsenic levels with increased reactive oxidants and decreased antioxidant capacity in a human population of north-eastern Taiwan. Environ Health Perspect 109:1011–1017

Yamanaka K, Hasegawa A, Sawamura R, Okada S (1991) Cellular response to oxidative damage in lung induced by the administration of dimethylarsinic acid, a major metabolite of inorganic arsenics, in mice. Toxicol Appl Pharmacol 108:205–213

Yun BH, Guo J, Bellamri M, Turesky RJ (2020) DNA Adducts: formation, biological effects and new biospecimens for mass spectrometric measurements in humans. Mass Spectr Rev 39(1–2):55–82

Zhang Z, Gao L, Cheng Y, Jiang J, Chen Y, Jiang H, Yu H, Shan A, Cheng B (2016) Resveratrol, a natural antioxidant, has a protective effect on liver injury induced by inorganic arsenic exposure. Biomed Res Int 1–7

# Chapter 7
# The Effects of Arsenic Exposure on Neurological and Cognitive Dysfunction in Human


**Itika Arya, Ashutosh Bhardwaj, and Santosh Kumar Karn**

**Abstract** Arsenic, one of the most prevalent naturally occurring elements is referred to as the King of Poisons and is frequently present in diet and drinking water. It is primarily found in an inorganic form. The most common and toxic forms of arsenic are the trivalent form called arsenite which has an oxidation state of + 3, and the pentavalent form called arsenate or As(V). Common organic arsenic compounds are arsanilic acid, monomethylarsonic acid (MMAV), dimethylarsonic acid (DMAV, also called cacodylic acid), trimethylarsonic acid (TMA) and arsenobetaine. Cancer in the lungs, skin, kidney, liver, bladder, and prostate is associated with arsenic toxicity in drinking water. Other sources of arsenic are soil, air, cosmetics, pesticides, chemotherapeutic agent, and the by-product of metal ore smelters. It serves benefits as pesticides, semiconductors, glassware, alloys, and preservatives. In addition, it can be used to treat many ailments like ulcers, syphilis, leukemia, trypanosomiasis, cancers, etc. The negative effects of arsenic are caused by several interdependent modes of action. One of the first proposed MOAs for arsenic, suggested by Binz and Schulz in 1879, was the interference of cellular oxidation from the cycling of oxygen during the interconversion of arsenate and arsenite. As a result, arsenolysis occurs that reduces ATP in the body due to the formation of anhydrides during glycolysis and oxidative phosphorylation. Additionally, the formation of reactive oxygen and nitrogen species also contributes to arsenic toxicity. Formed ROS are involved in genotoxicity, signalling, cell proliferation, and inhibition of DNA repair. Arsenic carcinogenicity includes inhibition of DNA repair under conditions of oxidative stress, inflammation, and proliferative signalling. There are many neurobehavioral disorders and nervous system disorders. Polyneuropathy, and electroencephalographic (EEG) abnormalities are some disorders caused due to arsenic exposure. Arsenic exposure to a mother during her pregnancy causes oxidative stress and slashes ATP production, causing improper development of the brain and altering normal neurobehavior. Arsenic exposure also interferes with cognitive function, particularly learning and remembering during childhood, and causes impaired learning and increased anxiety-like behaviour.

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Adults are more prone to peripheral and sensory neuropathy whereas children are more prone to neurodevelopmental syndromes such as attention-deficit hyperactivity disorder, intellectual disabilities, learning disorder, and autism.

**Keywords** Arsenic exposure · Toxicity · Arsenite · Arsenate · Arsenolysis · Neuropathy · Cognitive

## 7.1 Arsenic: An Overview

Arsenic is one of the prevalent naturally occurring elements. It (As) is a metalloid possessing properties of both metals and non-metals and has atomic no. 33 and an atomic weight of 74.92. It is a trace element as it is present in less than 1% (< 1%) of most rocks, coals, and soils (Alam et al. 2002). It is characterized as a white, yellow, grey metallic, or black solid that is odorless. It is highly toxic in nature. For centuries arsenic and its compounds have been in produced and utilized for commercial purposes like in pharmaceutical industry, agricultural industry, and semiconductor industry. Agricultural and industrial processes like mining and smelting contributes to high arsenic levels in the environment. Several areas of Japan, Mexico, Thailand, Brazil, Australia, and the USA have high arsenic levels in local water sources, due to mining, smelting, and other industrial activities (IARC 2004). However, Minerals and geogenic sources are primary sources of arsenic contamination with anthropogenic activities also contributing to it via extensive soil and water contamination throughout the world (Smith et al. 1998). Arsenic comes in three major forms: inorganic, organic and arsine gas (− 3 oxidative state), as well as three major valence states arsenic element (0), arsenite (trivalent + 3), and arsenate (pentavalent + 5) among which arsenite (+ 3) and arsenate (+ 5) are the most common toxic inorganic forms (Yousef et al. 2008). In general, trivalent arsenic compounds; inorganic (arsenite) and organic (monomethyl arsenic) are considered more toxic than pentavalent compounds. Arsenic, "when combined with carbon and hydrogen (in plants and animals) forms organic arsenic compounds whereas when combine with oxygen, sulfur, and chlorine in environment form inorganic arsenic compounds" (Martinez et al. 2011). Inorganic arsenic compounds are more prevalent in the environment and contribute more to toxicity. Arsanilic acid, monomethylarsonic acid (MMAV), dimethylarsonic acid (DMAV, also called cacodylic acid), trimethylarsonic acid (TMA) and arsenobetaine are some common organic arsenic compounds. Until the 1970s arsenic was used for medicinal purposes. For the treatment of leukemia, psoriasis, and chronic bronchial asthma, inorganic arsenic was used and for the treatment of spirochetal and protozoal disease organic arsenic was used in antibiotics (ATSDR 2007). It was considered that the father of medicine, Hippocrates used arsenic as a paste for the treatment of ulcers and abscesses. The arsenic paste appears to be beneficial for chemotherapeutic purposes as suggested by the pharmacology texts from the 1880s (Antman 2001). Arsenic organic compounds are used in the agricultural

industry as well in the form of pesticides, herbicides, defoliants, and as soil sterilizing agents but in 2009 the US issued an order to remove organic arsenic-containing pesticides from agricultural practices by 2013 (EPA 2009) as the large area of agricultural land gets contaminated due to repeated use of arsenic-containing pesticides. Arsenic and its compounds are also used for a variety of industrial purposes like in the semiconductor and electronics industry, in the manufacturing of alloys, and also in the making of an anti-fungal wood preservative (Tchounwou et al. 1999).

Before the advent of penicillin, some organic arsenicals such as arsphenamine, salvarsan and their derivatives were used as anti-syphilitic agents (Globus and Ginsburg 1933; Osterberg and Kernohan 1934; Russell 1937). Some arsenic compounds are used to treat trypanosomiasis (Harrison et al. 1997) and acute promyelocytic leukemia (Look 1998).

## 7.2 Exposure to Arsenic

Based on known toxicity, arsenic is the most toxicant that poses substantial harm to human health and therefore ranked first among the toxicants (Hughes et al. 2011). Arsenic was used throughout history to kill the emperors for their wealth and empire because of many reasons like multiple ways of administration, its potency, and availability, and therefore called as "King of Poisons." Nonetheless, arsenic is ubiquitous in the environment, the majority of organic and inorganic arsenic uptake by an individual comes from the diet. An average adult in the United States has an intake of 3.2 μg/day as per Schoof et al. (1999) and similar results were found for children as well (Yost et al. 2004) but the European Food Safety Authority (EFSA) estimated a higher intake level 9.1–39.2 μg/day for a 70 kg adult as estimates include the ratio of inorganic arsenic to total arsenic in food i.e., 0.13–0.56 μg/kg/day for an average consumer (EFSA 2009). The diet of an individual has both organic as well as inorganic forms of arsenic compounds and 25% of daily dietary arsenic intake comes from inorganic sources. It is considered that organic forms of arsenic are less toxic than the inorganic forms. Arsenic is found in highest concentration in seafood. Monomethylarsonic acid, $DMAs^V$, arsenobetaine, arsenocholine, arsenosugars, and arsenolipids are arsenic compounds that are organic in nature and majorly found in food.

### *7.2.1 Exposure in Water*

Inorganic forms of arsenic predominantly exist in water which stabilizes as (trivalent, + 3) arsenite and (pentavalent, + 5) arsenate (Saxe et al. 2006). Arsenic in drinking water at levels over the WHO recommended threshold of 10 ppb (parts per billion) was estimated to have contaminated approximately 140 million people in 2009 (Ravenscroft 2009). Over 1.5 million people in India have been estimated to

be exposed to arsenic levels higher than the WHO threshold of 10 ppb leading to more than 200,000 cases of arsenicosis (de Castro et al. 2009). Arsenic ingestion via drinking water was found to be associated with increased cases of cancer and with some non-cancer effects like skin lesions, and neurological effects (NRC 2001).

### *7.2.2 Exposure in Soil*

Globally, arsenic levels present naturally in soil ranges from 0.01 to over 600 mg/kg with a mean of 2–20 mg/kg. Mostly, inorganic forms of arsenic (trivalent and pentavalent) are present in the soil. Due to the oxidation of trivalent arsenicals, pentavalent arsenic compounds are found predominately in soil (Gong et al. 2001). There are numerous ways to be exposed to arsenic in the soil. Dermal absorption and inhalation of soil particles carried by the wind are some potential exposure routes but incidental ingestion is the most common pathway for the intake of arsenic in soil (Yan-Chu 1994). Numerous studies have revealed that less than 50% of arsenic in soil that is taken by mouth can be absorbed and used by the body (Roberts et al. 2002).

### *7.2.3 Exposure in Air*

Arsenic exposure from the air is quite minimal compared to that of food and water. The contribution of air in arsenic exposure is less than 1% as per the data collected by European Commission (2000). Arsenic trioxide is an inorganic compound primarily involved in contaminating the air with arsenic. Cosmetic Products also contain arsenic in some amount and act as a source for direct arsenic exposure (Chung et al. 2014). Increasing exposure to arsenic via drinking water and contaminated food to a large population is a matter of great concern due to many toxic effects associated with arsenic (Chatterjee et al. 2010; Rahman et al. 2009).

## 7.3 Mode of Action of Toxicity by Arsenic

It is challenging to determine the method of action using the epidemiological literature since long-term exposures to arsenic are probably amplified by exposures to pollution. The harmful effects of arsenic are presumably the result of several pathways; in fact, these mechanisms may be interrelated. Trivalent arsenic compounds (arsenite) have more toxicity as compared to pentavalent arsenic compounds (arsenate) due to higher solubility and slower excretion rate.

Binz and Schulz suggested the arsenic's initial proposed route of action in 1879 (Parascandola 1977). It suggested that both arsenicals are equally potent by

describing how cellular oxidation is interfered with by oxygen cycling during the interconversion of arsenate and arsenite, but as it soon became clear that arsenite is more potent than arsenate, this hypothesis was quickly abandoned.

Phosphate and arsenate have similar properties (after protonation) due to their comparable structure, making arsenate capable of substituting phosphate in different metabolic reactions. Arsenate also forms a less stable ester bond with a higher bond length between As–O in comparison to the P–O bond formed between phosphate and its hydroxyl groups (Dixon 1996). In a process known as arsenolysis, arsenate decouples the production of adenosine 5-triphosphate (ATP) in vitro. This process occurs in the presence of arsenate during glycolysis and oxidative phosphorylation (OXPHOS). Both reactions result in the formation of unstable arsenate anhydrides that are simple to hydrolyse like 3-phosphoglyceroyl arsenate in case of the glycolytic pathway. The end outcome is a reduction in the production of ATP (Gresser 1981).

One of the most extensively researched mode of action (MOA) for arsenic toxicity currently is the production of reactive oxygen and nitrogen species by arsenic (Hughes and Kitchin 2006). There are number of the hypothesised mode of actions for arsenic, such as genotoxicity, cell proliferation, and suppression of DNA repair, that include reactive oxygen species generated by arsenic. Reactive oxygen species (ROS) can be formed by arsenic in a variety of reactions such as during the conversion of arsenite to arsenate (Del Razo et al. 2001), during the metabolism of arsenic resulting in the formation of arsine (Yamanaka and Okada 1994).

"Deletion mutations, oxidative DNA damage, breaks in DNA strand, sister chromatid exchanges, chromosomal abnormalities, aneuploidy, and micronuclei are some of the impacts of arsenic's genotoxicity" (Basu et al. 2001; Hei et al. 1998; Rossman 2003). Studies on human cell nuclear extracts revealed that arsenic's indirect effect of inhibiting DNA repair was brought on by the generation of ROS or by altered cell signalling that altered gene expression (Hu et al. 1998). Arsenic also affects the working of enzymes involved in repair mechanisms such as nucleotide and base excision repair (Hartwig et al. 2003). Arsenic trivalent compounds interact with the zinc finger motifs of proteins and disrupt the function of proteins by moving zinc from its binding site causing inhibition of base excision repair (BER) and nucleotide excision repair (NER) activity (Ding et al. 2009; Piątek et al. 2008).

Gentry et al. (2009) examined in vitro cellular and in vivo gene expression alterations after exposure to inorganic arsenic and concluded that arsenic inhibits DNA repair as a method of action for its carcinogenic effect. The findings suggested that DNA repair inhibition under the influence of oxidative stress, inflammation, and proliferative signalling is one of the important processes in arsenic's carcinogenicity. Such circumstances could result in mitosis progressing without preserving the integrity of the cellular DNA.

Arsenic by altering the signal transduction pathways can regulate the expression of transcription factors and proteins (Bode and Dong 2002; Druwe and Vaillancourt 2010; Huang et al. 2004; Kumagai and Sumi 2007; Leonard et al. 2004; Platanias 2009). In vitro, arsenite activated the protein p38, a component of the mitogen-activated protein kinase (MAPK) cascade (Rouse et al. 1994). Arsenic also activates the c-Jun N-terminal kinases (JNKs) and extracellular-regulated protein

kinases (ERKs), two other components of the MAPK pathway (Bode and Dong 2002; Yang and Frenkel 2002). Arsenic also affects the transcription factors nuclear factor-κβ (NF-κβ) and (Nrf2) nuclear factor erythroid-2-related factor 2 (Kumagai and Sumi 2007). By altering a reactive thiol in Iκβ kinase, arsenite seems to prevent activation of tumor necrosis factor-α induced NF-κβ (Roussel and Barchowsky 2000; Shumilla et al. 1998). With the help of generating ROS, arsenic also found to activate NF-κβ (Felix et al. 2005; Wijeweera et al. 2001).

Inorganic arsenic compounds expresses the growth factors to such an extent that it results in a condition called hyperkeratosis which is an indication of arsenic toxicity in humans (Germolec et al. 1997).

Arsenic alters the methylation in DNA, according to investigations done by Zhao et al. (1997). It is unclear what the mechanism is for this. However, dietary factors, DNA methyltransferase inhibition, or shunting of the methyl donor, S-adenosylmethionine for the methylation of both DNA and arsenic are some of the reasons for hypomethylation (Chanda et al. 2006).

Arsenite and arsenate can be transported by human RBCs using anion exchange proteins (Zhang et al. 2000). The necessary sulfhydryl groups of proteins and enzymes are blocked by arsenite due to its interactions with thiol groups present in them. As a result, it disrupt the activity of enzymes involved in the metabolism of carbohydrates such as pyruvate dehydrogenase (Aposhian 1989). Arsenite causes cytoskeletal components to become disorganized once it enters the cell (Li and Chou 1992; Ramirez et al. 1997).

## 7.4 Effect of Arsenic on Neurological Function in Human

An unidentified mechanism allows arsenic to reach the brain. It builds up in the choroid plexus, preventing arsenic from entering the brain (Zheng et al. 1991). It induces changes in neurotransmitter levels and cause alterations in functions (Rodríguez et al. 2001). Neural health and behaviour of an individual get affected by the accumulation of arsenic during the childhood stage (Tsai et al. 2003). Arsenic-induced neuritis is a well-known side effect of arsenic toxicity and is known to impair the sensory capabilities of the peripheral nerves. Several other neurological conditions, such as polyneuropathy and aberrant electroencephalographic (EEG) are also induced by arsenic exposure (Rodríguez et al. 2003). Additionally, it has the ability to activate the p38 MAPK and JNK3 genes, which may result in Alzheimer's disease (Gharibzadeh and Hoseini 2008).

According to the studies, arsenic exposure via drinking water is linked to neurodegeneration, including oxidative stress, damaged protein degradation, intracellular accumulation and autophagy, mitochondrial dysfunction, and more (Escudero-Lourdes 2016). Arsenic exposure via dust and drinking water can also cause damage to the peripheral nerves (Gerr et al. 2000; Mazumder et al. 2010). Arsenic exposure during pregnancy causes oxidative stress and decreased ATP generation, endangering

the structural and functional maturity of nerve cells and impairing brain development as well as associated behaviours (Gandhi and Kumar 2013). Arsenic exposure to copper smelters causes them to exhibit a lower rate of conduction of nerve signals and damage to peripheral nerves (Lagerkvist and Zetterlund 1994). Additionally, they may have muscle tiredness, irritability, headaches, severe muscle spasms in their extremities, and lethargy or lack of sleep (Sinczuk-Walczak et al. 2010). Rising urine arsenic levels negatively affect processing speed and fine motor function (Carroll et al. 2017). Arsenic exposure at workplace can lead to neurological and electromyographic abnormalities (Blom et al. 1985). Exposure in mines can be harmful and causes sensory neuropathy and hearing impairment (Ishii et al. 2018).

## 7.5 Effect of Arsenic on Cognitive Function in Human

Numerous epidemiological studies have indicated that arsenic exposure can affect how well people think and learn, especially in young children. Children's intellectual development may be harmed more by chronic moderate exposure to arsenic than by severe acute exposure. Children exposed to arsenic had an IQ drop of 0.4, which can have collective effects in later stage of life (Rodríguez-Barranco et al. 2013). In youngsters between the ages of 6 and 8 years old, a 2007 study discovered a strong correlation between urine arsenic concentrations above 50 g/L and poor performance on tests of remembrance, cognitive, visual and spatial reasoning, linguistic development (Rosado et al. 2007). These children also exhibited symptoms of Attention Deficit Hyperactive Disorder (Roy et al. 2011). Additionally, several studies suggested that arsenic hinders young females' growth and development more than males, which may have an impact on cognitive function (Gardner et al. 2013). The likelihood of intellectual disability in children rises as the concentration of arsenic and lead increases in the soil, and the prevalence of mental retardation is significantly connected with the presence of soil metals like arsenic, copper, lead, manganese, etc. (Aelion et al. 2008; McDermott et al. 2011). Exposure to arsenic during the gestation and lactation period can cause nitric oxide dysfunction in brain (Zarazúa et al. 2006). "The research showed that prolonged exposure can impair pattern memory and attention switching" (Tsai et al. 2003). Low-level prenatal arsenic exposure and early children's neurobehavioral performance have been found to have an inverse relationship. Prenatal arsenic exposure can impact newborn infant neurobehavioral development (Wang et al. 2018). In addition, postnatal exposure exhibited impaired learning and increased anxiety-like behaviors (Zhou et al. 2018). Flawed Memory, sleep dysfunction, and visual disruption are among the signs of temporal and occipital lobe exposure to DPAA that are brought on by water consumption (Ishi and Tamaoka 2015). Inorganic arsenic exposure during pregnancy, according to Ramos-Chávez et al. (2015), affected the development of cysteine/glutamate transporters in the cortex and hippocampus and also caused an unfavourable regulation of the NMDA receptor (NMDAR) NR2B subunit in the hippocampus. When exposed to arsenic, there is also a decrease in acetylcholinesterase (AChE) and butyrylcholinesterase

(BChE) levels as well as a drop in motor coordination (Sharma et al. 2018). Children are more likely to have neurodevelopmental syndromes such as autism spectrum disorders, cognitive impairments, intellectual disabilities, and attention deficit hyperactivity disorder (Schug et al. 2015).

## 7.6 Conclusion

A common metalloid, arsenic can be found in food, water, and items manufactured by humans. Numerous epidemiological investigations have produced evidence pointing to a substantial link between exposure to arsenic and neurological and cognitive impairment in both children and adults. Multiple systems and particular pathways involved in various elements of learning, memory, mobility, decision-making, and mood are all impacted by arsenic exposure. Most people are exposed to arsenic through their diet and water consumption. Other sources of exposure include using arsenic as a pesticide, a by-product of smelting metal ore, a chemotherapeutic agent, or coming into contact with arsenic-contaminated soil. Chronic exposure to arsenic damages the peripheral nervous system by causing peripheral neuropathy, whereas acute and occupational exposure to arsenic compounds has been linked to encephalopathy and the impairment of higher neurological processes in patients. Arsenic exposure has been linked to skin, lung, and bladder cancers, according to research. Arsenic exposure results in a large number of health-related problems around the world, and it should be considered a serious threat to humans. Treatment of the afflicted areas should have broader consequences for issues with public health. Arsenic exposure needs to be reduced or eliminated. Arsenic levels in drinking water need to be constantly tracked and checked. Affected areas by arsenic should also have access to clean drinking water. When using cosmetics and when eating a diet, precautions should be made. Arsenic levels in drinking water need to be constantly tracked and checked. Affected areas by arsenic should also have access to clean drinking water. When using cosmetics and when eating a diet, precautions should be made. Arsenic-related health risks to people can be lessened by carefully examining potential sources of exposure.

## References

Aelion CM, Davis HT, McDermott S, Lawson AB (2008) Metal concentrations in rural topsoil in South Carolina: potential for human health impact. Sci Total Environ 402(2–3):149–156

Alam MGM, Allinson G, Stagnitti F, Tanaka A, Westbrooke M (2002) Arsenic contamination in Bangladesh groundwater: a major environmental and social disaster. Int J Environ Health Res 12(3):235–253

Antman KH (2001) Introduction: the history of arsenic trioxide in cancer therapy. Oncologist 6(S2):1–2

Aposhian HV (1989) Biochemical toxicology of arsenic. Rev Biochem Toxicol 10:265–299

ATSDR (2007) CERCLA priority list of hazardous substances. http://www.atsdr.cdc.gov/cercla/07list.html

Basu A, Mahata J, Gupta S, Giri AK (2001) Genetic toxicology of a paradoxical human carcinogen, arsenic: a review. Mutat Res/rev Mutat Res 488(2):171–194

Blom S, Lagerkvist B, Linderholm H (1985) Arsenic exposure to smelter workers: clinical and neurophysiological studies. Scand J Work Environ Health 265–269

Bode AM, Dong Z (2002) The paradox of arsenic: molecular mechanisms of cell transformation and chemotherapeutic effects. Crit Rev Oncol Hematol 42(1):5–24

Carroll CR, Noonan C, Garroutte EM, Navas-Acien A, Verney SP, Buchwald D (2017) Low-level inorganic arsenic exposure and neuropsychological functioning in American Indian elders. Environ Res 156:74–79

Chanda S, Dasgupta UB, GuhaMazumder D, Gupta M, Chaudhuri U, Lahiri S, Das S, Ghosh N, Chatterjee D (2006) DNA hypermethylation of promoter of gene p53 and p16 in arsenic-exposed people with and without malignancy. Toxicol Sci 89(2):431–437

Chatterjee D, Halder D, Majumder S, Biswas A, Nath B, Bhattacharya P et al (2010) Assessment of arsenic exposure from groundwater and rice in Bengal Delta Region, West Bengal, India. Water Res 44(19):5803–5812

Chung JY, Yu SD, Hong YS (2014) Environmental source of arsenic exposure. J Prev Med Public Health 47(5):253

de Castro MR, Lima JV, de Freitas DPS, de Souza Valente R, Dummer NS, de Aguiar RB et al (2009) Behavioral and neurotoxic effects of arsenic exposure in zebrafish (*Danio rerio*, Teleostei: Cyprinidae). Comp Biochem Physiol C Toxicol Pharmacol 150(3):337–342

Del Razo LM, Quintanilla-Vega B, Brambila-Colombres E, Calderón-Aranda ES, Manno M, Albores A (2001) Stress proteins induced by arsenic. Toxicol Appl Pharmacol 177(2):132–148

Ding W, Liu W, Cooper KL, Qin XJ, de Souza Bergo PL, Hudson LG, Liu KJ (2009) Inhibition of poly (ADP-ribose) polymerase-1 by arsenite interferes with repair of oxidative DNA damage. J Biol Chem 284(11):6809–6817

Dixon HB (1996) The biochemical action of arsonic acids especially as phosphate analogues. In: Advances in inorganic chemistry, vol 44. Academic Press, pp 191–227

Druwe IL, Vaillancourt RR (2010) Influence of arsenate and arsenite on signal transduction pathways: an update. Arch Toxicol 84:585–596

EPA (U.S. Environmental Protection Agency) (2009) Organic arsenicals; Product cancellation order and amendments to terminate uses (EPA-HQ-OPP-2009-0191; FRL-8437-7)

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

European Commission (2000) Ambient air pollution by As, Cd and Ni compounds (position paper—final), p 318. Available at: http://ec.europa.eu/environment/air/pdf/pp_as_cd_ni.pdf

European Food Safety Authority (EFSA) (2009) Scientific opinion on arsenic in food. EFSA J 7:1351

Felix K, Manna SK, Wise K, Barr J, Ramesh GT (2005) Low levels of arsenite activates nuclear factor-κB and activator protein-1 in immortalized mesencephalic cells. J Biochem Mol Toxicol 19(2):67–77

Gandhi DN, Kumar R (2013) Arsenic toxicity and neurobehaviors: a review. Innov Pharm Pharmacother 1(1):1–15

Gardner RM, Kippler M, Tofail F, Bottai M, Hamadani J, Grandér M, Nermell B, Palm B, Rasmussen KM, Vahter M (2013) Environmental exposure to metals and children's growth to age 5 years: a prospective cohort study. Am J Epidemiol 177(12):1356–1367

Gentry PR, McDonald TB, Sullivan DE, Shipp AM, Yager JW, Clewell HJ (2009) Analysis of genomic dose-response information on arsenic to inform key events in a mode of action for carcinogenicity. Environ Mol Mutagen 51(1):1–4. https://doi.org/10.1002/em.20505

Germolec DR, Spalding J, Boorman GA, Wilmer JL, Yoshida T, Simeonova PP et al (1997) Arsenic can mediate skin neoplasia by chronic stimulation of keratinocyte-derived growth factors. Mutat Res/rev Mutat Res 386(3):209–218

Gerr F, Letz R, Ryan PB, Green RC (2000) Neurological effects of environmental exposure to arsenic in dust and soil among humans. Neurotoxicology 21(4):475–487

Gharibzadeh S, Hoseini SS (2008) Arsenic exposure may be a risk factor for Alzheimer's disease. J Neuropsychiatry Clin Neurosci 20(4):501–501

Globus JH, Ginsburg SW (1933) Pericapillary encephalorrhagia due to arsphenamine: so-called arsphenamine encephalitis. Arch Neurol Psychiatry 30(6):1226–1247

Gong Z, Lu X, Cullen WR, Le XC (2001) Unstable trivalent arsenic metabolites, monomethylarsonous acid and dimethylarsinous acid. J Anal at Spectrom 16(12):1409–1413

Gresser MJ (1981) ADP-arsenate. Formation by submitochondrial particles under phosphorylating conditions. J Biol Chem 256(12):5981–5983

Harrison SM, Harris RW, Bales JD Jr (1997) Attempt to correlate urine arsenic excretion with clinical course during melarsoprol therapy of patients with *Rhodesian trypanosomiasis*. Am J Trop Med Hygiene 56(6):632–636

Hartwig A, Blessing H, Schwerdtle T, Walter I (2003) Modulation of DNA repair processes by arsenic and selenium compounds. Toxicology 193(1–2):161–169

Hei TK, Liu SX, Waldren C (1998) Mutagenicity of arsenic in mammalian cells: role of reactive oxygen species. Proc Natl Acad Sci 95(14):8103–8107

Hu Y, Su L, Snow ET (1998) Arsenic toxicity is enzyme specific and its affects on ligation are not caused by the direct inhibition of DNA repair enzymes. Mutat Res/DNA Rep 408(3):203–218

Huang C, Ke Q, Costa M, Shi X (2004) Molecular mechanisms of arsenic carcinogenesis. Mol Cell Biochem 255:57–66

Hughes MF, Kitchin KT (2006) Arsenic, oxidative stress, and carcinogenesis. In: Oxidative stress, disease and cancer, pp 825–850

Hughes MF, Beck BD, Chen Y, Lewis AS, Thomas DJ (2011) Arsenic exposure and toxicology: a historical perspective. Toxicol Sci 123(2):305–332

IARC (2004) Working group on the evaluation of carcinogenic risks to humans, international agency for research on cancer. Some drinking-water disinfectants and contaminants, including arsenic. IARC

Ishi K, Tamaoka A (2015) Ten-years records of organic arsenic (diphenylarsinic acid) poisoning: epidemiology, clinical feature, metabolism, and toxicity. Brain and Nerve = Shinkei Kenkyu no Shinpo 67(1):5–18

Ishii N, Mochizuki H, Ebihara Y, Shiomi K, Nakazato M (2018) Clinical symptoms, neurological signs, and electrophysiological findings in surviving residents with probable arsenic exposure in Toroku, Japan. Arch Environ Contam Toxicol 75:521–529

Kumagai Y, Sumi D (2007) Arsenic: signal transduction, transcription factor, and biotransformation involved in cellular response and toxicity. Annu Rev Pharmacol Toxicol 47:243–262

Lagerkvist BJ, Zetterlund B (1994) Assessment of exposure to arsenic among smelter workers: a five-year follow-up. Am J Ind Med 25(4):477–488

Leonard SS, Harris GK, Shi X (2004) Metal-induced oxidative stress and signal transduction. Free Radic Biol Med 37(12):1921–1942

Li W, Chou IN (1992) Effects of sodium arsenite on the cytoskeleton and cellular glutathione levels in cultured cells. Toxicol Appl Pharmacol 114(1):132–139

Look AT (1998) Arsenic and apoptosis in the treatment of acute promyelocytic leukemia. JNCI J Natl Cancer Inst 90(2):86–88

Martinez VD, Vucic EA, Becker-Santos DD, Gil L, Lam WL (2011) Arsenic exposure and the induction of human cancers. J Toxicol 2011

Mazumder DNG, Ghosh A, Majumdar KK, Ghosh N, Saha C, Mazumder RNG (2010) Arsenic contamination of ground water and its health impact on population of district of Nadia, West Bengal, India. Indian J Community Med 35(2):331

McDermott S, Wu J, Cai B, Lawson A, Aelion CM (2011) Probability of intellectual disability is associated with soil concentrations of arsenic and lead. Chemosphere 84(1):31–38

NRC (2001) Arsenic in drinking water. Update to the 1999 arsenic in drinking water report

Osterberg AE, Kernohan JW (1934) The presence of arsenic in the brain and its relation to pericapillary hemorrhages or so-called acute hemorrhagic encephalitis. Am J Clin Pathol 4(4):362–369

Parascandola J (1977) Carl Voegtlin and the 'arsenic receptor' in chemotherapy. J Hist Med Allied Sci 32(2):151–171

Piątek K, Schwerdtle T, Hartwig A, Bal W (2008) Monomethylarsonous acid destroys a tetrathiolate zinc finger much more efficiently than inorganic arsenite: mechanistic considerations and consequences for DNA repair inhibition. Chem Res Toxicol 21(3):600–606

Platanias LC (2009) Biological responses to arsenic compounds. J Biol Chem 284(28):18583–18587

Rahman MM, Naidu R, Bhattacharya P (2009) Arsenic contamination in groundwater in the Southeast Asia region. Environ Geochem Health 31:9–21

Ramirez P, Eastmond DA, Laclette JP, Ostrosky-Wegman P (1997) Disruption of microtubule assembly and spindle formation as a mechanism for the induction of aneuploid cells by sodium arsenite and vanadium pentoxide. Mutat Res/rev Mutat Res 386(3):291–298

Ramos-Chávez LA, Rendón-López CR, Zepeda A, Silva-Adaya D, Del Razo LM, Gonsebatt ME (2015) Neurological effects of inorganic arsenic exposure: altered cysteine/glutamate transport, NMDA expression and spatial memory impairment. Front Cell Neurosci 9:21

Ravenscroft P, Brammer H, Richards K (2009) Arsenic pollution: a global synthesis. John Wiley & Sons

Roberts SM, Weimar WR, Vinson JRT, Munson JW, Bergeron RJ (2002) Measurement of arsenic bioavailability in soil using a primate model. Toxicol Sci 67(2):303–310

Rodríguez VM, Carrizales L, Jimenez-Capdeville ME, Dufour L, Giordano M (2001) The effects of sodium arsenite exposure on behavioral parameters in the rat. Brain Res Bull 55(2):301–308

Rodríguez VM, Jiménez-Capdeville ME, Giordano M (2003) The effects of arsenic exposure on the nervous system. Toxicol Lett 145(1):1–18

Rodríguez-Barranco M, Lacasaña M, Aguilar-Garduño C, Alguacil J, Gil F, González-Alzaga B, Rojas-García A (2013) Association of arsenic, cadmium and manganese exposure with neurodevelopment and behavioural disorders in children: a systematic review and meta-analysis. Sci Total Environ 454:562–577

Rosado JL, Ronquillo D, Kordas K, Rojas O, Alatorre J, Lopez P et al (2007) Arsenic exposure and cognitive performance in Mexican schoolchildren. Environ Health Perspect 115(9):1371–1375

Rossman TG (2003) Mechanism of arsenic carcinogenesis: an integrated approach. Mutat Res/fundam Mol Mech Mutagenesis 533(1–2):37–65

Rouse J, Cohen P, Trigon S, Morange M, Alonso-Llamazares A, Zamanillo D, Hunt T, Nebreda AR (1994) A novel kinase cascade triggered by stress and heat shock that stimulates MAPKAP kinase-2 and phosphorylation of the small heat shock proteins. Cell 78(6):1027–1037

Roussel RR, Barchowsky A (2000) Arsenic inhibits NF-κB-mediated gene transcription by blocking IκB kinase activity and IκBα phosphorylation and degradation. Arch Biochem Biophys 377(1):204–212

Roy A, Kordas K, Lopez P, Rosado JL, Cebrian ME, Vargas GG, Ronquillo D, Stoltzfus RJ (2011) Association between arsenic exposure and behavior among first-graders from Torreón, Mexico. Environ Res 111(5):670–676

Russell DS (1937) Changes in the central nervous system following arsphenamine medication. J Pathol Bacteriol 45(2):357–366

Saxe JK, Bowers TS, Reid KR (2006) Arsenic. In: Morrison RD, Murphy BL (eds) Environmental forensics: contaminant specific guide. Academic Press, Burlington, MA, pp 279–292

Schoof RA, Eickhoff J, Yost LJ, Crecelius EA, Cragin DW, Meacher DM, Menzel DB (1999) Dietary exposure to inorganic arsenic. In: Arsenic exposure and health effects III. Elsevier Science Ltd., pp 81–88

Schug TT, Blawas AM, Gray K, Heindel JJ, Lawler CP (2015) Elucidating the links between endocrine disruptors and neurodevelopment. Endocrinology 156(6):1941–1951

Sharma A, Kshetrimayum C, Sadhu HG, Kumar S (2018) Arsenic-induced oxidative stress, cholinesterase activity in the brain of Swiss albino mice, and its amelioration by antioxidants Vitamin E and Coenzyme Q10. Environ Sci Pollut Res 25:23946–23953

Shumilla JA, Wetterhahn KE, Barchowsky A (1998) Inhibition of NF-κB binding to DNA by chromium, cadmium, mercury, zinc, and arsenite in vitro: evidence of a thiol mechanism. Arch Biochem Biophys 349(2):356–362

Sinczuk-Walczak H, Szymczak M, Halatek T (2010) Effects of occupational exposure to arsenic on the nervous system: clinical and neurophysiological studies. Int J Occup Med Environ Health 23(4):347–355

Smith ERG, Naidu R, Alston AM (1998) Arsenic in the soil environment

Tchounwou PB, Wilson B, Ishaque A (1999) Important considerations in the development of public health advisories for arsenic and arsenic-containing compounds in drinking water. Rev Environ Health 14(4):211–229

Tsai SY, Chou HY, The HW, Chen CM, Chen CJ (2003) The effects of chronic arsenic exposure from drinking water on the neurobehavioral development in adolescence. Neurotoxicology 24(4–5):747–753

Wang B, Liu J, Liu B, Liu X, Yu X (2018) Prenatal exposure to arsenic and neurobehavioral development of newborns in China. Environ Int 121:421–427

Wijeweera JB, Gandolfi AJ, Parrish A, Lantz RC (2001) Sodium arsenite enhances AP-1 and NFκ B DNA binding and induces stress protein expression in precision-cut rat lung slices. Toxicol Sci 61(2):283–294

Yamanaka K, Okada S (1994) Induction of lung-specific DNA damage by metabolically methylated arsenics via the production of free radicals. Environ Health Perspect 102(Suppl. 3):37–40

Yan-Chu H (1994) Arsenic distribution in soils. In: Nriagu JO (ed) Arsenic in the environment, part I; cycling and characterization. Wiley, Hoboken, NJ, pp 17–47

Yang C, Frenkel K (2002) Arsenic-mediated cellular signal transduction, transcription factor activation and aberrant gene expression: implications in carcinogenesis. J Environ Pathol Toxicol Oncol 21:331–342

Yost LJ, Tao SH, Egan SK, Barraj LM, Smith KM, Tsuji JS, Lowney YW, Schoof RA, Rachman NJ (2004) Estimation of dietary intake of inorganic arsenic in US children. Hum Ecol Risk Assess 10(3):473–483

Yousef MI, El-Demerdash FM, Radwan FM (2008) Sodium arsenite induced biochemical perturbations in rats: ameliorating effect of curcumin. Food Chem Toxicol 46(11):3506–3511

Zarazúa S, Pérez-Severiano F, Delgado JM, Martínez LM, Ortiz-Pérez D, Jiménez-Capdeville ME (2006) Decreased nitric oxide production in the rat brain after chronic arsenic exposure. Neurochem Res 31:1069–1077

Zhang TL, Gao YX, Lu JF, Wang K (2000) Arsenite, arsenate and vanadate affect human erythrocyte membrane. J Inorg Biochem 79(1–4):195–203

Zhao CQ, Young MR, Diwan BA, Coogan TP, Waalkes MP (1997) Association of arsenic-induced malignant transformation with DNA hypomethylation and aberrant gene expression. Proc Natl Acad Sci USA 94:10907–10912

Zheng W, Perry DF, Nelson DL, Aposhian HV (1991) Choroid plexus protects cerebrospinal fluid against toxic metals. FASEB J 5(8):2188–2193. https://doi.org/10.1096/fasebj.5.8.1850706

Zhou H, Zhao W, Ye L, Chen Z, Cui Y (2018) Postnatal low-concentration arsenic exposure induces autism-like behavior and affects frontal cortex neurogenesis in rats. Environ Toxicol Pharmacol 62:188–198

# Part III
# Arsenic Remediation Strategies

# Chapter 8
# Alginate-Based Biotechnological Approaches for Arsenic Removal


**Biswajit Pramanik, Ruchi Bharti, Rahul Kumar Gupta, Buddhadeb Duary, Kalipada Pramanik, and Sandip Debnath**

**Abstract** Arsenic (As) has created a jarring consequence on health of humans by diffusing in ground water to a much higher extent. Diverse natural as well as anthropological disturbance has created its path of release to the environment. Long-term exposure to this heavy metal not only results in skin cancer but also possesses the ability to cause malignance to several distinct organs like lungs, bladders and many more. Therefore, a numerous strategies have been investigated and applied for removal of this carcinogenic metal in order to refrain it from contaminating water. The alginate-based biotechnological tool has now evolved as an emerging hope in today's world. The larger surface to volume ratio, water-permeable and biocompatible nature have provided these adsorbent-impregnated alginate beads a much higher place in the arsenic removal technologies. Also, its easy generation procedures in a wider range of pH and concentrations have put an added advantage to it. Notably, its usage in commercial level has not been that much popularized till date. Hence, this chapter will elaborately describe the aspects from the evolution of alginate beads to regeneration through its encapsulation and impregnation, following its future scope of mass scale applications.

**Keywords** Alginate-encapsulation · Alginate-associated biotechnology · Arsenic contamination · Arsenic removal · Ground water

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## 8.1 Introduction

The carcinogenic effects of arsenic (As) toxicity, especially when dissolved in drinking water, has created a major global issue throughput the nations (Debnath et al. 2017). Arsenic, in its inorganic form, has already been declared as a potent carcinogen for human. More than 140 million inhabitants in almost 70 countries are undergoing arsenic contamination in groundwater, which has posed varying stages of threat to human health, when exposed for long term (Chatterjee et al. 2013; Kabir and Chowdhury 2017). Skin lesions due to this heavy metal toxicity were prevalent among the dwellers of various south-east Asian nations such as India, Vietnam, Bangladesh, and Cambodia (Chowdhury et al. 2016; Seth et al. 2020). Various general long-term impacts of arsenic exposure include malignancy, skin blemishes, gastrointestinal illness, etc. Further, peripheral neuropathy, diabetes, renal impairment, and cardiovascular diseases are four of the most prevalent medical conditions, as reported till date (Chowdhury et al. 2019). Throughout the globe, a few notable arsenic effected countries include India (Krishna et al. 2009; Chatterjee et al. 2011), Bangladesh (Chakraborti et al. 2013), Iran, China (Wade et al. 2009; Xia et al. 2009), Austria, New Zealand, different regions of Northern parts of Mali, Afghanistan, Taiwan, and Thailand (Ning 2002) and Argentina and Mexico (Chowdhury et al. 2016). Village communities in arsenic-striken developing nations are the most affected because of the scarcity of current technologies, higher expenses and complexity of arsenic removal technologies. In order to safeguard human population, World Health Organization (WHO), one of the leading regulatory bodies all over the world, limit the inorganic form of arsenic concentration in drinking water to 10 ppb (WHO 2017).

Among various conformations of inorganic arsenic (e.g., As(0, III, -III, V, etc.)), the most prevalent species are the pentavalent (arsenate) and trivalent (arsenite) one in groundwater, respectively, although the toxicity of the later is 20–60 times greater than that of former one (Debnath et al. 2016). In addition, As(III) possess greater thermodynamic stability and mobility (Chowdhury et al. 2019) in groundwater under reducing conditions than As(V). Researchers from numerous nations have been collaborating on several methodologies such as ion exchange, coagulation/co-precipitation, oxidation/precipitation, membrane adsorption technology, etc. for eliminating arsenic from the groundwater sources. Among all these approaches, the most prevalent one was adsorption, as reported (Mueller 2016). Inefficient operation and failure to minimize arsenic level below the WHO threshold of 10 parts per billion ppb, high operational and capital expenditures, sludge production, and numerous operational challenges remain the primary obstacles to the widespread implementation of the majority of accessible mechanisms (Jadhav et al. 2015; Kabir and Chowdhury 2017). The lesser costly arsenic removal techniques (namely chemical precipitation, oxidation, coagulation-precipitation-filtration, etc.) are typically not so much efficient at reducing both forms i.e. As(III) as well as As(V), below the recommended value. Nonetheless, minerals or biomaterials-mediated adsorption have demonstrated effective removal for aforesaid two forms of arsenic. The Fe-containing adsorbents

(i.e. iron oxides, hydroxides, and iron minerals), and alumina ($Al_2O_3$) have demonstrated superior removal performance of them. A number of previous investigations revealed the greater affinity of Fe oxides or hydroxides towards As(III) and As(V) (Giles et al. 2011). The lesser particle size an adsorbent owns, the higher surface area it possesses, which ultimately anticipate with higher removal rate of arsenic. Previous researches have revealed the inversely proportional relationship between the removal efficiency of arsenic with the particle size of iron i.e. magnetite ($Fe_3O_4$) (Yean et al. 2005; Mayo et al. 2007). Mayo et al. (2007) reported 200-fold enhancement in As(III), and As(V) removal efficiency by lowering the magnetite particle size 25 times. The maximal capacity for absorption increases 20 times in case of As(III), and 10 times for As(V), correspondingly, by lowering the magnetite particle size from 300 to 20 nm, i.e. 15 times (Yean et al. 2005). Additionally, generation and employment of adsorbents can cut down the total expense and formation of arsenic-stuffed sludge, which is essential for low-income families of the developing nations. Nonetheless, by means of the traditional protocols, it is frequently challenging to regenerate and reuse Fe-based adsorbents, mostly because of the strong reactivity and chemical stability of the nano-sized particles (Chung et al. 2014).

The efficiency of arsenic removal has been improved by doping or varnishing the Fe-originated adsorbents with several supportive substances such as activated carbon (AC), sand, zeolite, polymer, etc. (Chen et al. 2014). However, the all over expenses of those adsorbents (e.g., nanoparticles), sludge generation, and their re-employment are all causes for concern. Therefore, irregular alginate beads have now been utilized to address these concerns. Alginate comes with several major advantages like lower pricing, superior biological compatibility, higher aqua-permeability, abundance in marine condition, etc. Prior researches have demonstrated the implementation of iron-based adsorbents-encapsulated alginate beads such as goethite, hydrous Fe-oxide, mineral akageneite, Fe-containing wastewater residuals and many more in arsenic removal treatment (Basu et al. 2015; Ociński et al. 2016; Sigdel et al. 2016). The aforementioned adsorbents provided more than 95% elimination across a wide spectra of preliminary arsenic concentrations between 10 and 1000 ppb, as well as pH i.e. 3.0–7.5 (Basu et al. 2015; Ociński et al. 2016).

The present chapter elaborately deals with the research-oriented advancements regarding the deployment of alginate-based adsorbents including the generation of alginate beads, encapsulation and impregnation of the adsorbents inside the beads, their application, performance, and regeneration, for arsenic eradication from water. Furthermore, the pros and cons of the methodologies were assessed along the scopes of future research. In addition, the current circumstances of knowledge and future directions of research were emphasised in the following sections.

## 8.2 Forms of Arsenic in Water

Natural water predominantly contains two species of arsenic i.e. trivalent and pentavalent one. The particulate or colloidal state occupies almost 10–20% of total arsenic in water, whereas the dissolved state contributes the majority. These states were defined according to their weight viz. the dissolved state consists of less than 3000 Da weight, the colloidal form owns a weight between 3000 Da and 0.45 μm, and more than 0.45 μm is considered as particulate one (Chowdhury et al. 2019). The proportion of colloidal and dissolved state shares a directly proportional relationship to the presence of dissolved organic matter (DOM) in groundwater. Further, both the ratio of Fe to C, and the molecular dispersion of humic acid also influence the colloidal percentage of arsenic. At pH status of 4.0, particle arsenic concentrations reach the maximum limit (Bauer and Blodau 2009). Further to mention, arsenite [As(III)] is predominant in groundwater, whereas arsenate [As(V)] predominantly occupies a major portion in surface water.

## 8.3 Current Technological Adaptations Towards Arsenic Removal

There are five basic categories of arsenic removal technologies, namely membrane separation, precipitation, ion exchange, adsorption, and biotechnological approaches. Among them, biotechnological approach trends the most in recent times. Each category carries its own pros and cons. There is no single low-cost solution for removing arsenic to levels below the WHO standard. While summarizing all the adaptive technologies in the following sections, biotechnological approach has been widely researched, with a particular emphasis on alginate-based technologies in this present chapter.

### *8.3.1 Membrane Separation*

Micropore containing membranes serve as a barrier for selected components. Two approaches are usually used to separate arsenic viz. size exclusion on the basis of pore sizes and Donnan exclusion principal using charge repulsion technology (Shih 2005). Forward osmosis (FO), reverse osmosis (RO), microfiltration (MF), nanofiltration (NF), ultrafiltration (UF), electrodialysis (ED), and porous ceramic membranes (PCM) are the most prevalent membrane techniques for arsenic removal. Larger diameters of bigger pores prevent MF or UF from removing dissolved arsenic from water (Velizarov et al. 2004), which can be made effective by enlarging the particle size of As-containing species itself. Singh et al. (2015) found that coagulation and precipitation techniques followed by MF or UF can be an efficient method for

arsenic removal. Further to mention, both RO and NF are very much effective at lowering arsenic concentrations, especially arsenate, to < 10 μg/l. This indicates that water must be oxidised beforehand (Nicomel et al. 2016). Nonetheless, costing of these procedures remains at higher side.

### 8.3.2 Precipitation

The whole precipitation process involves coagulation and flocculation, or oxidation followed by precipitation itself and subsequently separation (Pal 2015). During the procedure, chemicals are introduced to transform solubility status of arsenic, resulting in precipitation. The coagulation-flocculation procedures consist of alum or iron (Fe) coagulation, electrocoagulation, lime softening, and Mn and Fe co-precipitation (Singh et al. 2015). As(III) is commonly transformed to As(V) through oxidation to improve performance during the removal procedure (Nicomel et al. 2016). An array of oxidants is used during oxidation processes, which include chlorine ($Cl_2$), chlorine dioxide ($ClO_2$), chloramine ($NH_2Cl$), hydrogen peroxide ($H_2O_2$), ozone ($O_3$), ferrate ($FeO_4^{2-}$), and permanganate ($MnO_4^-$). Moreover, photocatalytic oxidation, photochemical oxidation, and biological oxidation are other oxidation technologies (Singh et al. 2015). Notably, As(III) is reportedly highly hazardous than As(V), followed by monomethylarsonate (MMA) and dimethylarsinate (DMA) (Jain and Singh 2012).

### 8.3.3 Ion Exchange

During this procedure, ions exchange take place between the feed water and the solid resin state. The exchange basically happens between ions with similar charges, and its rate is dependent upon the exchange affinity of the resin. To remove arsenic, strong-base anion exchange resins are utilised. The negatively charged functional group of resins is replaced by oxy-anionic species of pentavalent arsenical compounds (such as $H_2AsO_4^-$, $HAsO_4^{2-}$, and $AsO_4^{3-}$) (Choong et al. 2007). Therefore, the peroxidation of As(III) to As(V) is the most prevalent prerequisite of the ion exchange mechanism. However, excess oxidants must be eliminated to prevent harm to the sensitive resin (Singh et al. 2015).

The effectiveness of the whole procedure depends on pH, and concentration of competing ions, such as sulphate ($SO_4^{2-}$) and nitrate ($NO_2^-$), and the type of resin used (Singh et al. 2015). The concentrations of total dissolved solids can have a substantial effect on efficiency, as reported (Singh et al. 2015). This costly procedure is able to lower the level of arsenic within 10 g/l.

### 8.3.4 Adsorption

One of the most affordable protocols for arsenic removal is adsorption (Zhang et al. 2007). The most common adsorbents include AC, Zr-loaded AC, alumina, zeolites, Fe oxides, clay, amorphous $FePO_4$, $TiO_2$, $MnO_2$, $MnO_2$-loaded resin, goethite, gibbsite, kaolinite, natural zeolites (e.g., clinoptilolite), clinoptilolite-iron oxide, iron oxide-coated cement, portland cement, etc. (Han et al. 2013; Pal 2015).

Chowdhury et al. (2016) found that despite being little bit more expensive, Fe- and $Al_2O_3$-based adsorption techniques are effective in reducing arsenic to < 10 g/l. Typically, low-cost adsorbents are ineffective at lowering arsenic below this amount (Kabir and Chowdhury 2017). As this method do not require extra chemicals, the chance of producing harmful byproducts is also very much less (Jang et al. 2008). Similarly, like aforesaid procedures, adsorption efficiency is strongly reliant on pH and the accumulation of certain ions. As instance, lower range of pH (mostly within 3–5) is recommended for the As(V) adsorption, but the optimal pH range for the adsorption of the other form of arsenic i.e. As(III) is 4–9 (Lenoble et al. 2002). In the presence of additional ions like phosphate and silicate, the loss of adsorption sites can reduce the efficiency (Giles et al. 2011). In addition, the effectiveness of the procedures depends on the adsorbent itself. The operations are expected to generate arsenic-contaminated sludge, which must be disposed of with care.

### 8.3.5 Bio-integrated Technologies

Bioremediation or biotechnologies for the elimination of arsenic are a recent development. In general, phytoremediation and bio-filtration are used as two major pillars of these bio-integrated technologies (Fazi et al. 2016). The former one is a plant-based method in which plants (such as Chinese brake fern) and microorganisms are employed to remove arsenic (Behera 2013), whereas only several genera of bacteria (such as *Bacillus* sp., *Paenibacillus*, *Haemophilus*, sulfate-reducing bacteria, etc.) are employed to remove arsenic from water in the latter (Singh et al. 2015). However, biofiltration comes with a backdrop of recontamination ability of bacteria, their toxicity, and adverse effects on humans, which are still in research though (Singh et al. 2015).

Now-a-days, biosorption has gained popularity in this regard (Baig et al. 2010). The biodegradability and environmental friendliness of bio-composites has attracted numerous researchers in recent years (Ray 2013; Mishra 2015; Aizat and Aziz 2019). Bio-composites are mostly composed of biopolymers viz. chitin, alginate, chitosan, and microalgae. These easily available composites are eco-friendly in nature, and inexpensive too (Zhang et al. 2013; Rahim and Mas Haris 2015; Abdellaoui et al. 2021; Basu et al. 2021; Zeng et al. 2022). Among the biopolymers, adsorbent-impregnated, or coated alginate beads have shown > 95% eradication efficiencies for arsenic concentrations ranging between 10 and 1000 g/l, embracing a much wide

pH range (3.0–7.5) (Bezbaruah et al. 2014; Singh et al. 2014; Ociński et al. 2016). The subsequent sections will discuss the bio-integrated technologies based on alginate in greater depth.

## 8.4 Alginate-Based Biotechnological Advancement

### *8.4.1 Structure of Alginate*

Alginate is basically an alginic acid-derived salt and is classified as an exopolysaccharide. It consists of nonrepetitive copolymers of β-D-mannuronic acid (M) and α-L-glucuronic acid (G), linked through 1 → 4 glycosidic bond. These comonomers are generally organised in M-blocks, G-blocks, sometimes even alternating both. The alginate is derived from the cell walls of various brown seaweeds (e.g., *Laminaria hyperborea*, *L. digitate*, *Macrocystis pyrifera*, *Ascophyllum nodosum*, etc.). These naturally abundant, inexpensive material possess low toxicity and mild gelation properties, which make them well-known for adsorbent impregnation (Gombotz and Wee 2012; Lee and Mooney 2012). Brown seaweeds are crushed and dispersed in distilled water after which, HCl is added. This procedure converts alginate into insoluble alginic acid, which gets solubilized through reaction with $Na_2CO_3$ or NaOH to generate sodium alginate. In the presence of NaCl, sodium alginate is precipitated, after which it is rinsed with ethanol ($C_2H_5OH$) (Rahelivao et al. 2013). The molecular weight of commercial sodium alginate varies between 32 and 400 kDa (Lee and Mooney 2012). Alginate's viscosity can be enhanced by lowering its pH to an acidic range, among which maximum viscosity occurs between pH 3.0 and 3.5 (Lee and Mooney 2012). Alginate polymers biosynthesized by bacteria (e.g., *Azotobacter*, *Pseudomonas*, etc.) have superior physical as well as chemical characteristics for encapsulation. Further to mention, alginate is generally used as a gelling or thickening ingredient (Pramanik et al. 2021; Das et al. 2021).

Calcium alginate beads are produced by mixing an aqueous alginate solution with cross-linking divalent cations like $Ca^{2+}$. Gel structure is created when the G-blocks of one polymer combine with that of the neighbouring polymer in sequence (Lee and Mooney 2012). $CaCl_2$ is the most prevalent cross-linking agent due to its high solubility. The accelerated gelation process may be regulated by the introduction of a phosphate buffer such as sodium hexametaphosphate, or by cross-linking with $CaSO_4$ or $CaCO_3$ when extra reaction time is provided (Crow and Nelson 2006). By regulating the gelation rate, flow, and reaction temperature, the homogeneity and strength of alginate beads may be maintained. Gel strength rises according to the increasing molecular weight of alginate (Kakita and Kamishima 2008). Therefore, mixing both high and low molecular alginate, the gel's elasticity modulus may be improved with little viscosity rise (Lee and Mooney 2012).

## 8.4.2 Generation of Cross-Linked Alginate Beads

### 8.4.2.1 Ca-Alginate Beads

The 1–3% (w/v) Na alginate is added in deionized water to produce aqueous solution of alginate, which is mechanically shaken to convert into a viscous one. First, this solution is introduced at a constant stream rate from a height of 6 to 7 cm into a $CaCl_2$ solution, that is agitated at 60 rpm (Zouboulis and Katsoyiannis 2002). Following proper formation of Ca-alginate beads, they undergo curation procedure for specific period of time. Then the beads are rinsed with water. Singh et al. (2014) found that Ca-alginate removes nearby high of the arsenic from water samples. As(V) adsorption capacity of Ca-alginate, cross-linked with carboxymethyl cellulose, was 4.39 mg/g, as reported by Tiwari et al. (2008).

### 8.4.2.2 Fe-Alginate Beads

The generation of Fe-alginate beads follows two major steps. Among them, in the first step, sodium is introduced into deionized water to generate the aqueous solution of sodium alginate, which, in the later step, mixed with ferric chloride ($FeCl_3$) solution, at a very steady pace. After this, these beads are thoroughly washed with distilled water many times after proper curation, for maintaining proper aseptic condition. During their experiment, Dong et al. (2011) generated Fe-alginate beads by adding 5 ml Na-alginate solution into 250 ml $FeCl_3$ solution at a constant rate of 1 ml/min, after which the solution was agitated at a pace of 60 rpm. Moreover, the beads have undergone a curation period of 6 h. In order to create Fe-alginate beads, coordination of $Fe^{3+}$ ions with oxygen atoms in –COOH groups from alginate glucose chains took place (Dong et al. 2011). Further to mention, Fe-alginate beads have poor structural stability. due to surface cracking and excessive peeling, which also added a major disadvantage behind its implementation.

### 8.4.2.3 Ca–Fe Alginate Beads

Ca–Fe alginate beads are produced by entrapping hydrous or typical Fe oxide on Ca-alginate beads. $Ca^{2+}$ ions operate as a gel-formative agent and thus, offer a strong framework for the creation of a polymeric net like structure in the beads. The substitution of Ca ions by Fe ions provides suitable arsenic sorption sites. Beads' porous structure permits the diffusion as well as migration of trace pollutants towards the impregnated adsorbent. Several regulatory conditions operate these Ca–Fe bead production as well (Table 8.1).

There are several methods for producing Ca–Fe alginate beads with varying efficiency for removing arsenic from drinking water (Bezbaruah et al. 2014). Fe can

**Table 8.1** Effect of various parameters on different alginate beads

| Types of alginate beads | Bead size (mm/nm*) | Prerequisites for bead formation | Conc. of Na-alginate (w/v) | Gelation matrix | Curing time (h) | References |
|---|---|---|---|---|---|---|
| Fe(III) treated | 2 | Peristaltic pump, 0.30 mm ID tubing, 7 cm height | 2% | 0.1 M $FeCl_3$ | 72 | Min and Hering (1998) |
| Fe-oxide loaded | 3 | One drop of polymer solution dispensed per second, 6 cm height | 2% | 0.3 M $CaCl_2$ | 24 | Zouboulis and Katsoyiannis (2002) |
| Fe-doped | 1.5–1.7 | Drop wise addition with continuous agitation | 3% | 0.1 M $FeCl_3$ + 0.1 M $CaCl_2{\cdot}2H_2O$ | 24 | Banerjee et al. (2007) |
| Goethite composite | 2.23 | Plastic pipe at tip of pipette, 6 cm height, 400 rpm | 1% | 0.3 M $CaCl_2$ | 24 | Lazaridis and Charalambous (2005) |
| Fe NPs | 0.5 | Peristaltic pump, 0.5 mm ID tubing, 2.5 ml/min flow rate | 2% | 3.5% (v/v) $CaCl_2$ | | Bezbaruah et al. (2009) |
| Waste metal hydroxide | 3 | Peristaltic pump, 350 ml/h flow rate | 1% | 0.1 M $CaCl_2$ | 24 | Escudero et al. (2009) |
| $Fe_3O_4$ particles | NM | Synthesized $Fe_3O_4$ dripped through a needle connected to a high voltage power generator | NM | Particles of diameter of 309.6 μm | NM | Lim et al. (2009) |
| $Fe_3O_4$ NPs | 2 | Dispersion of $Fe_3O_4$ NPs into Na-alginate | 2% | 0.2 M $CaCl_2$ | 24 | Luna-Pineda et al. (2009) |
| nZVI | 1 | Peristaltic pump | 2% | 0.05 M $Fe^{3+}$ | 48 | Kim et al. (2010) |
| Immobilization of $Fe_3O_4$ NPs | 2–3 | 2% w/v $Fe_2O_3$ + 2% w/v Na alginate into $CaCl_2$ solution | 2% | 10% w/v $CaCl_2$ | 12 | Harikumar and Joseph (2012) |

(continued)

**Table 8.1** (continued)

| Types of alginate beads | Bead size (mm/nm*) | Prerequisites for bead formation | Conc. of Na-alginate (w/v) | Gelation matrix | Curing time (h) | References |
|---|---|---|---|---|---|---|
| Cross-linking of $Fe(OH)_3$ colloids | 2.2 ± 0.3 | Cross-linking of $Fe(OH)_3$ colloids | 2% alginic acid | 0.1 M $CaCl_2$ + 0.02 M $FeCl_3$ | 24 | Sánchez-Rivera et al. (2013) |
| nZVI loaded | 3.4 ± 0.13 | Peristaltic pump, 0.5 mm ID tubing, 2.5 ml/min flow rate | 2% | 4.6% $CaCl_2$ | 6–9 | Bezbaruah et al. (2014) |
| Akaganeite nanorods | 0.4–2 | Akaganeite nanorods added to Ca-alginate using electrostatic droplet method | 2% | 1% $CaCl_2$ | NM | Cho et al. (2014) |
| Ca cross-linked | 31–43 | 1000 rpm agitation, 30 min, 30 °C | NM | 0.5 M $CaCl_2$ | 2 | Singh et al. (2014) |
| Fe(III) cross-linked | | | | 0.5 M $FeCl_3$ | | |
| Hydrous Fe oxide loaded | 1.1 | Addition of hydrous Fe oxide, 4 h magnetic mixing | 3% | 3% (v/v) $CaCl_2$ | 6 | Sigdel et al. (2016) |
| WTR | 2.5 | WTR suspension + Na alginate solution added to $CaCl_2$ | 1–4% (w/w) | 0.1 M $CaCl_2$ | 48 | Ociński et al. (2016) |
| Immobilized hydrous $Fe_2O_3$ | 3 | Addition by 5 ml syringe having 1.7 mm diameter needle | 3% | 0.05 M $CaCl_2$ | Overnight | Jung et al. (2017) |
| Crosslinked chitosan | 144 ± 11* | Drop wise addition and shaking for 3 h for cross-linking reaction at room temperature | 2% | 1 M $Na_5P_3O_{10}$ | 3 | Bajpai (2019) |
| | | | 8% | 1 M $CaCl_2$ | | |
| Alum sludge | 0.8 | $CaCl_2$ was added drop by drop using peristaltic pump and a needle syringe | 2% | 0.1 M $CaCl_2$ | 48 | Kang et al. (2019) |
| Heated CAFBs | 5.680* | Peristaltic pump and magnetic stirring at 200 rpm | 4.5% | 1% $CaCl_2$ | 24 | Zeng et al. (2020) |
| Fe–Zr composite | 0.35–0.40 | Dropwise mixed through a syringe under agitation | 2% | 0.5 M $CaCl_2$ | 2 | Abdellaoui et al. (2021) |

(continued)

**Table 8.1** (continued)

| Types of alginate beads | Bead size (mm/nm*) | Prerequisites for bead formation | Conc. of Na-alginate (w/v) | Gelation matrix | Curing time (h) | References |
|---|---|---|---|---|---|---|
| Graphene oxide-$MnO_2$-goethite | 1.9 ± 0.1 | Slow addition of $FeCl_2$ and $KMnO_4$ under continuous stirring at 400 rpm | 3% | 3% (w/v) $CaCl_2$ | 24 | Basu et al. (2021) |
| Zr-chitosan composite | 2–3 | Addition by continuous agitation for 1 h under heating condition | 2% | 2% $CaCl_2$ | 24 | Lou et al. (2021) |
| Fe-oxyhydroxide composite | 5 | Drop wise addition at agitation rate of 800 rpm | NM | 0.3 M $CaCl_2$ | 24 | Rawat and Maiti (2021) |
| Functionalized chitosan electrospun nanofiber | 164* | Electrospinning at 16 kV at a flow rate of 0.6 ml/min, needle height 15 cm | 3% | 8% PVA | 24 | Talukder et al. (2021) |
| Mn-crosslinked composite | NM | Peristaltic pump, flow rate 1.5 ml/min | 2% | 200 ml $MnSO_4$ or $MnCl_2$ | 24 | Mao et al. (2022) |

Abbreviations: *°C* degree Celsius, *Ca* calcium, *$CaCl_2$* calcium chloride, *CAFBs* chitosan alginate Fe-sludge beads, *Conc.* concentration, *cm* centimetre, *$Fe(OH)_3$* ferric hydroxide, *Fe* iron, *$Fe_2O_3$* ferric oxide, *$Fe_3O_4$* magnetite, *$FeCl_3$* ferric chloride, *h* hours, *$H_2O$* water, *kV* kilo volt, *min* minutes, *ml* millilitre, *mm* millimetre, *Mn* manganese, *$MnCl_2$* manganese chloride, *$MnSO_4$* manganese sulphate, *$Na_5P_3O_{10}$* sodium tripolyphosphate, *NM* not mentioned, *Na* sodium, *NPs* nanoparticles, *nZVI* nano zero valent iron, *PVA* poly vinyl alcohol, *rpm* revolutions per minute, *WTR* water treatment residuals

* denotes nm (nanometer)

be added to Ca–Fe alginate beads before or during gel formation in various protocols followed. During the first method, Na-alginate is solubilized in 1–3% (w/v) deoxygenated and deionized water, and aggressively stirred by a magnetic stirrer for 3–5 h at 25 ± 2 °C in order to create a homogenous mixture, after which the same is allowed to wait for near about 30 min for the bubbles to be evacuated. After that, various Fe-based adsorbents like Fe-containing minerals and wastes, nano zero valent iron (nZVI) are introduced to the solution and agitated using a glass rod. Finally, the well-mixed sample is again allowed to rest for around 30 min for the air bubbles to expel out. The solution is then introduced drop-by-drop into the $Ca^{2+}$ solution at a predetermined flow rate and from a specified height. Continuous stirring of the solution during pumping transforms the entire volume into beads. Bezbaruah et al. (2014) reported that the hardening procedure in $CaCl_2$ solution ran for about 6–9 h to attain the desired hardness and porosity of the beads. Instead of Na-alginate, $FeCl_3$ is added to the $Ca^{2+}$ solution in the second method. $CaCl_2$ and $FeCl_3$ of concentrations ranging from 0.1 to 0.3 M and 0.1 to 0.5 M, respectively, are mixed at 60 rpm (Singh et al. 2014), and following that, drop-wise addition of Na-alginate to the Ca–Fe solution took place at a constant rate of 300–400 ml/h from a height of 6 to 12 cm. Escudero et al. (2009) described about the implication of a peristaltic pump to achieve an adequate flow rate. The combination undergoes a prolonged period of cross-linking process of 9–24 h. This step helps in immobilization of the Fe ions inside the beads, which are subsequently dried at 25 ± 2 °C for about 3 days (Sánchez-Rivera et al. 2013).

Reportedly, Ca–Fe beads are able to remove roughly 94% of arsenic (Chowdhury et al. 2019). Another previous report suggested complete removal of inorganic arsenic with the implementation of Ca–Fe alginate beads at a rate of 34 mg/kg at a pH of 3.0 (Banerjee et al. 2007). The Fe-based adsorbents viz. nZVI, Fe minerals etc. impregnated into Ca-alginate beads retained their adsorption ability, which took an advantage over the traditional one (Bezbaruah et al. 2009). Zouboulis and Katsoyiannis (2002) compared the efficacy of three distinct types of Ca-alginate beads for arsenic elimination, namely hydrous iron oxide (HIO)-doped, HIO-coated, and a mixture of the both, among which the last one was proven to be more efficient. Both Ca-alginate as well as Ca–Fe alginate beads undergo $Fe(NO_3)_3$ treatment at pH 5, where insoluble $Fe_2O_3$ are found, to complete the coating.

The optimal period for Fe coating was found to be 24 h, although the arsenic removal rate for longer durations (i.e. 96 h) was observed to be the same as for 24 h. By raising the concentration of the $Fe(NO_3)_3$ solution, it is possible to enhance the iron content of the beads. As a fixed bed, alginate beads-filled glass columns with 40 cm height, 1.43 cm inner radius, and porosity of 0.33, were utilised. The greatest quantity of arsenic sorbed onto HIO-doped, HIO-coated, and HIO-doped and coated Ca-alginate beads were 4.75, 2.6, and 7.2 μg/g of wet alginate beads, accordingly (Zouboulis and Katsoyiannis 2002). The effluent concentrations of As(V) were lower than the WHO recommended value of 10 g/l for bed volumes of 80, 45, and 230, subsequently.

#### 8.4.2.4 Cross-Linked Alginate Nanoparticles

By dissolving Na-alginate in deionized water and paraffin oil, the aqueous and oil states of alginate solutions may be formed, respectively. $FeCl_3$ is admixed to the solutions at the time of vigorous agitation at 1000 rpm for 30 min, for Fe cross-linking (Table 8.1). Singh et al. (2014) determined that 2 h of cross-linking reaction at a regulated temperature of 30 °C was able to generate brownish-white Fe cross-linked alginate particles with a size of 31–43 nm. They also stated that these Fe cross-linked alginate nanoparticles possessed the capability of eliminating almost 70% of As(V). $FeCl_3$ was replaced by $CaCl_2$ while the reaction of Ca cross-linking, which ultimately resulted in the formation of white hue. They also demonstrated 45% elimination of As(V) using these nanoparticles. In addition, Bajpai (2019) employed chitosan nanoparticles cross-linked with alginate beads for removal of arsenic. Three hours were utilised for proper cross-linking reaction to occur in room temperature.

### *8.4.3 Alginate-Based Technologies for Arsenic Removal*

#### 8.4.3.1 Hydrous Iron Oxides (HIO)

Metal oxide adsorbents (such as ferric and aluminium oxides) were previously reported to exhibit excellent adsorption efficiency for arsenic elimination (Reddy et al. 2013). Both higher porosity and larger surface area made the HIO or Fe(III) oxide-hydroxide encapsulated alginate beads excellent for arsenic removal (Sigdel et al. 2016). Several researchers reported of adsorbing 4.4–13.8 mg/g of arsenic, especially As(V), with the employment of HIO-impregnated beads (Table 8.2). Jung et al. (2017) demonstrated that the presence of $Cu^{2+}$ ions generated an elevation in the adsorption efficiency. The adsorption efficiency of As(III) was found to be 47.8 mg/g and the same for As(V) was 55.1 mg/g, for a 9:1 Na-alginate to Fe ratio (Sigdel et al. 2016). More than 99% elimination of both the forms was also reported by using alginate beads-loaded ferric hydroxide [$Fe(OH)_3$] microcapsules (Table 8.2). Notably, the concentration of HIO was inversely proportional to the adsorption efficiency of As(V), most likely reason behind which was the change in the adsorption area. Moreover, increased residence time enhanced the adsorption capabilities for As(III) as well as As(V). Although the optimal pH range for As(V) adsorption was found between 6 and 9, slightly acidic solutions were desirable (Sigdel et al. 2016). The higher pH (more than 9.0) resulted in the increase in negatively charged adsorption sites, which eventually enhanced the repulsive forces in order to decrease arsenic adsorption capacity (Jung et al. 2017).

**Table 8.2** Activities of different adsorbents impregnated or coated in alginate beads

| Adsorbents | Advantages | Disadvantages | References |
|---|---|---|---|
| Fe(III) treated alginate beads | Up to 94% elimination of As(V) from an initial concentration of 400 μg/l by equilibration with 20 Ca–Fe beads at pH 4.0 for 120 h | Slow sorption kinetics | Min and Hering (1998) |
| Fe-coated Ca–Fe alginate beads | Maximum absorption capacity was 7.2 μg of As/g of wet alginate bead, or 1.8 μg of As/mg of Fe | Essential pre-oxidation step | Zouboulis and Katsoyiannis (2002) |
| Fe-doped Ca beads | 96.6% adsorption of As(V) at pH 3.0 and 40% adsorption of As(III) at pH 8. Maximum adsorption was found at 20 min for pH 3.0 | Up to 70% As(V) can be eliminated from Ca–Fe beads | Banerjee et al. (2007) |
| $Fe_3O_4$ particles encapsulated by Ca alginate | 6.75 mg/g of As can be absorbed | Pre-oxidation of As(III) is essential | Lim and Chen (2007) |
| Adsorption onto alginate and carboxymethyl cellulose beads | Adsorption capacity 4.39 mg/g for As(V) | Adsorption rate is reduced when temperature goes beyond 26 °C | Tiwari et al. (2008) |
| Alginate-based magnetic nanocomposites | The uptake capacity of $Fe_3O_4$ was 1.10 mg/g sorbent for As(V), and 1.04 mg/g sorbent for As(III). The corresponding removal efficiencies were 45.9 and 32.3% | The uptake capacity of the beads is lower than the bare magnetic nanocomposites | Luna-Pineda et al. (2009) |
| $Fe(OH)_3$ microencapsulated in Ca-alginate | Loading capacity 3.8 mg As/g of adsorbent, removal efficiency > 99% for both As(V) and As(III) from a starting concentration of 300 μg/l | Safe disposal of the bed is necessary | Sarkar et al. (2010) |
| Ca–Fe(III) alginate beads | Maximum uptake 0.364 mg/g for and 0.117 (mg/g) for As(V) and As(III), respectively. Initial As concentration of 100 μg/l removed up to 54% for As(III) (at pH 4.0–8.0) and 80% for As(V) (maximum at pH 2.0) | The sorption capacity of As(V) was inversely proportional to pH | Sánchez-Rivera et al. (2013) |

(continued)

**Table 8.2** (continued)

| Adsorbents | Advantages | Disadvantages | References |
|---|---|---|---|
| Ca alginate/activated carbon composite beads (GC) | Highest As(V) adsorption of 66.7 mg/g at 30 °C within 60 min | Lower adsorption at acidic condition (pH less than 6.0) | Hassan et al. (2014) |
| Fe(III) oxide-hydroxide/ chloride, mineral akageneite [$Fe^{3+}O(OH,Cl)$] | 100 ppb concentration of As can be reduced up to 0.9 ppb in 10 min | The adsorption capacity was higher in bare akageneite nanorods | Cho et al. (2014) |
| nZVI entrapped Ca-alginate beads | Initial 50–10,000 μg/l aqueous arsenic reduced up to 85–100% within 2 h, groundwater with 53 μg/l As(V) reduced to below 10 μg/l within 1 h | Necessary step of pre-oxidation of As(III) to be followed | Bezbaruah et al. (2014) |
| Fe(III) cross-linked alginate nanoparticles (31–43 nm) | Equilibrium loading capacity 0.0553 ± 0.0016 mg/g. Removal efficiency 69.12% for initial As(V) concentration of 1000 μg/l | Difficult separation procedure of nanoparticles from treated water | Singh et al. (2014) |
| Fe bearing hydroxide mineral goethite (α-FeO(OH)) impregnated Ca alginate beads | Removal is > 95% for concentration range of 10–10,000 ppb. Maximum adsorption 30.44 mg/g. Reduced to 8–25 ppb from 10 to 500 ppb initial concentration | Adsorption decreases in both acidic as well as alkaline condition | Basu et al. (2015) |
| WTR alginate beads | Maximum sorption capacity 4 mg/g and 2.9 mg/g for As(III) and As(V) in pH range of 3.0–7.5, respectively | Pre-treatment of WTR was necessary | Ociński et al. (2016) |
| HZO immobilized alginate beads | Maximum sorption capacities of 32.3 mg/g for As(III) and 28.5 mg/g for As(V) | Bare HZO possess greater adsorption capacity | Kwon et al. (2016) |

(continued)

**Table 8.2** (continued)

| Adsorbents | Advantages | Disadvantages | References |
|---|---|---|---|
| HIO loaded alginate beads | Adsorption efficiency for both As(III) and As(V) directly proportional to HIO loading capacity, 47.8 mg/g adsorption for As(III) and 55.1 mg/g adsorption for As(V) at pH ranging within 6–9 | Lesser efficiency at both lower and higher pH condition | Sigdel et al. (2016) |
| HIO loaded alginate beads | The maximum sorption capacity of As(V) was 13.8 mg/g after 168 h. The adsorption level of As(V) was higher in strongly acidic pH solution | Adsorption rate decreases in alkaline condition (pH > 7) | Jung et al. (2017) |

Abbreviations: *°C* degree celsius, *As* arsenic, *Ca* calcium, *$Fe(OH)_3$* ferric hydroxide, *Fe* iron, *$Fe_3O_4$* magnetite, *g* grams, *h* hours, *HIO* hydrous iron oxide, *HZO* hydrous zirconium oxide, *l* litres, *mg* milligrams, *min* minutes, *nZVI* nano zero valent iron, *ppb* parts per billion, *WTR* water treatment residuals, *$\mu g$* microgram

#### 8.4.3.2 Magnetite ($Fe_3O_4$)

Magnetite nanoparticles (MNP) possess higher arsenic absorption ability due to available porosity inside (Liu et al. 2015). After combining 2,3-dimercaptosuccinic acid (DMSA)-functionalized ultrasonicated MNP with Na-alginate, this combination was admixed with $CaCl_2$ solution to generate encapsulated beads (Luna-Pineda et al. 2009). MNP alginate beads were able to adsorb 1.10 mg and 1.04 mg for per gram of As(V) and As(III), respectively, which was significantly lower than that of MNP only. Notably, the capacity for absorption of singular MNP for both the arsenical forms were 4.78 and 3.34 mg/g, subsequently (Luna-Pineda et al. 2009). The diminishing adsorption rates were observed for MNP alginate beads because of the presence of –COOH or S atoms during the functionalization process in the presence of DMSA. Harikumar and Joseph (2012) reported that deployment of 10 g of MNP alginate beads possessed the ability to eliminate around 75% of As(III) from an aqueous solution concentrating 2 mg/l, and 97.5% elimination could occur 25 g of the same beads were employed in the same concentration of solution. Moreover, to indicate, 39% and almost 99% of the arsenic found in a air-free and nitrogen-free circumstances, respectively, within the MNP alginate beads, as reported (Lim et al. 2009).

#### 8.4.3.3 Industrial Wastes

One of the most efficient techniques to remove arsenic is the utilization of industrial wastes. Metal oxides carried with industrial wastes such as water treatment plant

residuals (WTR) impregnated within the beads' matrix were reportedly effective at extracting arsenic (Ociński et al. 2016). WTR alginate beads were produced by dripping a combination of ultrasonically disrupted WTR and Na-alginate into the $CaCl_2$ solution. These beads possessed the sorption capacity of 3.4 mg/g for As(III) and 2.9 mg/g for As(V) throughout a broad pH range (3.0–7.5) (Ociński et al. 2016). According to the WTR content in alginate beads and their use, the adsorption capacities for As(III) was reported to be 38.2 mg/g, and that for As(V) was 32.6 mg/g. Nonetheless, these concentrations were much lower than that of only WTR (77 mg/g and 132 mg/g for As(V) and As(III), respectively). The WTR was made of oxo-hydroxides (containing 25% Fe), Fe oxides and Mn oxides (composed of 5% Mn). It also owned a wider surface area of 120 $m^2$/g. The lower capabilities of WTR alginate beads were due to the negatively charged –COOH groups inside. For arsenic adsorption, one of the most crucial characteristics is Na-alginate: metal oxides. 5% WTR along with 1% alginate solution exhibited the highest performance of the beads (Ociński et al. 2016). Alginate solution, at a higher concentration, resulted in an elevation in –COOH groups, which eventually depleted the arsenic adsorption capability.

#### 8.4.3.4 Iron (Fe) Minerals

Fe-bearing minerals (such as akaganeite [$Fe_3O(OH{\cdot}Cl)$], and goethite [α-FeO(OH)]) infused within alginate beads have been studied for arsenic elimination in various prior researches (Cho et al. 2014; Basu et al. 2015). Increased amount of goethite inside the alginate beads improved arsenic adsorption capability, whereas the optimal arsenic adsorption rate for goethite was 18% (Basu et al. 2015). In the same study, higher goethite concentrations (more than 24%) reportedly led to the ill-formation of proper bead structure, causing their fragility. From a broad spectrum of early arsenic concentrations of 10–10,000 ppb, goethite-entrapped Ca-alginate beads were able to eliminate 90% of arsenic at 2535 °C temperature with a pH value ranging within 3.0–7.5 (Basu et al. 2015).

#### 8.4.3.5 Nano Zero Valent Iron (nZVI)

Using nZVI-impregnated alginate beads to remove arsenic from groundwater has been proven before (Bezbaruah et al. 2014). In that experiment, nZVI-entrapped Ca-alginate was able to remove almost cent percent of As(V) from a prior concentration ranging between 1 and 10 mg/l. Generally, nZVI possessed a widely spread surface area of 22–54 $m^2$/g (Moraci and Calabrò 2010). Surface precipitation and/or adsorption were two most significant methodologies applied to eliminate As(V), whereas As(III) could be eradicated from water by the spontaneous adsorption and co-precipitation of Fe oxides/hydroxides followed by oxidation procedure of nZVI (Kanel et al. 2005). The latter group of researchers also demonstrated an efficient

protocol for retrieving arsenic-containing nZVI, even without sacrificing their performances. Implementation of nZVI in drinking water was advantageous due to the low aqueous solubility and poor leaching ability of nZVI from the beads (Bezbaruah et al. 2014).

#### 8.4.3.6 Zirconium Oxide ($ZrO_2$)

Zr-containing oxides were found to be stable, non-toxic, and water insoluble, with a larger surface area of around 327.1 $m^2/g$. It was already established that $ZrO_2$-encapsulated alginate beads (ZOAB) could remove arsenic (Kwon et al. 2016). The highest adsorption capabilities of ZOAB were determined to be 32.3 mg/g for As(III) and slightly less for As(V) i.e. 28.5 mg/g. Further to mention, As(III) adsorption was enhanced up to neutral pH condition, whereas elevated adsorption of the other form was found better under acidic condition i.e. pH value less than 7.0 (Kwon et al. 2016). Notably, ZOAB owned around 13.2 $m^2/g$ surface area, which was more than that of the alginate beads (having surface area of 2.4 $m^2/g$). Hydrous $ZrO_2$ may have led to the formation of fractures, that eventually increased the overall surface area of the particle. The presence of $Cu^{2+}$ ions caused arsenic adsorption at a much higher rate, probably due to co-removal of arsenic along with the ion.

#### 8.4.3.7 Coconut Shell Charcoal

This highly porous particle contains around 3% ash and possesses a surface area ranging from 1150 to 1250 $m^2/g$. Both micro- and meso-porous surfaces were found in the coconut shell charcoal Ca-alginate beads (CCAB) (Hlaing et al. 2011). At an prior concentration of 500 ppm, these beads were able to removal almost 76.8% of arsenic. The adsorption capacity improved when the CCAB dosage was increased. Moreover, the CCAB may also be used to remove As, Pb, and Cd alongside (Hlaing et al. 2011).

#### 8.4.3.8 Polymer Beads

In recent times, numerous polymer beads, especially hybrid anion exchanger (HAIX), hybrid ion exchanger (HIX), chitosan, cationic hydrogels, etc. have been detected to be much more effectual for arsenic elimination (Table 8.3). Among all of them, HIX is a low-cost, long-lasting, and widely accessible adsorbent, as reported by Cumbal and Sengupta (2005). These beads may be formed on-site with NaOH, and subsequently $CO_2$-saturated water rinses thereafter. On the contrary, rinsing with a combination of sodium hydroxide (NaOH) and brine can regenerate HAIX (Cumbal and Sengupta 2005). Barakat and Sahiner (2008) showed that the cationic hydrogel could remove up to 98% of arsenate. Biosorbents coated with chitosan have a larger

**Table 8.3** Characteristics of different polymer beads

| Adsorbents | Advantages | Disadvantages | References |
|---|---|---|---|
| Spherical microporous cation-exchange polymer beads (HIX) | For nearly 5000 bed volumes, final arsenic concentration less than 50 μg/l | Intraparticle diffusion was identified as the primary rate-limiting step for both As(III) and As(V) sorption | De Marco et al. (2003) |
| Polymer-supported hydrated Fe(III) oxide NPs | Sharp decrease in concentration | The Donnan membrane effect did not allow permeation of As(III) into the polymer phase | Cumbal and Sengupta (2005) |
| Cationic hydrogels | The maximum removal efficiency values obtained were 97.6%, 93.1%, 80.4%, and 73.1% for 25, 50, 75, and 100 ppm As(V) concentration, respectively | Not effective against As(III) | Barakat and Sahiner (2008) |
| Chitosan-coated $Al_2O_3$ | The sorption capacity was 56.5 mg/g and 96.5 mg/g for As(III) and As(V), respectively. Effective over wide spectrum of pH | Adsorption experiments at lower concentrations have not been executed | Boddu et al. (2008) |

*Abbreviations* $Al_2O_3$: alumina; As: arsenic; Fe: iron; g: grams; l: litres; mg: milligrams; NPs: nanoparticles; ppm: parts per million; μg: micrograms

surface area (almost 125.2 $m^2$/g), and their sorption capacities for As(III) and As(V) are 56.5 and 96.5 mg per gram of arsenic, accordingly (Boddu et al. 2008).

## 8.5 Comparison Between the Alginate-Based Adsorbents

Ca–Fe alginate beads removed 94.0% of As(V) from an preliminary concentration of 400 μg/l (Min and Hering 1998), whereas Banerjee et al. (2007) observed a complete elimination of As(V) at 20 mg/l concentration. However, the former group of researchers discovered sluggish sorption rate at lower pH i.e. 4.0, resulting in a gradual rise in the mass of adsorbed As(V), and whole procedure took a wide range of timescale viz. 48–120 h. In contrast, the other group of researchers reached equilibrium within 20 min at a much lower pH condition i.e. 3.0. In case of comparable beads, Sánchez-Rivera et al. (2013) attained up to 54 and 80% removal efficiencies of As(III) and As(V), with respective adsorption capacities of 0.117 and 0.364 mg/g, eventually. In another study, Ca–Fe alginate beads filled glass columns were able to adsorb up to 4.75 μg/g of As(V) (Zouboulis and Katsoyiannis 2002). Using Fe-coated Ca–Fe alginate beads, the same group of researchers were able to

decrease both arsenical forms to less than 10 μg/l from 50 μg/l, despite the poor elimination capability of As(III). Reportedly, As(V) possessed an adsorption capacity of 7.2 μg/g.

Ca-alginate beads containing $Fe_3O_4$ had an adsorption capacity up to 6.75 mg/g for As(V) (Lim and Chen 2007). The As(V) adsorption capabilities of irregular oxide-based alginate beads and goethite were 7 and 4 mg/g, accordingly. The Ca-alginate encapsulated with goethite eliminated about 95% of As(V) at starting concentrations between 10 and 10,000 μg/l (Basu et al. 2015). The highest adsorption capacity was reportedly 30.44 mg/g. Ca-alginate beads loaded with $Fe(OH)_3$ microcapsules eradicated both forms of arsenic almost fully from a prior concentration of 300 μg/l, whereas the absorption potential reportedly was 3.8 mg/g (Sarkar et al. 2010). Effective removal of As was achieved by encapsulating $Fe(OH)_3$ microparticles in cellulose acetate butyrate (CAB) polymer (III).

Ca-alginate nano-molecules having an adsorption capability of up to 0.034 mg/g removed almost 45% of As(V), although the Fe cross-linked Ca-alginate nanoparticles were able to absorb up to 0.07 mg/g of As(V) (Singh et al. 2014). The absorption capacities of Ca-alginate doped with magnetite nanoparticles for As(III) and As(V) were 3.34 mg/g and 4.78 mg/g of the adsorbents, respectively (Luna-Pineda et al. 2009).

Akaganeite nanorods of around 18 mg weight and 21–43 nm size impregnated in Ca-alginate micro-beads could deplete As(V) from 100 to 0.9 μg/l (Cho et al. 2014). Increasing the micro beads' size five times (400 μm → 2000 μm) doubled the concentration of residual arsenic. The nZVI-encapsulated Ca-alginate beads eliminated 85–100% of the original arsenic concentrations ranging between 50 and 10,000 μg/l (Bezbaruah et al. 2014). The sorption capacities of hydrous $ZrO_2$-loaded Ca-alginate beads for As(III) was 28.5 mg/g, and the same for As(V) was 32.3 mg/g, subsequently (Kwon et al. 2016).

## 8.6 Resource Recycling and Disposal

In various previous researches, the recyclability of alginate beads was studied. Sigdel et al. (2016) utilised an alkaline solution as the desorbing agent since the adsorption of both the forms of arsenic decreased abruptly at extremely high pH. The anionic sites as well as the Fe adsorbent increased the desorption rate of arsenic in alkaline solution. After reaching the saturation point, arsenic-contaminated alginate beads were rinsed with deionized water and stored in 0.01–0.2 M NaOH solution for 10–48 h. After that, the beads were neutralised with diluted mineral acid (such as 0.01 M $H_2SO_4$). These were rinsed again for the second time with deionized water and dried before undergoing the practical phase of application.

For up to eight cycles, the HIO-impregnated alginate beads removed 51.3–56.6% and 26.7–29.1% of As(III) and As(V), respectively. This result resembled the efficiency of the freshly produced HIO-alginate beads viz. 55.7 and 30.5% elimination of both the conformations, subsequently (Sigdel et al. 2016). After the completion of 8th

cycle, beads of both the forms lost respectively 15% and 20% of their initial weights, suggesting the successful regeneration and reusability of entrapped alginate beads by alkaline solution treatment. Another study revealed that $H_2SO_4$ and HCl desorb arsenic by up to 100% and more than 65%, individually (Sánchez-Rivera et al. 2013). Banerjee et al. (2007) observed that rinsing Ca–Fe alginate beads with a solution of 0.1 M HCl might desorb maximum 70% As(V) while also caused leaching half of Fe from the beads. On the other hand, Ca–Fe alginate beads washed with 0.1 M NaOH might take away as much as 66% of As(V). On the contrary, the beads lost 42% of their Fe content during that procedure (Banerjee et al. 2007). As(V) adsorption capabilities were presumably diminished by the elimination of Fe from regenerated beads. However, the volumes of rinsing solutions utilised in the regeneration trials were not mentioned in these researches. Therefore, the inclusion of washing solution quantities would enhance comprehension of the reproduction procedure and the viability of reproducing adsorbent-containing alginate beads. Additionally, the enhanced performance of the beads is projected to minimise the total expenses of arsenic elimination.

Discarding of arsenic-containing alginate beads is a concern that must be addressed. Procreation of alginate beads is anticipated to minimise the overall waste production. Sánchez-Rivera et al. (2013) observed that $H_2SO_4$ and HCl could desorb arsenic by up to 100% and more than 65%, accordingly. The desorbed arsenic-containing solutions can be discarded securely following the conventional strategy. Moreover, after multiple sequences of recycling of the desorbed beads, the debris from the concluding cycle can be discarded according to the typical approaches available. After reuse, for instance, alginate beads with the desorbed arsenic from the previous cycle may be transformed into stable compounds, which ultimately prevent environmental contamination.

## 8.7 Future Possibilities

Multiple researches have reported the efficacy of alginate-constructed adsorbents in the removal of arsenic from drinkable water, although effectiveness in lowering arsenic below the WHO approved level of 10 μg/l at a cheaper expense is very rare. To achieve entire success in this regard, further research is required to fulfil current gaps. Multifaceted research directions are required for comprehensive success in the low-cost removal techniques of arsenic from drinkable water.

Alumina ($Al_2O_3$) is known to be an effective arsenic adsorbent. Till date, no use of $Al_2O_3$-impregnated or coated alginate beads for As removal has been documented, probably due to the higher costing of $Al_2O_3$ manufacturing and the complexity in the impregnation procedure. The cost of producing alumina by the sol–gel method is significantly at higher side. Sen and Pal (2009) employed the partial thermal dehydration process to manufacture nano-$Al_2O_3$ with an overall surface area ranging from 335 to 340 $m^2/g$. The partial thermal dehydration method reportedly produced $Al_2O_3$ at a cost of 1152 USD per tonnes, which was around 39% less costly than the

gel precipitation approach. Overall, this technology reduced the cost per 1000 l of water by 30–50% (Pal 2015). In addition, the capacity to regenerate alginate beads generally minimises the overall expenses of water treatment. In a nutshell, arsenic removal via alumina-based alginate beads requires further research.

Elimination of As(V) was comparatively simpler than As(III). Singular or Fe-plated Ca–Fe alginate beads were effective in removing As(V), but removal of As(III) remained unsatisfactory following this methodology. Hence, the conversion of As(III) to the other form by oxidation is predicted to increase arsenic removal proficiency. The outcomes of oxidation on the sorption efficiencies of As(III) and As(V) by alginate beads must be investigated in the future.

At a prior concentration of 300 μg/l, Sarkar et al. (2010) exhibited almost entire elimination of both arsenical forms by the implementation of Ca-alginate beads loaded with $Fe(OH)_3$ microcapsules. On the other hand, cellulose acetate butyrate (CAB) polymer was utilised to entrap the $Fe(OH)_3$ micro-molecules. Prior to its use in drinking water, it is necessary to explore the effects of CAB polymer on people through more research. Additionally, further studies are required to manufacture more cheaper polymers from naturally occurring substances.

Magnetite ($Fe_3O_4$) nanoparticles-doped Ca-alginate demonstrated good results in eliminating As(V), although these exhibited inadequate reduction of As(III). Therefore, upcoming researches might examine the consequences of following oxidation protocol on the beads before application.

Cho et al. (2014) found an improvement in arsenic elimination effectiveness with a reduction in the diameter of alginate beads, perhaps because of the reduction in diffusional gap and an enlargement of surface area. The same study suggested that akaganeite nanorods, of 21–43 nm size, encased in Ca-alginate micro beads was capable to lower arsenic concentrations to 0.9 μg/l from 100 μg/l. To find the optimal size and form of alginate beads for optimum elimination effectiveness, further research is required.

Ca-alginate beads encapsulated with nZVI eliminated 85–100% of the arsenic from an early concentration of 50–10,000 μg/l (Bezbaruah et al. 2014). Implication of nZVI in drinking water was advantageous due to poor leaching ability of nZVI from the lower aqua-soluble alginate beads. Moreover, the manufacturing procedure and maintenance of nZVI is quite difficult due to its oxidation characteristic, and thus, additional research is required in this field.

Additionally, a variety of natural materials (sand, fly ash, red muds, etc.) and Fe or $Al_2O_3$-treated activated carbon are frequently used to remove arsenic from water. Prior to their execution in drinking water, it is vital to understand their impacts on human health. Additionally, biodegradation is a common approach for arsenic removal. Hence, such a method requires careful consideration for its application in drinking water due to health concerns.

## 8.8 Conclusion

This present chapter studied arsenic eliminatory strategies for water, with an emphasis on biotechnological approaches regarding alginate application. Among all, adsorption emerges as an efficient methodology for eliminating arsenic from aqueous solutions. Fe and its compounds (iron oxides, hydroxides and oxyhydroxides, akageneite, goethite, etc.) are utilised extensively as alginate-based adsorbents. It is convenient for drinking water applications because of its enhanced removal efficiency and reduced expenses. Additionally, the encapsulated alginate beads of the Fe compounds can be recycled post regeneration. Moreover, biocompatible nature, higher aqueous permeability, lower cost, wider accessibility, and effective reusability of alginate beads are further benefits of these alginate-based adsorbents. However, various Fe-based alginate beads frequently face trouble in depleting the metalloid beyond the WHO-restricted value, and thus, they generate substantial quantities of arsenic-contaminated wastes. These wastes ultimately pose a disposal problem. The deployment of nano-$Al_2O_3$-entrapped alginate beads and their procreation for diversified implementations can overcome these concerns. Therefore, for achieving a complete success in decreasing arsenic in drinking water, further research is required in the aforementioned areas.

## References

Abdellaoui Y, El Ibrahimi B, Abou Oualid H, Kassab Z, Quintal-Franco C, Giácoman-Vallejos G, Gamero-Melo P (2021) Iron-zirconium microwave-assisted modification of small-pore zeolite W and its alginate composites for enhanced aqueous removal of As(V) ions: experimental and theoretical studies. Chem Eng J 421:129909. https://doi.org/10.1016/j.cej.2021.129909

Aizat A, Aziz F (2019) Chitosan nanocomposite application in wastewater treatments. In: Ahsan A, Ismail AF (eds) Nanotechnology in water and wastewater treatment. Elsevier, Amsterdam, The Netherlands, pp 243–265. https://doi.org/10.1016/B978-0-12-813902-8.00012-5

Baig JA, Kazi TG, Shah AQ, Kandhro GA, Afridi HI, Khan S, Kolachi NF (2010) Biosorption studies on powder of stem of *Acacia nilotica*: removal of arsenic from surface water. J Hazard Mater 178(1–3):941–948. https://doi.org/10.1016/j.jhazmat.2010.02.028

Bajpai AK (2019) Facile preparation of ionotropically crosslinked chitosan-alginate nanosorbents by water-in-oil (W/O) microemulsion technique: optimization and study of arsenic (V) removal. J Water Process Eng 32:100920. https://doi.org/10.1016/j.jwpe.2019.100920

Banerjee A, Nayak D, Lahiri S (2007) Speciation-dependent studies on removal of arsenic by iron-doped calcium alginate beads. Appl Radiat Isot 65:769–775. https://doi.org/10.1016/j.apradiso.2007.02.007

Barakat MA, Sahiner N (2008) Cationic hydrogels for toxic arsenate removal from aqueous environment. J Environ Manage 88:955–961. https://doi.org/10.1016/j.jenvman.2007.05.003

Basu H, Singhal RK, Pimple MV, Reddy AVR (2015) Arsenic removal from groundwater by goethite impregnated calcium alginate beads. Water Air Soil Pollut 226:22. https://doi.org/10.1007/s11270-014-2251-z

Basu H, Singh S, Venkatesh M, Pimple MV, Singhal RK (2021) Graphene oxide-$MnO_2$-goethite microsphere impregnated alginate: a novel hybrid nanosorbent for As(III) and As(V) removal from groundwater. J Water Process Eng 42:102129. https://doi.org/10.1016/j.jwpe.2021.102129

Bauer M, Blodau C (2009) Arsenic distribution in the dissolved, colloidal and particulate size fraction of experimental solutions rich in dissolved organic matter and ferric iron. Geochim Cosmochim Acta 73:529–542. https://doi.org/10.1016/j.gca.2008.10.030

Behera KK (2013) Phytoremediation, transgenic plants and microbes. Sustain Agric Rev 13:1–29. https://doi.org/10.1007/978-94-007-5449-2

Bezbaruah AN, Krajangpan S, Chisholm BJ, Khan E, Elorza Bermudez JJ (2009) Entrapment of iron nanoparticles in calcium alginate beads for groundwater remediation applications. J Hazard Mater 166:1339–1343. https://doi.org/10.1016/j.jhazmat.2008.12.054

Bezbaruah AN, Kalita H, Almeelbi T, Capecchi CL, Jacob DL, Ugrinov AG, Payne SA (2014) Ca-alginate entrapped nanoscale iron: arsenic treatability and mechanism studies. J Nanopart Res 16:1–10. https://doi.org/10.1007/s11051-013-2175-3

Boddu VM, Abburi K, Talbott JL, Smith ED, Haasch R (2008) Removal of arsenic (III) and arsenic (V) from aqueous medium using chitosan-coated biosorbent. Water Res 42:633–642. https://doi.org/10.1016/j.watres.2007.08.014

Chakraborti D, Rahman MM, Das B, Nayak B, Pal A, Sengupta MK, Hossain MA, Ahamed S, Sahu M, Saha KC, Mukherjee SC, Pati S, Dutta RN, Quamruzzaman Q (2013) Groundwater arsenic contamination in Ganga-Meghna-Brahmaputra plain, its health effects and an approach for mitigation. Environ Earth Sci 70:1993–2008. https://doi.org/10.1007/s12665-013-2699-y

Chatterjee M, Sarkar S, Debnath S, Ghosh S, Bhattacharyya S, Sanyal SK (2011) Genetic analysis of arsenic accumulation in grain and straw of rice using recombinant inbred lines. Oryza 48:270–273

Chatterjee M, Sarkar S, Debnath S, Mukherjee A, Chakraborty A, Bhattacharyya S (2013) Genotypic difference in temporal variation of arsenic accumulation and expression of silicon efflux transporter ($LSi_2$) gene in field grown rice. Indian J Genet Plant Breed 73(1):94–97. https://doi.org/10.5958/j.0019-5200.73.1.01

Chen B, Zhu Z, Ma J, Yang M, Hong J, Hu X, Qiu Y, Chen J (2014) One-pot, solid-phase synthesis of magnetic multiwalled carbon nanotube/iron oxide composites and their application in arsenic removal. J Colloid Interface Sci 434:9–17. https://doi.org/10.1016/j.jcis.2014.07.046

Cho K, Shin BY, Park HK, Cha BG, Kim J (2014) Size controlled synthesis of uniform akaganeite nanorods and their encapsulation in alginate microbeads for arsenic removal. RSC Adv 4:21777–21781. https://doi.org/10.1039/c4ra01998a

Choong TSY, Chuah TG, Robiah Y, Gregory Koay FL, Azni I (2007) Arsenic toxicity, health hazards and removal techniques from water: an overview. Desalination 217:139–166. https://doi.org/10.1016/j.desal.2007.01.015

Chowdhury S, Mazumder MAJ, Al-Attas O, Husain T (2016) Heavy metals in drinking water: occurrences, implications, and future needs in developing countries. Sci Total Environ 569–570:476–488. https://doi.org/10.1016/j.scitotenv.2016.06.166

Chowdhury S, Chowdhury IR, Kabir F, Mazumder MAJ, Zahir M, Alhooshani K (2019) Alginate-based biotechnology: a review on the arsenic removal technologies and future possibilities. J Water Supply Res Technol AQUA 68(6):369–389. https://doi.org/10.2166/aqua.2019.005

Chung SG, Ryu JC, Song MK, An B, Kim SB, Lee SH, Choi JW (2014) Modified composites based on mesostructured iron oxyhydroxide and synthetic minerals: a potential material for the treatment of various toxic heavy metals and its toxicity. J Hazard Mater 267:161–168. https://doi.org/10.1016/j.jhazmat.2013.12.056

Crow BB, Nelson KD (2006) Release of bovine serum albumin from a hydrogel-cored biodegradable polymer fiber. Biopolymers 81:419–427. https://doi.org/10.1002/bip.20442

Cumbal L, Sengupta AK (2005) Arsenic removal using polymer-supported hydrated iron (III) oxide nanoparticles: role of Donnan membrane effect. Environ Sci Technol 39:6508–6515

Das A, Mahanta M, Pramanik B, Gantait S (2021) Artificial seed development of selected anti-diabetic plants, their storage and regeneration: progress and prospect. In: Gantait S, Verma SK, Sharangi AB (eds) Biotechnology of anti-diabetic medicinal plants. Springer, Singapore, pp 409–436. https://doi.org/10.1007/978-981-16-3529-8_14

Debnath S, Bhattacharyya S, Sarkar S, Chatterjee M (2016) Expression of multidrug and toxic compound extrusion (MATE) genes in response to the presence of arsenic in irrigation water and soil in rice (*Oryza sativa* L.). Int J Bio-Resour Stress Manag 7(1):88–91. https://doi.org/10.23910/IJBSM/2016.7.1.1488

Debnath S, Bhattacharyya S, Sarkar S, Chatterjee M (2017) Whole genome transcriptional analysis of rice grown in arsenic contaminated field conditions. Trends Biosci 10(2):850–855

De Marco MJ, SenGupta AK, Greenleaf JE (2003) Arsenic removal using a polymeric/inorganic hybrid sorbent. Water Res 37(1):164–176. https://doi.org/10.1016/S0043-1354(02)00238-5

Dong Y, Dong W, Cao Y, Han Z, Ding Z (2011) Preparation and catalytic activity of Fe alginate gel beads for oxidative degradation of azo dyes under visible light irradiation. Catal Today 175:346–355. https://doi.org/10.1016/j.cattod.2011.03.035

Escudero C, Fiol N, Villaescusa I, Bollinger JC (2009) Arsenic removal by a waste metal (hydr)oxide entrapped into calcium alginate beads. J Hazard Mater 164:533–541. https://doi.org/10.1016/j.jhazmat.2008.08.042

Fazi S, Amalfitano S, Casentini B, Davolos D, Pietrangeli B, Crognale S, Lotti F, Rossetti S (2016) Arsenic removal from naturally contaminated waters: a review of methods combining chemical and biological treatments. Rend Lincei 27:51–58. https://doi.org/10.1007/s12210-015-0461-y

Giles DE, Mohapatra M, Issa TB, Anand S, Singh P (2011) Iron and aluminium based adsorption strategies for removing arsenic from water. J Environ Manage 92:3011–3022. https://doi.org/10.1016/j.jenvman.2011.07.018

Gombotz WR, Wee SF (2012) Protein release from alginate matrices. Adv Drug Delivery Rev 31:267–285. https://doi.org/10.1016/j.addr.2012.09.007

Han C, Li H, Pu H, Yu H, Deng L, Huang S, Luo Y (2013) Synthesis and characterization of mesoporous alumina and their performances for removing arsenic(V). Chem Eng J 217:1–9. https://doi.org/10.1016/j.cej.2012.11.087

Harikumar PS, Joseph L (2012) Kinetic and thermodynamics studies of As(III) adsorption onto iron nanoparticles entrapped Ca-alginate beads. Int J Plant Anim Environ Sci 2:159–166

Hassan AF, Abdel-Mohsen AM, Fouda MM (2014) Comparative study of calcium alginate, activated carbon, and their composite beads on methylene blue adsorption. Carbohydr Polm 102:192–198. https://doi.org/10.1016/j.carbpol.2013.10.104

Hlaing CS, Kyu KK, Win T (2011) Removal of some toxic heavy metals by means of adsorption onto biosorbent composite (coconut shell charcoal-calcium alginate) beads. Drug House Chemical Ltd., Poole, UK; Kanto Chemical Co., Tokyo, Japan

Jadhav SV, Bringas E, Yadav GD, Rathod VK, Ortiz I, Marathe KV (2015) Arsenic and fluoride contaminated groundwaters: a review of current technologies for contaminants removal. J Environ Manage 162:306–325. https://doi.org/10.1016/j.jenvman.2015.07.020

Jain CK, Singh RD (2012) Technological options for the removal of arsenic with special reference to South East Asia. J Environ Manage 107:1–18. https://doi.org/10.1016/j.jenvman.2012.04.016

Jang M, Chen W, Cannon FS (2008) Preloading hydrous ferric oxide into granular activated carbon for arsenic removal. Environ Sci Technol 42:3369–3374. https://doi.org/10.1021/es7025399

Jung W, Park YK, An J, Park JY, Oh HJ (2017) Sorption of arsenic and heavy metals using various solid phase materials. Int J Environ Sci Dev 8:8–11. https://doi.org/10.18178/ijesd.2017.8.2.923

Kabir F, Chowdhury S (2017) Arsenic removal methods for drinking water in the developing countries: technological developments and research needs. Environ Sci Pollut Res 24:24102–24120. https://doi.org/10.1007/s11356-017-0240-7

Kakita H, Kamishima H (2008) Some properties of alginate gels derived from algal sodium alginate. J Appl Phycol 20:543–549. https://doi.org/10.1007/s10811-008-9317-5

Kanel SR, Manning B, Charlet L, Choi H (2005) Removal of arsenic(III) from groundwater by nanoscale zero-valent iron. Environ Sci Technol 39:1291–1298. https://doi.org/10.1021/es048991u

Kang S, Park S-M, Park J-G, Baek K (2019) Enhanced adsorption of arsenic using calcined alginate bead containing alum sludge from water treatment facilities. J Environ Manage 234:181–188. https://doi.org/10.1016/j.jenvman.2018.12.105

Kim H, Hong HJ, Jung J, Kim SH, Yang JW (2010) Degradation of trichloroethylene (TCE) by nanoscale zero-valent iron (nZVI) immobilized in alginate bead. J Hazard Mater 176(1–3):1038–1043. https://doi.org/10.1016/j.jhazmat.2009.11.145

Krishna AK, Satyanarayanan M, Govil PK (2009) Assessment of heavy metal pollution in water using multivariate statistical techniques in an industrial area: a case study from Patancheru, Medak District, Andhra Pradesh, India. J Hazard Mater 167:366–373. https://doi.org/10.1016/j.jhazmat.2008.12.131

Kwon OH, Kim JO, Cho DW, Kumar R, Baek SH, Kurade MB, Jeon BH (2016) Adsorption of As(III), As(V) and Cu(II) on zirconium oxide immobilized alginate beads in aqueous phase. Chemosphere 160:126–133. https://doi.org/10.1016/j.chemosphere.2016.06.074

Lazaridis NK, Charalambous C (2005) Sorptive removal of trivalent and hexavalent chromium from binary aqueous solutions by composite alginate–goethite beads. Water Res 39(18):4385–4396. https://doi.org/10.1016/j.watres.2005.09.013

Lee KY, Mooney DJ (2012) Alginate: properties and biomedical applications. Prog Polym Sci 37:106–126. https://doi.org/10.1016/j.progpolymsci.2011.06.003

Lenoble V, Bouras O, Deluchat V, Serpaud B, Bollinger JC (2002) Arsenic adsorption onto pillared clays and iron oxides. J Colloid Interface Sci 255:52–58. https://doi.org/10.1006/jcis.2002.8646

Lim SF, Chen JP (2007) Synthesis of an innovative calcium alginate magnetic sorbent for removal of multiple contaminants. Appl Surf Sci 253:5772–5775. https://doi.org/10.1016/j.apsusc.2006.12.049

Lim S, Zheng Y, Zou S, Chen JP (2009) Uptake of arsenate by an alginate-encapsulated magnetic sorbent: process performance and characterization of adsorption chemistry. J Colloid Interface Sci 333:33–39. https://doi.org/10.1016/j.jcis.2009.01.009

Liu CH, Chuang YH, Chen TY, Tian Y, Li H, Wang MK, Zhang W (2015) Mechanism of arsenic adsorption on magnetite nanoparticles from water: thermodynamic and spectroscopic studies. Environ Sci Technol 49:7726–7734. https://doi.org/10.1021/acs.est.5b00381

Lou S, Liu B, Qin Y, Zeng Y, Zhang W, Zhang L (2021) Enhanced removal of As(III) and As(V) from water by a novel zirconium-chitosan modified spherical sodium alginate composite. Int J Biol Macromol 176:304–314. https://doi.org/10.1016/j.ijbiomac.2021.02.077

Luna-Pineda T, Ortiz-Rivera M, Perales-Pérez O, Román-Velázquez F (2009) Removal of arsenic from aqueous solutions with alginate based-magnetic nanocomposites. NSTI-Nanotech 2:395–398. www.nsti.org

Mao W, Zhang L, Zhang Y, Wang Y, Wen N, Guan Y (2022) Adsorption and photocatalysis removal of arsenite, arsenate, and hexavalent chromium in water by the carbonized composite of manganese-crosslinked sodium alginate. Chemosphere 292:133391. https://doi.org/10.1016/j.chemosphere.2021.133391

Mayo JT, Yavuz C, Yean S, Cong L, Shipley H, Yu W, Falkner J, Kan A, Tomson M, Colvin VL (2007) The effect of nanocrystalline magnetite size on arsenic removal. Sci Technol Adv Mater 8:71–75. https://doi.org/10.1016/j.stam.200610.005

Min JH, Hering JG (1998) Arsenate sorption by Fe(III)-doped alginate gels. Water Res 32:1544–1552

Mishra AK (2015) Nanocomposites in wastewater treatment. Pan Stanford Publishing Pte. Limited, Singapore. https://doi.org/10.1201/b17789

Moraci N, Calabrò PS (2010) Heavy metals removal and hydraulic performance in zero-valent iron/pumice permeable reactive barriers. J Environ Manage 91:2336–2341. https://doi.org/10.1016/j.jenvman.2010.06.019

Mueller B (2016) Arsenic in groundwater in the southern lowlands of Nepal and its mitigation options: a review. Environ Rev 25:296–305. https://doi.org/10.1139/er-2016-0068

Nicomel NR, Leus K, Folens K, Voort P, Van Der Laing GD (2016) Technologies for arsenic removal from water: current status and future perspectives. Int J Environ Res Public Health 13(1):62. https://doi.org/10.3390/ijerph13010062

Ning RY (2002) Arsenic removal by reverse osmosis. Desalination 143:237–241. https://doi.org/10.1016/S0011-9164(02)00262-X

Ociński D, Jacukowicz-Sobala I, Kociołek-Balawejder E (2016) Alginate beads containing water treatment residuals for arsenic removal from water—formation and adsorption studies. Environ Sci Pollut Res 23:24527–24539. https://doi.org/10.1007/s11356-016-6768-0

Pal P (2015) Groundwater arsenic remediation: treatment technology and scale up. Elsevier, Amsterdam, The Netherlands. Available online at: https://www.elsevier.com/books/groundwater-arsenic-remediation/pal/978-0-12-801281-9

Pramanik B, Sarkar S, Bhattacharyya S, Gantait S (2021) *meta*-Topolin-induced enhanced biomass production via direct and indirect regeneration, synthetic seed production, and genetic fidelity assessment of *Bacopa monnieri* (L.) Pennell, a memory-booster plant. Acta Physiol Plant 43(7):107. https://doi.org/10.1007/s11738-021-03279-1

Rahelivao MP, Andriamanantoanina H, Heyraud A, Rinaudo M (2013) Structure and properties of three alginates from Madagascar seacoast algae. Food Hydrocoll 32:143–146. https://doi.org/10.1016/j.foodhyd.2012.12.005

Rahim M, Mas Haris MRH (2015) Application of biopolymer composites in arsenic removal from aqueous medium: a review. J Radiat Res Appl Sci 8:255–263. https://doi.org/10.1016/j.jrras.2015.03.001

Rawat S, Maiti A (2021) Facile preparation of iron oxyhydroxide–biopolymer (chitosan/alginate) beads and their comparative insights into arsenic removal. Sep Purif Technol 272:118983. https://doi.org/10.1016/j.seppur.2021.118983

Ray SS (2013) Environmentally friendly polymer nanocomposites. Woodhead Publishing Ltd., Cambridge, UK. https://doi.org/10.1533/9780857097828

Reddy DHK, Lee SM, Yang JK, Park YJ (2013) Characterization of binary oxide photoactive material and its application for inorganic arsenic removal. J Ind Eng Chem 20:3658–3662. https://doi.org/10.1016/j.jiec.2013.12.062

Sánchez-Rivera D, Perales-Pérez O, Román FR, Sa D (2013) Removal of inorganic arsenic oxyanions using Ca–Fe(III) alginate beads. Desal Water Treat 51:2162–2169. https://doi.org/10.1080/19443994.2012.734693

Sarkar P, Pal P, Bhattacharyay D, Banerjee S (2010) Removal of arsenic from drinking water by ferric hydroxide microcapsule-loaded alginate beads in packed adsorption column. J Environ Sci Health A 45:1750–1757. https://doi.org/10.1080/10934529.2010.513267

Sen M, Pal P (2009) Treatment of arsenic-contaminated groundwater by a low cost activated alumina adsorbent prepared by partial thermal dehydration. Desalin Water Treat 11:275–282. https://doi.org/10.5004/dwt.2009.857

Seth S, Debnath S, Chakraborty NR (2020) In silico analysis of functional linkage among arsenic induced MATE genes in rice. Biotechnol Rep 26:e00390. https://doi.org/10.1016/j.btre.2019.e00390

Shih MC (2005) An overview of arsenic removal by pressure driven membrane processes. Desalination 172:85–97. https://doi.org/10.1016/j.desal.2004.07.031

Sigdel A, Park J, Kwak H, Park PK (2016) Arsenic removal from aqueous solutions by adsorption onto hydrous iron oxide-impregnated alginate beads. J Ind Eng Chem 35:277–286. https://doi.org/10.1016/j.jiec.2016.01.005

Singh P, Singh SK, Bajpai J, Bajpai AK, Shrivastava RB (2014) Iron crosslinked alginate as novel nanosorbents for removal of arsenic ions and bacteriological contamination from water. J Mater Res Technol 3:195–202. https://doi.org/10.1016/j.jmrt.2014.03.005

Singh R, Singh S, Parihar P, Singh VP, Prasad SM (2015) Arsenic contamination, consequences and remediation techniques: a review. Ecotoxicol Environ Saf 112:247–270. https://doi.org/10.1016/j.ecoenv.2014.10.009

Talukder ME, Pervez MN, Jianming W, Gao Z, Stylios GK, Hassan MM, Song H, Naddeo V (2021) Chitosan-functionalized sodium alginate-based electrospun nanofiber membrane for As(III) removal from aqueous solution. J Environ Chem Eng 9(6):106693. https://doi.org/10.1016/j.jece.2021.106693

Tiwari A, Dewangan T, Bajpai AK (2008) Removal of toxic As(V) ions by adsorption onto alginate and carboxymethyl cellulose beads. J Chin Chem Soc 55:952–961. https://doi.org/10.1002/jccs.200800142

Velizarov S, Crespo JG, Reis MA (2004) Removal of inorganic anions from drinking water supplies by membrane bio/processes. Rev Environ Sci Biotechnol 3:361–380. https://doi.org/10.1007/s11157-004-4627-9

Wade TJ, Xia Y, Wu K, Li Y, Ning Z, Le XC, Lu X, Feng Y, He X, Mumford JL (2009) Increased mortality associated with well-water arsenic exposure in Inner Mongolia, China. Int J Environ Res Public Health 6:1107–1123. https://doi.org/10.3390/ijerph6031107

WHO (2017) Guidelines for drinking-water quality: fourth edition incorporating the first addendum. World Health Organization, Geneva, Switzerland. https://apps.who.int/iris/bitstream/handle/10665/254637/9789241549950-eng.pdf;jsessionid=A03BF55AAAB65FDEE990ED0001BCF997?sequence=1/

Xia Y, Wade TJ, Wu K, Li Y, Ning Z, Le Chris X, He X, Chen B, Feng Y, Mumford JL (2009) Well water arsenic exposure, arsenic induced skin-lesions and self-reported morbidity in Inner Mongolia. Int J Environ Res Public Health 6:1010–1025. https://doi.org/10.3390/ijerph6031010

Yean S, Cong L, Yavuz CT, Mayo JT, Yu WW, Kan AT, Colvin VL, Tomson MB (2005) Effect of magnetite particle size on adsorption and desorption of arsenite and arsenate. J Mater Res 20:3255–3264. https://doi.org/10.1557/jmr.2005.0403

Zeng H, Wang F, Xu K, Zhang J, Li D (2020) Optimization and regeneration of chitosan-alginate hybrid adsorbent embedding iron-manganese sludge for arsenic removal. Colloids Surf A Physicochem Eng 607:125500. https://doi.org/10.1016/j.colsurfa.2020.125500

Zeng H, Sun S, Xu K, Zhao W, Hao R, Zhang J, Li D (2022) Adsorption of As(V) by magnetic alginate-chitosan porous beads based on iron sludge. J Clean Prod 359:132117. https://doi.org/10.1016/j.jclepro.2022.132117

Zhang QL, Lin YC, Chen X, Gao NY (2007) A method for preparing ferric activated carbon composites adsorbents to remove arsenic from drinking water. J Hazard Mater 148:671–678. https://doi.org/10.1016/j.jhazmat.2007.03.026

Zhang L, Xia W, Teng B, Liu X, Zhang W (2013) Zirconium cross-linked chitosan composite: preparation, characterization and application in adsorption of Cr(VI). Chem Eng J 229:1–8. https://doi.org/10.1016/j.cej.2013.05.102

Zouboulis AI, Katsoyiannis IA (2002) Arsenic removal using iron oxide loaded alginate beads. Ind Eng Chem Res 41:6149–6155

# Chapter 9
# Bioaccumulation of Arsenic in Different Crop Plants and Its Remediation Using Molecular Breeding Tools and Biotechnological Interventions


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**Abstract** Arsenic is a systemic toxicant having significant implications in public health as human carcinogen. Contamination of soil with alarming concentrations of arsenic occurs mostly due to a heavy dependency syndrome on the use of inorganic fertilizers and pesticides containing residues of arsenic and irrigating crops using groundwater concentrated with arsenic in crop production processes. Aforesaid anthropogenic activities contributed to the accumulation of such toxic mettaloid arsenic in different tissues of edible crop plants. Further, consumption of edible produce of crops grown in soils polluted with arsenic increases its biomagnification in different components of food chain resulting in serious health risks and risks of global food and nutritional security. Crop growth and production is adversely compromised due to arsenic-mediated alterations in their metabolic rhythms including physiological and biochemical circuitry associated with sensing of

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water and nutrients, cellular homeostasis, repair of cellular and membrane damage, synthesis of cellular energy currency ATP and photosynthesis. Considering serious negative implications of arsenic on crop growth and productivity, global food and nutritional security, environmental and human health, priorities should be given on an urgent basis for minimizing arsenic accumulation in crop plants using innovative and sustainable interventions such as genetic engineering, breeding interventions, identification of low grain-arsenic cultivars and agronomic management modules. In this manuscript, a comprehensive arsenic accumulation landscape in different crop plants namely in cereals, pulses, oilseeds, vegetable crops and other crops is depicted. To minimize the arsenic accumulation in crop plants, the role of innovative molecular breeding approaches and emerging biotechnological interventions namely comprehension of existing natural variation for survival ability of crop plants and soil microbiota in arsenic-rich environments, and introgression of few candidate genes for detoxification, sequestration and efflux of arsenic are discussed. Information depicted in this manuscript would be useful for providing a way forward for minimizing arsenic bioaccumulation, evolving As-free safe cultivars of crops and controlling As-biomagnifications in the food chain.

**Keywords** Arsenic · Bioaccumulation · Biotechnology · Breeding · Remediation

## 9.1 Introduction

Heavy metals have attributes such as high atomic weight and significantly higher density than water and are found in trace amounts in different environmental matrices below 10 parts per billion (ppb) (Fergusson 1990; Kabata-Pendias and Pendias 2001). Majority of heavy metals (Hg, Cd, Pb, Cr, As, Zn, Cu, Ni, Sn and V) known for their toxicity including arsenic (As) which is a systemic toxicant having significance in public health as carcinogen (Tchounwou et al. 2012). Elevated concentrations toxic heavy metals in soil have serious adverse effects on crop productivity, global food security, human and environmental health (Su 2014; Das 2021). Bioaccumulation in different tissues of crop plants followed by biomagnification in different components of food chain of alarming concentrations of heavy metals impose a serious risk to the food and nutritional security, and human and environmental health in the globe.

Arsenic is a widely abundant mettaloid whose bioaccumulation in different tissues of crop plants including edible plant parts impose a serious threat to human and environmental health. Long-term exposures of arsenic enhance the carcinogenicity in mammalian system (Singh et al. 2015). Arsenic impairs the crop growth and productivity by disrupting their physiological, biochemical and molecular circuitry linked with uptake of water and nutrients, cellular redox homeostasis, different components associated with photosynthesis process, cellular and membrane damage, and energy currency ATP synthesis. Entry of soil arsenic into food chain causes arsenic-poisoning (Khanna et al. 2022). Further, arsenic is classified as a carcinogen whose presence poses disastrous environmental threat. Arsenite [As(III)] and arsenate

[As(V)] are the two major inorganic species of As in soil cause arsenic-mediated toxicity in the environment (Azam et al. 2016). Use of groundwater containing residues of As during irrigation of crops is one of the prime driver for arsenic-accumulation in soils and plants (Bhattacharya et al. 2012). Large areas of soils having elevated concentrations of As exceeding threshold value have been reported in many parts of the globe (Argos et al. 2010). Further, excessive dependency syndrome on the use of synthetic agrochemicals containing arsenic in agriculture sector for plant protection, adopting intensive cultivation of high yielding input-responsive semi-dwarf cultivars of crops such as rice responsive to fertilizers and pesticides help in expanding the footprint of arsenic contamination in soil and its biomagnifications in the environment.

Rice is one of the predominant cereal crop grown throughout the globe and its consumption is linked with the cause of arsenic-mediated diseases such as cancer in the population of Asian continent (Azam et al. 2016; Jayasumana et al. 2015). Similarly, heavy dependency on the use of phosphatic fertilizer triple super phosphate containing 31 mg/kg and herbicide glyphosate containing 1.9 mg/kg in agricultural sector are the major source of arsenic linked with chronic kidney disease in Sri Lanka is reported (Jayasumana et al. 2015). Considering negative implication of arsenic on crop productivity, global food and nutritional security, human and environmental health, there is an urgent need for minimizing arsenic accumulation in crop plants using innovative and sustainable interventions such as genetic engineering, breeding interventions, identification of low grain-arsenic cultivars and agronomic management modules.

This manuscript attempts to provide a broader landscape of arsenic bioaccumulation in different crop plants belongs to families of cereals (paddy, wheat, corn), pulses (urd bean, mung bean and pea), vegetable crops (potato, tomato, brinjal, okra and leafy vegetables), and many other crops with long-term impact of soil arsenic on bio-accumulation in crop plants. To minimize the arsenic accumulation in crop plants, the role of innovative molecular breeding approaches and emerging biotechnological interventions are discussed. Role of innovative molecular breeding tools including MAS (marker-assisted-selection), genetic mapping and identification of QTLs contributing to low-arsenic accumulation, association mapping tools GWAS (genome-wide association studies), and emerging genomic selection concepts in minimizing arsenic in many crop plants are briefly described. Further, the role of the biotechnological interventions including the comprehension of natural variation for arsenic tolerance in crop plants (in hyper-accumulating plants and non-hyper accumulating plants for As-accumulation) and soil microbiota, and the use of transgenic technology for introgression of few candidate genes for detoxification, sequestration and efflux of arsenic using recombinant DNA technology for reducing As in crop plants are discussed. Information depicted in this manuscript would be useful for providing a way forward for minimizing arsenic bioaccumulation, evolving As-free safe cultivars of crops and controlling As-biomagnifications in the environment.

## 9.2 Bioaccumulation of Arsenic in Crop Plants

Among different crop plants, arsenic accumulation takes place more than the permissible limit in major cereal group of crops namely paddy (Rahman and Hasegawa 2011), wheat (Pigna et al. 2009, 2010), and corn (Rosas-Castor et al. 2014a, b), in vegetables (Alam et al. 2003; Roychowdhury et al. 2002) and in fruits (Ahiamadjie et al. 2011). Similarly, higher degree of arsenic bioaccumulation takes place in roots compared to fruits and leafy vegetables (Bhatti et al. 2013; Zhao et al. 2010a). Transport of arsenic from soil followed by its accumulation in edible parts of crop plants serve as the major source for As-biomagnification in different components of food chain and exposure to human through consumption of crop produce containing As in the long run.

### *9.2.1 Bioaccumulation of Arsenic in Important Cereals*

Mostly Gramineae family members are important cereal crops which includes paddy, wheat, and corn occupy dominant positions in the dietary landscape of many people in the globe for fulfillment of their daily calorie requirements. Therefore, contamination of produce of these crops even at low levels with toxic arsenic species is going to have disastrous consequences especially risks of human exposure to arsenic through consumption and risks of human health towards dreadful disease like cancer.

#### 9.2.1.1 Arsenic Accumulation in Rice

Among different cereals, rice occupies a vital place in the dietary requirement of many people for fulfilling their caloric needs in the globe especially in Asia (Das et al. 2018a, b, 2021). Rice is a hyper-accumulators of arsenic as it is primarily grown under anaerobic conditions. Rice plant is reported to accumulate ten-fold more arsenic than other cereals mainly in its grains which primarily contains the inorganic As species and DMA (Dimethyl arsenic acid) (Williams et al. 2005a, b, 2007; Torres-Escribano et al. 2008). Accumulation pattern of arsenic follows a descending order from root to straw to leaves to husk to grain (Liu et al. 2006) in rice. Grain arsenic content of rice is exacerbated by many anthropogenic activities involved in rice production system including the use of groundwater concentrated with As during irrigation and use of pesticides and herbicides containing residues of As for plant protection purpose, many mining and mineral processing activities (Lee et al. 2008; Lu et al. 2009). Bioaccumulation of As in different tissues of rice and subsequent biomagnification of As in food chain is reviewed by Bhattacharya et al. (2012). The temporal variation in As-accumulation in different tissues of two important crops namely rice and jute grown under submerged conditions having high bio-availability of arsenic soil is reported (Bhattacharya et al. 2014). Interestingly,

they found a time-dependent decrease in arsenic accumulation in both rice and jute. Further, a higher accumulation of arsenic in rice than jute was recorded (Bhattacharya et al. 2014).

#### 9.2.1.2 Arsenic Accumulation in Wheat

Many researchers have studied the role of arsenic-contaminated soil and irrigation water on the accumulation behavior of As in different tissues of wheat. The bioaccumulation, distribution and speciation of arsenic investigation in wheat revealed a direct relationship between total grain As content and the level of As in soil (Zhao et al. 2010a). Further, maximum accumulation of arsenic was found in wheat bran and was reduced by milling process in its flour (Zhao et al. 2010b). Differential accumulation of As in different tissues of wheat in four Chinese varieties grown in arsenic contaminated soil is reported by Zhang et al. (2009) and they found a dependency between grain arsenic content and level of arsenic in polluted soils. Also, they recorded a higher accumulation of As in wheat bran than in wheat flour. The role of phosphate fertilizer on the distribution of arsenic and phosphate in different tissues namely root, shoot and grain of wheat is studied by Pigna et al. (2009) using three different concentrations of As in irrigation water. Based on their study, they found a relationship between tissue accumulation of As and concentration of As in irrigation water and speculated the role of phosphate in minimizing the translocation of As to above ground tissues namely shoots and grains. Correlation between the level of arsenic in grains and arsenic-translocation factor is reported by Shi et al. (2015b) based on the investigation of uptake, accumulation and translocation of As, Cd and P in 12 different cultivars of wheat. Variation in the accumulation of arsenic, efflux and translocation of As, and its relation with arsenate (As(V)) tolerance in wheat seedling in 57 varieties was studied by Shi et al. (2015a) under hydroponic condition. Positive correlation for arsenate tolerance of wheat seedlings with root As concentration and a negative correlation between seedling arsenate tolerance and arsenite efflux and translocation factors were recorded.

#### 9.2.1.3 Arsenic Accumulation in Maize

Arsenic accumulation in maize has been studied by many researchers on different aspects of maize ranging from linkage of soil conditions with As phytotoxicity to the As-mediated effect on physiological attributes, antioxidant response modulation, and the role of mycoremediation on As accumulation and speciation (Rosas-Castor et al. 2014a, b; Gulz et al. 2005; Stoeva et al. 2003; Mylona et al. 1998; Yu et al. 2009; Anjum et al. 2016; Cattani et al. 2015). Rosas-Castor et al. (2014a, b) reviewed the summary of linkage of soil conditions and mechanisms involved in the influx and uptake, metabolism and toxicity behavior of As in maize plant. Non-linear relationship between accumulation behavior of As and different soluble concentrations of soil arsenic in four different crops (corn, ryegrass, rape and sunflower) under two

different soil conditions is reported (Gulz et al. 2005). Negative effect of arsenic on physiological attributes in early phenophase of corn using hydroponic experiments with maize seedlings under three different concentrations of As is reported (Stoeva et al. 2003). Mylona et al. (1998) reported a increase in the abundance of transcripts of enzyme involved in antioxidant response namely Cat1, Cat2, Cat3, Sod3, Sod4, Sod4A and Gst1 under stresses imposed by arsenic in different tissues of maize and at different developmental timings. Yu et al. (2009) reported the role of arbuscular mycorrhizal (AM) fungus (*Glomus mosseae*) in the alleviation of As toxicity in maize grown under As-spiked soils by the inhibition of the uptake of arsenate and reduction of arsenate to arsenite. Similarly, Anjum et al. (2016) reported an enhancement in the osmoregulation and antioxidant production during the course of time under Cd (100 μM) and As (200 μM) in two different maize cultivars at different phenophases. Individual application of phosphorus (P) or in combination with arbuscular mycorrhizal (AM) fungus *Rhizophagus irregularis* inoculation to maize plants grown under high-arsenic soil containing 200 mg $kg^{-1}$ of As resulted in biomass augmentation in maize plants is reported by Cattani et al. (2015).

### *9.2.2 Bioaccumulation of Arsenic in Pulses*

Pulses including green gram, black gram, red gram, and pea are important legumes known for their high protein content and for their nitrogen fixation ability in soil. Produce of these crops are mostly consumed either in sprout form or as dal in cooked form by many people in the globe. Therefore, arsenic-contamination of edible tissues of these crops increases the chance of human exposure to As and serious health risks such as incidences of cancer in the long run.

#### 9.2.2.1 Bioaccumulation of Arsenic in Green Gram

Mostly toxicity studies of arsenic on physiological attributes and metal tolerance index in green gram are reported (Mumthas et al. 2010; Chintey et al. 2022).

#### 9.2.2.2 Bioaccumulation of Arsenic in Black Gram

Many research focused on the effect of arsenic toxicity on growth parameters, chlorophyll, nucleic acid and protein content, oxidative stress response, antioxidant response, and role of nanoparticles in minimizing arsenic-mediated induction of toxicity in black gram are reported (Srivastava and Sharma 2013, 2014; Banerjee et al. 2023). Negative effect of arsenate stress on the growth, vigor, chlorophyll content, nucleic acid and protein content in the seedlings of black gram and role of phosphorus in amelioration of arsenate mediated problems in black gram is reported. Further, upregulation of antioxidant response, lipid peroxidation, osmoprotection

under arsenic-mediated toxicity regime is reported in black gram (Srivastava and Sharma 2014). Similarly, vital role of priming with biogenic nanoparticles of zinc (ZnO NPs) has been shown in arsenic-stress attenuation in seedling and vegetative stage of black gram (Banerjee et al. 2023). ZnO NPs promoted the enhancement of seed germination rate and morpho-physiological attributes, decreased build up of ROS, osmo-regulator accumulation and upregulation of antioxidant response enzymes (Banerjee et al. 2023).

#### 9.2.2.3 Bioaccumulation of Arsenic in Pea

Studies related to the uptake of As and its effect on different morpho-physiological traits and biochemical attributes of pea (*Pisum sativum* L.) and amelioration of arsenic induced stresses are reported (Rodríguez-Ruiz et al. 2019; Garg et al. 2015; Alsahli et al. 2021). The effect of arsenate (50 μM) on roots and leaves was studied by Rodríguez-Ruiz et al. (2019) in pea. They found an alteration in the ionic balance and metabolism of sulfur and nitric oxide in root and leaf tissues of pea under arsenate stress regime. Decrease in growth parameters, upregulation of oxidative markers, induction of enriched sulfur compound namely phytochelatins (PC2 and PC3) biosynthesis with concomitant decrease of reduced glutathione (GSH) was triggered due to arsenate stress in root and leaf tissues in pea (Rodríguez-Ruiz et al. 2019). Role of mycorrhization in arresting uptake of As and Cd, reduction of oxidative stress and reinforcement of antioxidant response components in red gram (*Cajanus cajan*) and pea (*Pisum sativum*) under stress regime of cadmium and arsenic was studied by Garg et al. (2015). They found that a higher uptake of As compared to Cd, and among red gram and pea, pea was found to be more sensitive to metal stress induced by As and Cd (Garg et al. 2015). Role of $H_2S$ in the mitigation of arsenic-induced stress in pea through the modulation of osmoregulatory machinery, antioxidant response, cycles of ascorbate–glutathione and glyoxalase system in pea grown under arsenic stress regimens is reported by Alsahli et al. (2021).

### *9.2.3 Arsenic Accumulation in Oilseed Crops*

The major oilseeds such as the Groundnut (*Arachis hypogaea*), Indian mustard (*Brasica juncea*), Sunflower (*Helianthus annuus*), Sesamum (*Sesamum indicum*) and Soybean (*Glycine max*) are important oilseeds play a role in shaping the edible oil economy. Many studies on arsenic accumulation and its alleviation is reported in literature. In Indian mustard studies related to genotypic variation for tolerance against arsenic toxicity (Chaturvedi 2006), role of antioxidant modulation in arsenic detoxification (Khan et al. 2009), and analysis of As accumulation and comparative transcriptome profiling (Thakur et al. 2019) is reported. Similarly, accumulation behaviour of arsenic in various tissues and amelioration of arsenic toxicity using organic interventions in Sesamum (Kundu and Pal 2012; Sinha et al. 2011) is

reported. Further, uptake and accumulation studies on arsenic (Sahito et al. 2021), role of phosphate and arsenate interactions in affecting arsenic concentration (Azeem et al. 2017) and importance of salicylic acid in improving the antioxidant response under arsenic-mediated oxidative stresses in tissues of sunflower (Saidi et al. 2017) are reported. Role of arbuscular mycorrhiza (AM) fungus (Spagnoletti and Lavado 2015), metal(loid)-resistant bacteria of the rhizospheric zone (Oller et al. 2020), symbiotic species of Bradyrhizobium (*Bradyrhizobium diazoefficiens* USDA110) (Bianucci et al. 2018), glutathione (GSH) (γ-glutamyl-cysteinyl-glycine) (Vezza et al. 2019) and nanoparticles of zinc (ZnO NPs) (Ahmad et al. 2020) in the alleviation and arsenic accumulation in Soybean has been reported.

#### 9.2.3.1 Bioaccumulation of Arsenic in Mustard

Chaturvedi (2006) studied variations in the tolerance to As toxicity among genotypes of Indian mustard in greenhouse experiments and reported a higher rate of uptake for arsenite compared to arsenate by Indian mustard genotypes. The upregulation of the activities of antioxidant response enzymes and metabolites act as antioxidants namely glutathione and ascorbate in 20 days-seedlings of mustard under arsenic-induced stress in hydroponic experiment is reported by Khan et al. (2009). Comparative transcriptome profiling and arsenic accumulation behavior in five genotypes of mustard under arsenic stress revealed an upregulation of gene expression of genes related signal transduction, regulatory players of transcription, stress response and metabolic processes and down regulation of genes related to cellular growth and developmental processes, and photosynthesis (Thakur et al. 2019).

#### 9.2.3.2 Bioaccumulation of Arsenic in Sesamum

Differential accumulation of arsenic in different tissues of sesamum cultivars is reported. The highest accumulation was recorded in root tissue while the lowest accumulation was recorded in seed (Kundu and Pal 2012) irrespective of the background of cultivars. Use of irrigation with surface water and organic amendments in minimizing arsenic accumulation in sesamum is found by Sinha et al. (2011).

#### 9.2.3.3 Bioaccumulation of Arsenic in Sunflower

Analysis of accumulation pattern of different species of arsenic in 37 oilseed sunflower accessions revealed a relatively higher accumulation of inorganic species (arsenate and arsenite) compared to organic species (dimethyl arsenic acid; monomethyl arsenic acid) of As under natural field conditions. Further, higher level of arsenate was recorded in roots while shoots recorded higher level of arsenite (Sahito et al. 2021). Interaction between phosphate and arsenate in the modulation of arsenic in plant tissues, growth behavior and antioxidant ability of sunflower under three

different levels of arsenic stresses is reported (Azeem et al. 2017). Effect of salicylic acid in improving the antioxidant response in sunflower under As-mediated oxidative stress is reported and salicylic acid was found to enhance the activity of antioxidant enzymes including catalase, ascorbate peroxidase, and glutathione peroxidase under arsenic-stress (Saidi et al. 2017).

#### 9.2.3.4 Bioaccumulation of Arsenic in Soybean

The potential of mycoremediation using arbuscular mycorrhiza (AM) fungus *Rhizophagus intraradices* in counteracting the adverse effects of arsenic on soybean under arsenic stress is reported by Spagnoletti and Lavado (2015). Oller et al. (2020) investigated the effect of six arsenic metal(loid)-resistant bacteria of the rhizospheric zone. They found plant growth promoting bacteria (PGPB) in positively influencing soybean growth in arsenic-mediated stress situations by enhancing the soybean growth and modulating the uptake of arsenic. The role of nanoparticles of zinc (ZnO NPs) in alleviating arsenic-mediated toxicity in soybean by minimizing uptake of As, and modulation of antioxidant response enzymes in soybean is reported (Ahmad et al. 2020). The potential role of symbiotic species of Bradyrhizobium in the alleviation of arsenic toxicity in soybean is reported (Bianucci et al. 2018). The effect of GSH (Glutathione) in the modulation of arsenic stress tolerance by the regulation of redox balance, gas exchange and accumulation behavior of As in soybean is reported (Vezza et al. 2019).

#### 9.2.3.5 Bioaccumulation of Arsenic in Groundnut

The role of lime, vermicompost combined with *Rhizobium* inoculants in enhancing the production of groundnut by minimizing the accumulation of arsenic is reported by Tuan and Van Chuong (2021).

### *9.2.4 Arsenic Bioaccumulation in Vegetables*

Many vegetables such as potato, tomato, brinjal, okra, leafy vegetables are mostly consumed by people on the globe in their diet. In this context, accumulation of arsenic in these vegetable crops will aggravate the chance of human exposure to arsenic. Therefore, a growing body of scientific evidences focused on arsenic accumulation, arsenic toxicity on growth, induction of stress response machinery, and possible amelioration measures for minimizing arsenic toxicity in vegetables.

#### 9.2.4.1 Bioaccumulation of Arsenic in Potato

The differential accumulation behavior of arsenic in different tissues were recorded during the evaluation of potato cultivars in arsenic contaminated zone with arsenic-enriched irrigation water in Eastern India. The highest accumulation was recorded in root tissue while the lowest accumulation was seen in potato tuber (Kundu et al. 2012) in all potato cultivars. Haque et al. (2015) reported the negative effect of arsenic contaminated soil on potato tuber yield. More accumulation of arsenic in potato peels than in peeled tubers in four potato cultivars grown under soils contaminated with lead-arsenate (Codling et al. 2016). The role of selenium in the alleviation of cadmium and arsenic toxicity through the modulation of glycolysis in potato grown under hydroponic conditions under the stress regimen of Cd and As on 48th day is reported (Shahid et al. 2019).

#### 9.2.4.2 Bioaccumulation of Arsenic in Tomato

Burlo et al. (1999) reported the negative effect of organic species of arsenic namely MA and DMA in reducing growth and yield of tomato plant. Alteration in growth and pigment content of tomato plants grown under As-polluted soils at different sublethal doses is studied by Miteva (2002) and they found a positive effect of lower dose of arsenic in promoting elongation of root system and increased height and weight of stem while a decreased the growth of both the vegetative and root system was recorded with higher dose of arsenic.

#### 9.2.4.3 Bioaccumulation of Arsenic in Brinjal

Alamri et al. (2021) studied the effect of ASC (Ascorbic acid) and GSH (Glutathione) in counteracting the arsenate-mediated toxicity in brinjal roots with the use of nitric oxide (NO). They found negative effects of arsenate treatment in terms of greater accumulation of arsenic in roots and shoots, reduction in the endogenous level of NO through the inhibition of Nitric Oxide Synthase-like (NOS-like) activity, stimulation of oxidative stress markers and protein damage, disruption of cellular redox status in brinjal. Further, they proved the role of both ASC and GSH in the alleviation of arsenate toxicity in brinjal roots independently with the requirement of endogenous NO using inhibitors of ASC biosynthesis or GSH biosynthesis which simply increased the toxic effects of arsenate. Role of GABA with the requirement of NO in counteracting arsenate-mediated stress in the seedlings of brinjal and tomato (Suhel et al. 2022).

#### 9.2.4.4 Bioaccumulation of Arsenic in Okra

Effect of different species of As including inorganic species (Arsenite and Arsenate) and organic species (Dimethyl arsenic acid (DMA)) mediated toxicity on growth is studied by Chandra et al. (2016) in Okra with two different doses (20 and 50 mg $kg^{-1}$) of each species of arsenic. Both growth and yield of okra was negatively affected by different species of As. Inorganic species arsenate followed by arsenite were accumulated in aerial parts compared to DMA in roots. Therefore, arsenite and DMA mainly accumulated in roots of okra (Chandra et al. 2016).

#### 9.2.4.5 Bioaccumulation of Arsenic in Leafy and Other Vegetables

Arsenic accumulation in leafy vegetables cultivated in soils contaminated with mine water and remedial potential of biochar in minimizing As accumulation in leafy vegetables is reported by Qin et al. (2021). The bioaccumulation pattern of antimony and arsenic in vegetables including *Coriandrum sativum* L., *Allium fistulosum* L., *Brassica pekinensis* L., and *Daucus carota* L. grown in antimony-mining area is studied. *Allium fistulosum* L. recorded the highest accumulation of arsenic while *Brassica pekinensis* L. recorded the lowest accumulation of arsenic and antimony. Capacity for redistribution of antimony and arsenic within the plant was maximum in *Coriandrum sativum* L. (Zeng et al. 2015). Vegetable crops grown in soils contaminated with lead arsenate pesticides on an old orchard amended with different doses of compost in a three year study was analyzed for their uptake and accumulation behavior for As and Pb. A maximum accumulation of arsenic (As) was found in lettuce followed by carrot followed by bean (McBride et al. 2015). Maximum accumulation of arsenic in the bulbs of onion and in berries of grapevine beyond the safety limits is reported by Pinter et al. (2018).

### *9.2.5 Effect of Soil Arsenic on Bio-accumulation in Crop Plants in Long-Term*

Metal-content analysis of soil crop plants including cereals (paddy, corn and sorghum), pulses and vegetables grown at the mine spilling site 17 years after the soil-cleaning-up drive have been conducted which revealed a maximum allowable concentration (MAC) levels for As and Cd in soil. Further, maximum concentrations of metals were found in edible tissues of leaves or stems of crop plants than in seeds or fruits as witnessed by the lower bioaccumulation factor (BAF) in edible seeds or fruits than in stems and leaves. Among different crops, most severe contamination was observed in *Ipomoea.* Crops such as sorghum, Adzuki bean, soybean and mung bean recorded lower than threshold level concentrations of toxic elements. In these

crops, maximum BAF was found for Cd while the lowest BAFs was recorded for As (Liu et al. 2005).

## 9.3 Mitigation of Arsenic Bioaccumulation in Crop Plants

### *9.3.1 Role of Molecular Breeding-Based Interventions in Minimizing Arsenic Bioaccumulation in Crop Plants*

Accumulation of As in grains or edible parts of crop plants is a serious problem for human health as it enters food chain through the dietary crop produce. Therefore, it is very imperative to promote development and deployment of one of the best choice such as plant breeding-based interventions in arsenic-contaminated areas for minimizing exposure of arsenic to the population of human. Plant breeding primarily depends on the existing natural variation, creation of genetic variation, selection of desired variation based on phenotypic evaluation in target environments, station trials, coordinated multi-location trials followed by release of promising entries as varieties for a specific geographical location or an agro-ecological situation. Similarly, molecular plant breeding is similar to conventional plant breeding but here, molecular-marker based information is used to accelerate the accurate genotyping and phenotyping in lesser time in advance.

In the context of reducing bioaccumulation of arsenic in crop plants, molecular plant-breeding mainly aims at identification of genetic variation for low arsenic accumulation, identification of QTLs and genes involved in mediating tolerance against arsenic stress in crop plants, discovery of specific molecular markers for putative QTLs or candidate genes for easier selection of desired low-arsenic accumulating genotypes from a pool of large number of genotypes having significant variation for arsenic-accumulation, introgression of desired genetic variation into the genomic background of agronomically adapted cultivars for development of low-grain-arsenic cultivars and their deployment in arsenic-contaminated regions. Role of different tools of molecular breeding namely MAS (Marker-assisted selection), genomic selection and emerging genome editing tools can help in designing of low-arsenic accumulating cultivars of crops and providing tolerance against arsenic stresses.

#### 9.3.1.1 Screening of Natural Variation for Low-Arsenic Accumulating Genotypes in Crop Plants

Report on screening of genotypes for genetic variation in crop plants for low-arsenic content is reported (Chi et al. 2018; Dasgupta et al. 2004; Kuramata et al. 2013; Das et al. 2021). Chi et al. (2018) analyzed the influence of cultivar, season (environment), interaction between cultivar and environment (CEI) on grain arsenic content in 51

cultivars of rice grown under Cd and As contaminated soil. They found lower levels of Cd and higher level of arsenic in grains in conventional *japonica* cultivars compared to *indica* cultivars. Further, they did a screening for stable low-accumulating cadmium and arsenic co-excluder cultivars in multi-environment trials in two seasons and found two stable lines taking into account of yield, CEI and Cd and As levels. Similarly, screening for decreased root growth under arsenate treatment regimen (13.3 μM) in genotypes of *indica*, and *japonica* subspecies of *Oryza sativa*, *Oryza glaberrima* have been reported (Dasgupta et al. 2004). Genetic variation in the accumulation and speciation of As in grain in 69 different accession of world rice core collection is reported (Kuramata et al. 2013). Among all the accessions, two accessions namely Local Basmati and Tima (indica type) recorded the lowest content for total-As and inorganic species of As in grain (Kuramata et al. 2013). Das et al. (2021) recorded a large variation for grain-arsenic content (0.05–0.49 mg/kg) by screening 100 genotypes of rice.

#### 9.3.1.2 Selection of Genotypes for Low Arsenic Content Using MAS (Marker-Assisted Selection)

In molecular plant breeding programme, MAS is routinely used for the selection of target trait phenotype using information derived from the molecular markers linked to the target trait in lesser time. MAS can accelerate the pace of the varietal development. In the context of marker-assisted selection for low arsenic accumulation, Das et al. (2021) developed a PCR-based co-dominant marker an SNP (T/G) between the two contrasting genotypes of rice for grain-arsenic content (low-accumulating variety Gobindaraj and high-accumulating variety Shatabdi) and differing for upregulation of transcripts of arsenic sequestering ATP binding cassette C1 type gene (ABCC1). Such marker information was used for discriminating between cultivars with low, high and mean-levels of arsenic accumulation. Identification of low-accumulating arsenic alleles for OsABCC1-transporter would help in introgression of such allele into high-accumulating arsenic genotypes using marker-assisted selection.

### *9.3.2 Identification of Potential QTLs for Arsenic Stress Tolerance: QTL Mapping for Low Arsenic Accumulation*

QTL refers to the "Quantitative Trait Loci" reflect the patches of genome that explain the variations observed in a quantitative trait. Polygenes contribute to the quantitative traits and these traits are highly influenced by the environment. Therefore, synonyms such as "polygenic traits" or "multi-factorial traits" or "complex traits" are used for quantitative traits. Identification of QTLs which explains the genetic basis for a trait and the associated genomic regions that modulate the trait is very useful

in crop breeding program. Identification of QTL is also known as QTL mapping. Different steps in QTL mapping are: (1) Development of a mapping population, (2) Phenotyping and genotyping of mapping population, (3) Construction of a linkage map, and (4) Mapping of QTL for target trait on the linkage map (Collard et al. 2005). QTL identification for arsenic accumulation has been done by many researchers.

Screening of recombinant inbred lines derived from a mapping population of Bala × Azucena cross for arsenate tolerance in rice revealed a major determinant in genomic region of 6th chromosome for arsenate tolerance between markers RZ516 and RG213 (Dasgupta et al. 2004). QTL mapping for organic species of As namely grain DMA-content is conducted by Kuramata et al. (2013) using a mapping population from the cross between two contrasting parents (high-DMA parent: adiPerak, low-DMA parent: Koshihikari) for grain DMA-content and by such approach, they identified three QTLs (two QTLs *qDMAs6.1* and *qDMAs in chromosome-6, and qDMAs in chromosome-8*) in the genomic regions. Identification of three QTLs for arsenic concentrations in shoot and root tissues in chromosome-2 and chromosome-3, respectively at seedling stage and QTLs for grain-arsenic content mapped to chromosome 6 and 8 at maturity are reported (Zhang et al. 2008) from rice anther-culture derived double haploid mapping population. Four main effect QTLs linked with seedling stage tolerance against arsenic-mediated phytotoxicity were identified by Syed et al. (2016) using a F2-mapping population between sensitive BRRI dhan45 and arsenic tolerant BRRI dhan47 in rice. Role genetic loci influencing flowering time on element concentrations including As concentration in grains using ICP_MS tool is reported (Norton et al. 2012). Identification of 14 number of QTLs in maize explaining phenotypic variance for accumulation pattern of arsenic in different tissues including kernels, axes, bracts and leaves are reported (Fu et al. 2016). QTL mapping in maize using RIL population identified 11 QTLs for arsenic accumulation in four different tissues of maize As concentrations in leaves (3 QTLs in chromosomes 1, 5 and 8), bract (2 QTLs), stem (3 QTLs), and kernels (3 QTLs in chromosomes 3, 5, and 7) (Ding et al. 2011).

### *9.3.3 Identification of Potential QTLs for Arsenic Stress Tolerance: Genome-Wide Association Studies*

Traits which are of agricultural and evolutionary importance are controlled by multiple genetic loci and are highly influenced by environments. These traits follow quantitative inheritance and are very sensitive to the influence of environment and genotype × environment interactions (Mackay et al. 2009). Understanding the genetic basis of such type of complex traits would help in crop breeding programme.

GWAS (Genome-wide association studies) exploits genome wide single nucleotide polymorphisms (SNPs) across an assembled population to elucidate the genetic basis of complex traits (Tibbs Cortes et al. 2021). In this, an association mapping population is created in model plants and other crops for examination of

trait variation across diverse genetic-backgrounds (Zhu et al. 2008). Many researchers have conducted genome-wide association studies in maize (Zhao et al. 2018), rice (Hwang et al. 2017; Norton et al. 2010), and wheat (Seed et al. 2022) for variations in As-content in plant tissues to elucidate its underlying genetic basis for arsenic accumulation.

### *9.3.4 Role of Genomic Selection for Low Arsenic Accumulation*

In genomic selection (GS), phenotypes are not used for selection but are used for training a prediction model (Heffner et al. 2009). Therefore, GS would help in redirecting resources and plant-breeding activities by accelerating the breeding cycle and increasing selection intensity for faster development of varieties in crop improvement (Heffner et al. 2009; Schaeffer 2006; Lorenz et al. 2011). The role of genomic prediction is suitable for minimizing uptake and grain accumulation of arsenic in rice is reported by Frouin et al. (2019) based on the phenotyping of 228 accessions of a *japonica* diversity panel for As-content in the flag leaf and dehulled rice grain and genotyping of 22,370 number of SNP loci. Similarly, the role of genomic selection based prediction for reducing As-content in rice is reported by Ahmadi et al. (2021); Ahmadi and Frouin (2021).

## 9.4 Mitigation of Arsenic Bioaccumulation in Crop Plants: Role of Biotechnological Interventions

### *9.4.1 Dissection and Enhanced Understanding of the Associated Mechanism of Arsenic Uptake, Translocation, Resistance, Accumulation, Sequestration, Transport and Toxicity*

Movement of arsenite from soil to root cell is driven by aquaporin transporters while uptake of arsenate to root cell is done by phosphate transporters. Among different inorganic species of As, arsenite is the most dominant species in cellular components of plants due to arsenate reductase-driven reduction of arsenate into arsenite. Most of the arsenic transport is studied in rice (Irshad et al. 2021).

#### 9.4.1.1 Uptake, Translocation and Transport of Inorganic Species of Arsenic

There are two types including high-affinity and low-affinity transport system for arsenic is reported (Mirza et al. 2014). Xylem plays a role in the translocation of arsenic from root to shoot and its redistribution in different tissues. Phosphate transporter helps in the uptake of arsenate in which As competes with phosphate molecules (Meharg and Macnair 1992). Arsenate reductase drives in catalyzing the conversion of intracellular arsenate to arsenite (Dhankher et al. 2006; Bleeker et al. 2006). Detoxification of toxic intracellular arsenite takes place by either of the ways including complex formation with thiol rich peptides (Liu et al. 2010) or with glutathione (GSH) is reported (Bleeker et al. 2006; Tripathi et al. 2007) and by effluxing out of cell. ABC transporter is required during the detoxification of GSH-Arsenite complex for its sequestration into vacuolar space of cell in *Arabidopsis thaliana* (Bleeker et al. 2006).

#### 9.4.1.2 Uptake, Translocation and Transport of Organic Species of Arsenic

Aquaporin protein NIP2; 1 drives the transport of methylated species of arsenic by root at a slower pace compared to inorganic species of As (Li et al. 2009). Xylem-mediated mobility of methylated arsenic species is faster from roots to shoots (Raab et al. 2007; Li et al. 2009). Further, rhizosphere-microbe mediated redox changes influences the uptake of As in rice (Jia et al. 2014).

#### 9.4.1.3 Cause of Arsenic-Induced Toxicity

Arsenite induced toxicity occurs mainly due to its interference with the sulfhydral groups found in various enzymes. Similarly, arsenate induced toxicity impairs key metabolic processes of cell by substituting inorganic phosphate with pentavalent arsenate. Further, excessive amounts of ROS are produced in arsenic-mediated toxicity which ultimately affect the plant's antioxidant defense response (Sharma et al. 2023; Irshad et al. 2021).

### *9.4.2 Molecular Basis of Arsenic Tolerance*

#### 9.4.2.1 Understanding of Natural Variation for Arsenic Tolerance in Crop Plants

Comprehension of the basic molecular logic in hyper-accumulating and non-hyper-accumulating plants for arsenic tolerance would help in engineering arsenic tolerant

crop plants by inserting genes from their natural genomic variation for arsenic tolerance into the genomic background of crop plants. Arsenic tolerance mechanisms are discussed in the following section.

#### 9.4.2.2 Deriving Principles from Hyper-Accumulating Plants for Arsenic Tolerance

Enhanced uptake of arsenate (*As5+*), decreased complexation between arsenite (*As3+*) and thiol, efflux of arsenite (*As3+*), significant enhancement in the xylem translocation and sequestration of arsenite (*As3+*) in vacuoles of leaves are the mechanisms responsible for arsenic tolerance in arsenic hyper-accumulating plants (Sharma et al. 2023). Xylem and PvACR3 mediates efficient transportation of arsenite into vacuoles (Su et al. 2008; Indriolo et al. 2010), restricted complex formation between arsenite and thiol (Raab et al. 2004), higher uptake of pentavalent arsenate (Poynton et al. 2004) are the key features seen in arsenic hyperaccumulating *Pteris* species compared to their counterpart non-hyperaccumulating plants.

#### 9.4.2.3 Borrowing Principles from Non-hyper Accumulating Plants for Arsenic Tolerance

Non-hyper-accumulating plants mediate arsenic stress tolerance by two broad ways namely: limiting the uptake of arsenate from the soil by suppressing the high affinity phosphate uptake system and by the transformation of absorbed arsenate into arsenite using arsenate reductase enzyme followed by complex formation with thiol mainly phytochelatins and glutathione and sequestration of chelated-arsenite in roots helps in the detoxification arsenate and promote arsenic tolerance in plants (Sharma et al. 2023).

#### 9.4.2.4 Understanding of Natural Variation for Arsenic Tolerance in Soil and Natural Microbiota

A wide number of weapons in terms of genes, operons and mechanisms are available in microbiota for their survival in arsenic-rich environments which can be explored for reducing arsenic in contaminated soil and plants. Ectopic expression of genes for arsenic tolerance using constitutive root-specific promoter can help in minimizing arsenic accumulation in edible plant parts. Role of some important microorganisms are discussed as follows.

Arsenic detoxification system is widely distributed in microorganisms. Role of arsenic-transforming bacteria is reviewed by Yamamura and Amachi (2014). For detoxification of arsenic, microbes surviving in high-arsenic environment have evolved a mechanism for molecular detoxification of arsenic. In this approach, microbes perform reduction of arsenate [As(V)] to arsenite [As(III)] followed by

extrusion of arsenite with the help of *arsenite permeases. Corynebacterium glutamicum*—a gram positive bacterium has resistance to arsenic environments is the workhorse of biotechnological research. *C. glutamicum* bacteria has been modified for their use as sanitation of contaminated soil and water as arsenic-"biocontainer" harboring two operons ars1 and ars2 for encoding resistance against As (Mateos et al. 2017). Role of detoxification genes (aoxB, aoxA and arsM) in microbes playing a role in the arsenic detoxification in low-arsenic continental paddy soils in four climatic zones of China (Zhang et al. 2021). Metal-binding metallothionein proteins are found in many fungi. These proteins help in the immobilization of the arsenic from the soil which can help of removal of accumulated As in crops (Gupta et al. 2022).

### *9.4.3 Introgression of Few Candidate Genes for Detoxification, Sequestration and Efflux of Arsenic Using Recombinant DNA Technology*

Presence of different species of As mainly arsenate and arsenite in soil adversely affect the crop growth and productivity coupled with accumulation of arsenic in different tissues of crop plants. Therefore, most of the endeavors and strategies have been directed at developing transgenic plants using biotechnological interventions to enhance crop productivity in arsenic-contaminated regions by combating As-induced stresses (Kumar et al. 2015). Maximum focus has been concentrated on molecular players encoded by uptake and detoxification genes to develop genetically-engineered plants having the survival ability in arsenic-rich environments (Duan et al. 2012; Shukla et al. 2012; Xu et al. 2007; Zhao et al. 2010a, b). Further, attempts are directed towards inhibiting uptake of arsenic by roots (Duan et al. 2012), sequestration of arsenic in intracellular compartments (Duan et al. 2012; Shukla et al. 2012), moving out of arsenite from the root cells through efflux transporters (Xu et al. 2007) and biotransformation of toxic version of As into lesser toxic methylated species of As (Zhao et al. 2010a, b) for minimizing arsenic-mediated toxicity and its accumulation in crop plants. Further, transgenic technologies for overexpression of candidate genes namely PC synthase, OsGSTL2 encoding for lambda class GST-family member, PvGRX5 gene encoding for glutaredoxin in the genomic background of Indian mustard and *A. thaliana* are reported to confer resilience against arsenic-mediated stress (Li et al. 2004; Shukla et al. 2012, 2013; Wojas et al. 2010; Gasic and Korban 2007; Kumar et al. 2013; Sundaram et al. 2009).

Further, an urgent need for reducing arsenic concentration in one of the principal staple food rice is a priority area to minimize health-risks due to bio-magnification of As in different components food chain. Till date, very limited success is achieved in minimizing grain arsenic content in rice. Attempts have been directed at increasing the efflux of inorganic arsenite version of As and minimizing As accumulation in rice grains by expressing ScACR gene from *Saccharomyces cerevisiae* in the genomic background of rice (Duan et al. 2012). Similarly, biotransformation of As involving

methylation of toxic forms arsenic through overexpression of arsM gene of bacteria in rice helped in minimizing arsenic toxicity (Meng et al. 2011). Further, expression of CdPCS1 from *Ceratophyllum demersum* in rice promoted arsenic accumulation in root tissues and promoted minimum accumulation of As in grain of rice and aerial parts (Shri et al. 2014).

## 9.5 Conclusions

Arsenic is a systemic toxicant and a human carcinogen has serious negative implications on crop growth and productivity, global food and nutritional security, and risks of human and environmental health. Contamination of soil with alarming concentrations of arsenic occurs mostly due to a heavy dependency syndrome on the use of inorganic fertilizers and pesticides containing residues of arsenic and irrigating crops using groundwater concentrated with arsenic in crop production processes. Aforesaid anthropogenic activities contributed to the accumulation of such toxic mettaloid arsenic in different tissues of edible crop plants including cereals, pulses, vegetables, and oilseeds. Further, consumption of edible produce of crops grown in soils polluted with arsenic increases its bio-magnification in different components of food chain resulting in serious health risks and risks of global food and nutritional security. Therefore, there is an urgent need for minimizing arsenic accumulation in crop plants using innovative and sustainable interventions such as genetic engineering, breeding interventions, identification of low grain-arsenic cultivars and agronomic management modules. Application of innovative molecular breeding approaches and emerging biotechnological interventions namely comprehension of existing natural variation for survival ability of crop plants and soil microbiota in arsenic-rich environments, and introgression of few candidate genes for detoxification, sequestration, biotransformation and efflux of arsenic can help in broadening the ways for minimizing arsenic bioaccumulation, evolving As-free safe cultivars of crops and controlling As-biomagnifications in the food chain.

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## References

Ahiamadjie H, Serfor-Armah Y, Tandoh J, Gyampo O, Ofosu F, Dampare S, Adotey D, Nyarko B (2011) Evaluation of trace elements contents in staple foodstuffs from the gold mining areas in southwestern part of Ghana using neutron activation analysis. J Radioanal Nucl Chem 288(3):653–661

Ahmad P, Alyemeni MN, Al-Huqail AA, Alqahtani MA, Wijaya L, Ashraf M, Kaya C, Bajguz A (2020) Zinc oxide nanoparticles application alleviates arsenic (As) toxicity in soybean plants by restricting the uptake of as and modulating key biochemical attributes, antioxidant enzymes, ascorbate-glutathione cycle and glyoxalase system. Plants 9(7):825

Ahmadi N, Frouin J (2021) Molecular breeding for improving arsenic stress tolerance in rice: recent progress and future perspectives. In: Molecular breeding for rice abiotic stress tolerance and nutritional quality, pp 163–179

Ahmadi N, Frouin J, Norton GJ, Price AH (2021) Genomic prediction of arsenic tolerance and grain yield in rice: contribution of trait-specific markers and multi-environment models. Rice Sci 28(3):268–278

Alam MGM, Snow ET, Tanaka A (2003) Arsenic and heavy metal contamination of vegetables grown in Samta village, Bangladesh. Sci Total Environ 308(1–3):83–96

Alamri S, Kushwaha BK, Singh VP, Siddiqui MH, Al-Amri AA, Alsubaie QD, Ali HM (2021) Ascorbate and glutathione independently alleviate arsenate toxicity in brinjal but both require endogenous nitric oxide. Physiol Plant 173(1):276–286

Alsahli AA, Bhat JA, Alyemeni MN, Ashraf M, Ahmad P (2021) Hydrogen sulfide ($H_2S$) mitigates arsenic (As)-induced toxicity in pea (*Pisum sativum* L.) plants by regulating osmoregulation, antioxidant defense system, ascorbate glutathione cycle and glyoxalase system. J Plant Growth Regul 40:2515–2531

Anjum SA, Tanveer M, Hussain S, Shahzad B, Ashraf U, Fahad S, Hassan W, Jan S, Khan I, Saleem MF, Bajwa AA (2016) Osmoregulation and antioxidant production in maize under combined cadmium and arsenic stress. Environ Sci Pollut Res 23(12):11864–11875

Argos M, Kalra T, Rathouz PJ, Chen Y, Pierce B, Parvez F, Islam T, Ahmed A, Rakibuz-Zaman M, Hasan R, Sarwar G (2010) Arsenic exposure from drinking water, and all-cause and chronic-disease mortalities in Bangladesh (HEALS): a prospective cohort study. The Lancet 376(9737):252–258

Azam SMGG, Sarker TC, Naz S (2016) Factors affecting the soil arsenic bioavailability, accumulation in rice and risk to human health: a review. Toxicol Mech Methods 26(8):565–579

Azeem W, Ashraf M, Shahzad SM, Imtiaz M, Akhtar M, Rizwan MS (2017) Phosphate-arsenate relations to affect arsenic concentration in plant tissues, growth, and antioxidant efficiency of sunflower (*Helianthus annuus* L.) under arsenic stress. Environ Sci Pollut Res 24:24376–24386

Banerjee S, Islam J, Mondal S, Saha A, Saha B, Sen A (2023) Proactive attenuation of arsenic-stress by nano-priming: zinc oxide nanoparticles in *Vigna mungo* (L.) Hepper trigger antioxidant defense response and reduce root-shoot arsenic translocation. J Hazard Mater 130735

Bhattacharya S, Gupta K, Debnath S, Ghosh UC, Chattopadhyay D, Mukhopadhyay A (2012) Arsenic bioaccumulation in rice and edible plants and subsequent transmission through food chain in Bengal basin: a review of the perspectives for environmental health. Toxicol Environ Chem 94(3):429–441

Bhattacharya S, Guha G, Gupta K, Chattopadhyay D, Mukhopadhyay A, Ghosh UC (2014) Trend of arsenic pollution and subsequent bioaccumulation in *Oryza sativa* and *Corchorus capsularis* in Bengal Delta. Int Lett Nat Sci 16

Bhatti SM, Anderson CWN, Stewart RB, Robinson BH (2013) Risk assessment of vegetables irrigated with arsenic-contaminated water. Environ Sci Process Impacts 15(10):1866–1875

Bianucci E, Godoy A, Furlan A, Peralta JM, Hernández LE, Carpena-Ruiz RO, Castro S (2018) Arsenic toxicity in soybean alleviated by a symbiotic species of Bradyrhizobium. Symbiosis 74:167–176

Bleeker PM, Hakvoort HW, Bliek M, Souer E, Schat H (2006) Enhanced arsenate reduction by a CDC25-like tyrosine phosphatase explains increased phytochelatin accumulation in arsenate-tolerant *Holcus lanatus*. Plant J 45(6):917–929

Burlo F, Guijarro I, Carbonell-Barrachina AA, Valero D, Martinez-Sanchez F (1999) Arsenic species: effects on and accumulation by tomato plants. J Agric Food Chem 47(3):1247–1253

Cattani I, Beone GM, Gonnelli C (2015) Influence of *Rhizophagus irregularis* inoculation and phosphorus application on growth and arsenic accumulation in maize (*Zea mays* L.) cultivated on an arsenic-contaminated soil. Environ Sci Pollut Res 22(9):6570–6577

Chandra S, Saha R, Pal P (2016) Arsenic uptake and accumulation in okra (*Abelmoschus esculentus*) as affected by different arsenical speciation. Bull Environ Contam Toxicol 96:395–400

Chaturvedi I (2006) Effects of arsenic concentrations and forms on growth and arsenic uptake and accumulation by Indian mustard (*Brassica juncea* L.) genotypes. J Cent Eur Agric 7(1):31–40

Chi Y, Li F, Tam NFY, Liu C, Ouyang Y, Qi X, Li WC, Ye Z (2018) Variations in grain cadmium and arsenic concentrations and screening for stable low-accumulating rice cultivars from multi-environment trials. Sci Total Environ 643:1314–1324

Chintey R, Prakash P, Kumar K (2022) Evaluation of germination attributes, metal tolerance index and phytotoxicity index in green gram cultivars [*Vigna radiata* (L) Wilczek] under arsenic toxicity

Codling EE, Chaney RL, Green CE (2016) Accumulation of lead and arsenic by potato grown on lead–arsenate-contaminated orchard soils. Commun Soil Sci Plant Anal 47(6):799–807

Collard BCY, Jahufer MZZ, Brouwer JB, Pang ECK (2005) An introduction to markers, quantitative trait loci (QTL) mapping and marker-assisted selection for crop improvement: the basic concepts. Euphytica 142:169–196. https://doi.org/10.1007/s10681-005-1681-5

Das CK (2021) Nanomaterials in the bioremediation of metal-contaminated soils. In: Nanomaterials for soil remediation, pp 319–369

Das CK, Bastia D, Swain SC, Mahapatra SS (2018a) Computational analysis of genes encoding for molecular determinants of arsenic tolerance in rice (*Oryza sativa* L.) to engineer low arsenic content varieties. ORYZA Int J Rice 55(2):248–259

Das CK, Bastia D, Naik BS, Kabat B, Mohanty MR, Mahapatra SS (2018b) GGE biplot and AMMI analysis of grain yield stability and adaptability behaviour of paddy (*Oryza sativa* L.) genotypes under different agroecological zones of Odisha. ORYZA Int J Rice 55(4):528–542

Das D, Sen P, Purkayastha S, Saha AK, Roy A, Rai P, Sen S, Saha S, Senapati BK, Biswas T, Bhattacharyya S (2021) A perfect PCR based co-dominant marker for low grain-arsenic accumulation genotyping in rice. Ecotoxicol Environ Saf 212:111960

Dasgupta T, Hossain SA, Meharg AA, Price AH (2004) An arsenate tolerance gene on chromosome 6 of rice. New Phytol 45–49

Dhankher OP, Rosen BP, McKinney EC, Meagher RB (2006) Hyperaccumulation of arsenic in the shoots of Arabidopsis silenced for arsenate reductase (ACR2). Proc Natl Acad Sci 103(14):5413–5418

Ding D, Li W, Song G, Qi H, Liu J, Tang J (2011) Identification of QTLs for arsenic accumulation in maize (*Zea mays* L.) using a RIL population. PLoS ONE 6(10):e25646

Duan G, Kamiya T, Ishikawa S, Arao T, Fujiwara T (2012) Expressing ScACR3 in rice enhanced arsenite efflux and reduced arsenic accumulation in rice grains. Plant Cell Physiol 53(1):154–163

Fergusson JE (1990) The heavy elements: chemistry, environmental impact and health effects. Pergamon Press, Oxford, p 1990

Frouin J, Labeyrie A, Boisnard A, Sacchi GA, Ahmadi N (2019) Genomic prediction offers the most effective marker assisted breeding approach for ability to prevent arsenic accumulation in rice grains. PLoS ONE 14(6):e0217516

Fu Z, Li W, Xing X, Xu M, Liu X, Li H, Xue Y, Liu Z, Tang J (2016) Genetic analysis of arsenic accumulation in maize using QTL mapping. Sci Rep 6(1):1–8

Garg N, Singla P, Bhandari P (2015) Metal uptake, oxidative metabolism, and mycorrhization in pigeon pea and pea under arsenic and cadmium stress. Turk J Agric For 39(2):234–250

Gasic K, Korban SS (2007) Transgenic Indian mustard (*Brassica juncea*) plants expressing an Arabidopsis phytochelatin synthase (AtPCS1) exhibit enhanced As and Cd tolerance. Plant Mol Biol 64:361–369

Gulz PA, Gupta SK, Schulin R (2005) Arsenic accumulation of common plants from contaminated soils. Plant Soil 272(1):337–347

Gupta A, Dubey P, Kumar M, Roy A, Sharma D, Khan MM, Bajpai AB, Shukla RP, Pathak N, Hasanuzzaman M (2022) Consequences of arsenic contamination on plants and mycoremediation-mediated arsenic stress tolerance for sustainable agriculture. Plants 11(23):3220

Haque M, Ali M, Roy TS, Masum SM, Chowdhury IF (2015) Yield reduction and arsenic accumulation in potatoes (*Solanum tuberosum* L.) in an arsenic contaminated soil. Agron Colomb 33(3):315–321

Heffner EL, Sorrells ME, Jannink J-L (2009) Genomic selection for crop improvement. Crop Sci 49:1–12

Hwang SG, Chapagain S, Lee JW, Han AR, Jang CS (2017) Genome-wide transcriptome profiling of genes associated with arsenate toxicity in an arsenic-tolerant rice mutant. Plant Physiol Biochem 120:40–51

Indriolo E, Na G, Ellis D, Salt DE, Banks JA (2010) A vacuolar arsenite transporter necessary for arsenic tolerance in the arsenic hyperaccumulating fern *Pteris vittata* is missing in flowering plants. Plant Cell 22(6):2045–2057

Irshad S, Xie Z, Mehmood S, Nawaz A, Ditta A, Mahmood Q (2021) Insights into conventional and recent technologies for arsenic bioremediation: a systematic review. Environ Sci Pollut Res 28(15):18870–18892

Jayasumana C, Fonseka S, Fernando A, Jayalath K, Amarasinghe M, Siribaddana S, Gunatilake S, Paranagama P (2015) Phosphate fertilizer is a main source of arsenic in areas affected with chronic kidney disease of unknown etiology in Sri Lanka. SpringerPlus 4:1–8

Jia Y, Huang H, Chen Z, Zhu YG (2014) Arsenic uptake by rice is influenced by microbe-mediated arsenic redox changes in the rhizosphere. Environ Sci Technol 48(2):1001–1007

Kabata-Pendias A, Pendias H (2001) Trace elements in soils and plants. Boca Raton

Khan I, Ahmad A, Iqbal M (2009) Modulation of antioxidant defence system for arsenic detoxification in Indian mustard. Ecotoxicol Environ Saf 72(2):626–634

Khanna K, Kohli SK, Kumar P, Ohri P, Bhardwaj R, Alam P, Ahmad P (2022) Arsenic as hazardous pollutant: perspectives on engineering remediation tools. Sci Total Environ 155870

Kumar S, Asif MH, Chakrabarty D, Tripathi RD, Dubey RS, Trivedi PK (2013) Expression of a rice Lambda class of glutathione S-transferase, OsGSTL2, in Arabidopsis provides tolerance to heavy metal and other abiotic stresses. J Hazard Mater 248:228–237

Kumar S, Dubey RS, Tripathi RD, Chakrabarty D, Trivedi PK (2015) Omics and biotechnology of arsenic stress and detoxification in plants: current updates and prospective. Environ Int 74:221–230

Kundu R, Pal S (2012) Arsenic accumulation in sesame (*Sesamum indicum*) cultivars under deltaic Bengal conditions. Crop Res 43(1–3):42–46

Kundu R, Majumder A, Pal S (2012) Evaluation of potato cultivars against arsenic accumulation under an arsenic contaminated zone of Eastern India. Potato J 39(1):62–68

Kuramata M, Abe T, Kawasaki A, Ebana K, Shibaya T, Yano M, Ishikawa S (2013) Genetic diversity of arsenic accumulation in rice and QTL analysis of methylated arsenic in rice grains. Rice 6(1):1–10

Lee JS, Lee SW, Chon HT et al (2008) Evaluation of human exposure to arsenic due to rice ingestion in the vicinity of abandoned Myungbong Au–Ag mine site, Korea. J Geochem Explor 96:231–235

Li Y, Dhankher OP, Carreira L, Lee D, Chen A, Schroeder JI, Balish RS, Meagher RB (2004) Overexpression of phytochelatin synthase in Arabidopsis leads to enhanced arsenic tolerance and cadmium hypersensitivity. Plant Cell Physiol 45(12):1787–1797

Li RY, Ago Y, Liu WJ, Mitani N, Feldmann J, McGrath SP, Ma JF, Zhao FJ (2009) The rice aquaporin Lsi1 mediates uptake of methylated arsenic species. Plant Physiol 150(4):2071–2080

Liu H, Probst A, Liao B (2005) Metal contamination of soils and crops affected by the Chenzhou lead/zinc mine spill (Hunan, China). Sci Total Environ 339(1–3):153–166

Liu WJ, Zhu YG, Hu Y, Williams PN, Gault AG, Meharg AA, Charnock JM, Smith FA (2006) Arsenic sequestration in iron plaque, its accumulation and speciation in mature rice plants (*Oryza sativa* L.). Environ Sci Technol 40(18):5730–5736

Liu WJ, Wood BA, Raab A, McGrath SP, Zhao FJ, Feldmann J (2010) Complexation of arsenite with phytochelatins reduces arsenite efflux and translocation from roots to shoots in Arabidopsis. Plant Physiol 152(4):2211–2221

Lorenz AJ, Chao S, Asoro FG, Heffner EL, Hayashi T, Iwata H, Smith KP, Sorrells ME, Jannink JL (2011) Genomic selection in plant breeding: knowledge and prospects. Adv Agron 110:77–123

Lu Y, Adomako EE, Solaiman ARM et al (2009) Baseline soil variation is a major factor in arsenic accumulation in Bengal Delta paddy rice. Environ Sci Technol 43:1724–1729

Mackay TFC, Stone EA, Ayroles JF (2009) The genetics of quantitative traits: challenges and prospects. Nat Rev Genet 10:565–577. https://doi.org/10.1038/nrg2612

Mateos LM, Villadangos AF, Alfonso G, Mourenza A, Marcos-Pascual L, Letek M, Pedre B, Messens J, Gil JA (2017) The arsenic detoxification system in coryne bacteria: basis and application for bioremediation and redox control. Adv Appl Microbiol 99:103–137

McBride MB, Shayler HA, Russell-Anelli JM, Spliethoff HM, Marquez-Bravo LG (2015) Arsenic and lead uptake by vegetable crops grown on an old orchard site amended with compost. Water Air Soil Pollut 226(8):1–10

Meharg AA, Macnair MR (1992) Suppression of the high affinity phosphate uptake system: a mechanism of arsenate tolerance in *Holcus lanatus* L. J Exp Bot 43(4):519–524

Meng XY, Qin J, Wang LH, Duan GL, Sun GX, Wu HL, Chu CC, Ling HQ, Rosen BP, Zhu YG (2011) Arsenic biotransformation and volatilization in transgenic rice. New Phytol 191(1):49–56

Mirza N, Mahmood Q, Maroof Shah M, Pervez A, Sultan S (2014) Plants as useful vectors to reduce environmental toxic arsenic content. Sci World J 2014

Miteva E (2002) Accumulation and effect of arsenic on tomatoes. Commun Soil Sci Plant Anal 33(11–12):1917–1926

Mumthas S, Chidambaram AA, Sundaramoorthy P, Ganesh KS (2010) Effect of arsenic and manganese on root growth and cell division in root tip cells of green gram (*Vigna radiata* L.). Emir J Food Agric 285–297

Mylona PV, Polidoros AN, Scandalios JG (1998) Modulation of antioxidant responses by arsenic in maize. Free Radical Biol Med 25(4–5):576–585

Norton GJ, Deacon CM, Xiong L, Huang S, Meharg AA, Price AH (2010) Genetic mapping of the rice ionome in leaves and grain: identification of QTLs for 17 elements including arsenic, cadmium, iron and selenium. Plant Soil 329(1):139–153

Norton GJ, Duan GL, Lei M, Zhu YG, Meharg AA, Price AH (2012) Identification of quantitative trait loci for rice grain element composition on an arsenic impacted soil: influence of flowering time on genetic loci. Ann Appl Biol 161(1):46–56

Oller ALW, Regis S, Armendariz AL, Talano MA, Agostini E (2020) Improving soybean growth under arsenic stress by inoculation with native arsenic-resistant bacteria. Plant Physiol Biochem 155:85–92

Pigna M, Cozzolino V, Violante A, Meharg AA (2009) Influence of phosphate on the arsenic uptake by wheat (*Triticum durum* L.) irrigated with arsenic solutions at three different concentrations. Water Air Soil Pollut 197(1):371–380

Pigna M, Cozzolino V, Giandonato Caporale A, Mora ML, Di Meo V, Jara AA, Violante A (2010) Effects of phosphorus fertilization on arsenic uptake by wheat grown in polluted soils. J Soil Sci Plant Nutr 10(4):428–442

Pinter IF, Salomon MV, Gil R, Mastrantonio L, Bottini R, Piccoli P (2018) Arsenic and trace elements in soil, water, grapevine and onion in Jáchal, Argentina. Sci Total Environ 615:1485–1498

Poynton CY, Huang JW, Blaylock MJ, Kochian LV, Elless MP (2004) Mechanisms of arsenic hyperaccumulation in Pteris species: root As influx and translocation. Planta 219:1080–1088

Qin J, Niu A, Liu Y, Lin C (2021) Arsenic in leafy vegetable plants grown on mine water-contaminated soils: uptake, human health risk and remedial effects of biochar. J Hazard Mater 402:123488

Raab A, Feldmann J, Meharg AA (2004) The nature of arsenic-phytochelatin complexes in *Holcus lanatus* and *Pteris cretica*. Plant Physiol 134(3):1113–1122
Raab A, Williams PN, Meharg A, Feldmann J (2007) Uptake and translocation of inorganic and methylated arsenic species by plants. Environ Chem 4(3):197–203
Rahman MA, Hasegawa H (2011) High levels of inorganic arsenic in rice in areas where arsenic-contaminated water is used for irrigation and cooking. Sci Total Environ 409(22):4645–4655
Rodríguez-Ruiz M, Aparicio-Chacón MV, Palma JM, Corpas FJ (2019) Arsenate disrupts ion balance, sulfur and nitric oxide metabolisms in roots and leaves of pea (*Pisum sativum* L.) plants. Environ Exp Bot 161:143–156
Rosas-Castor JM, Guzmán-Mar JL, Hernández-Ramírez A, Garza-González MT, Hinojosa-Reyes L (2014a) Arsenic accumulation in maize crop (*Zea mays*): a review. Sci Total Environ 488:176–187
Rosas-Castor JM, Guzmán-Mar JL, Alfaro-Barbosa JM, Hernández-Ramírez A, Pérez-Maldonado IN, Caballero-Quintero A, Hinojosa-Reyes L (2014b) Evaluation of the transfer of soil arsenic to maize crops in suburban areas of San Luis Potosi, Mexico. Sci Total Environ 497:153–162
Roychowdhury T, Uchino T, Tokunaga H, Ando M (2002) Survey of arsenic in food composites from an arsenic-affected area of West Bengal, India. Food Chem Toxicol 40(11):1611–1621
Sahito ZA, Zehra A, Tang L, Ali Z, Bano N, Ullah MA, He Z, Yang X (2021) Arsenic and mercury uptake and accumulation in oilseed sunflower accessions selected to mitigate co-contaminated soil coupled with oil and bioenergy production. J Clean Prod 291:125226
Saidi I, Yousfi N, Borgi MA (2017) Salicylic acid improves the antioxidant ability against arsenic-induced oxidative stress in sunflower (*Helianthus annuus*) seedling. J Plant Nutr 40(16):2326–2335
Schaeffer LR (2006) Strategy for applying genome-wide selection in dairy cattle. J Anim Breed Genet 123:218–223
Seed M, Quraishi UM, Malik RN (2022) Identification of arsenic-tolerant varieties and candidate genes of tolerance in spring wheat (*Triticum aestivum* L.). Chemosphere 308:136380
Shahid MA, Balal RM, Khan N, Zotarelli L, Liu GD, Sarkhosh A, Fernández-Zapata JC, Nicolás JJM, Garcia-Sanchez F (2019) Selenium impedes cadmium and arsenic toxicity in potato by modulating carbohydrate and nitrogen metabolism. Ecotoxicol Environ Saf 180:588–599
Sharma KJ, Kumar N, Singh NP, Santal AR (2023) Phytoremediation technologies and their mechanism for removal of heavy metal from contaminated soil: an approach for a sustainable environment. Front Plant Sci 14. https://doi.org/10.3389/fpls.2023.1076876
Shi GL, Zhu S, Meng JR, Qian M, Yang N, Lou LQ, Cai QS (2015a) Variation in arsenic accumulation and translocation among wheat cultivars: the relationship between arsenic accumulation, efflux by wheat roots and arsenate tolerance of wheat seedlings. J Hazard Mater 289:190–196
Shi GL, Zhu S, Bai SN, Xia Y, Lou LQ, Cai QS (2015b) The transportation and accumulation of arsenic, cadmium, and phosphorus in 12 wheat cultivars and their relationships with each other. J Hazard Mater 299:94–102
Shri M, Dave R, Diwedi S, Shukla D, Kesari R, Tripathi RD, Trivedi PK, Chakrabarty D (2014) Heterologous expression of *Ceratophyllum demersum* phytochelatin synthase, CdPCS1, in rice leads to lower arsenic accumulation in grain. Sci Rep 4(1):1–10
Shukla D, Kesari R, Mishra S, Dwivedi S, Tripathi RD, Nath P, Trivedi PK (2012) Expression of phytochelatin synthase from aquatic macrophyte *Ceratophyllum demersum* L. enhances cadmium and arsenic accumulation in tobacco. Plant Cell Rep 31:1687–1699
Shukla D, Kesari R, Tiwari M, Dwivedi S, Tripathi RD, Nath P, Trivedi PK (2013) Expression of *Ceratophyllum demersum* phytochelatin synthase, CdPCS1, in *Escherichia coli* and Arabidopsis enhances heavy metal(loid)s accumulation. Protoplasma 250:1263–1272
Singh R, Singh S, Parihar P, Singh VP, Prasad SM (2015) Arsenic contamination, consequences and remediation techniques: a review. Ecotoxicol Environ Saf 112:247–270
Sinha B, Bhattacharyya K, Giri PK, Sarkar S (2011) Arsenic contamination in sesame and possible mitigation through organic interventions in the lower Gangetic Plain of West Bengal, India. J Sci Food Agric 91(15):2762–2767

Spagnoletti F, Lavado RS (2015) The arbuscular mycorrhiza *Rhizophagus intraradices* reduces the negative effects of arsenic on soybean plants. Agronomy 5(2):188–199
Srivastava S, Sharma YK (2013) Impact of arsenic toxicity on black gram and its amelioration using phosphate. Int Sch Res Notices 2013
Srivastava S, Sharma YK (2014) Arsenic induced changes in growth and metabolism of black gram seedlings (*Vigna mungo* L.) and the role of phosphate as an ameliorating agent. Environ Process 1:431–445
Stoeva N, Berova M, Zlatev Z (2003) Physiological response of maize to arsenic contamination. Biol Plant 47(3):449–452
Su C (2014) A review on heavy metal contamination in the soil worldwide: situation, impact and remediation techniques. Environ Skept Crit 3(2):24
Su YH, McGrath SP, Zhu YG, Zhao FJ (2008) Highly efficient xylem transport of arsenite in the arsenic hyperaccumulator *Pteris vittata.* New Phytol 180(2):434–441
Suhel M, Husain T, Prasad SM, Singh VP (2022) GABA requires nitric oxide for alleviating arsenate stress in tomato and brinjal seedlings. J Plant Growth Regul 1–14
Sundaram S, Wu S, Ma LQ, Rathinasabapathi B (2009) Expression of a *Pteris vittata* glutaredoxin PvGRX5 in transgenic *Arabidopsis thaliana* increases plant arsenic tolerance and decreases arsenic accumulation in the leaves. Plant Cell Environ 32:851–858
Syed M, Iftekharuddaula KM, Mian MA, Rasul M, Rahmam GKM, Panaullah GM, Lauren JG, Duxbury JM, Biswas PS (2016) Main effect QTLs associated with arsenic phyto-toxicity tolerance at seedling stage in rice (*Oryza sativa* L.). Euphytica 209(3):805–814
Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ (2012) Heavy metal toxicity and the environment. In: Molecular, clinical and environmental toxicology, pp 133–164
Thakur S, Choudhary S, Dubey P, Bhardwaj P (2019) Comparative transcriptome profiling reveals the reprogramming of gene networks under arsenic stress in Indian mustard. Genome 62(12):833–847
Tibbs Cortes L, Zhang Z, Yu J (2021) Status and prospects of genome-wide association studies in plants. Plant Genome 14(1):e20077
Torres-Escribano S, Leal M, Vélez D et al (2008) Total and inorganic arsenic concentrations in rice sold in Spain, effect of cooking, and risk assessments. Environ Sci Technol 42:3867–3872
Tripathi RD, Srivastava S, Mishra S, Singh N, Tuli R, Gupta DK, Maathuis FJ (2007) Arsenic hazards: strategies for tolerance and remediation by plants. Trends Biotechnol 25(4):158–165
Tuan HT, Van Chuong N (2021) Yield component, production and arsenic accumulation of groundnuts as swayed by application of lime, vermicompost combined with Rhizobium inoculant. Int J Mech Eng 6:5864–5869
Vezza ME, Luna DF, Agostini E, Talano MA (2019) Glutathione, a key compound for As accumulation and tolerance in soybean plants treated with AsV and AsIII. Environ Exp Bot 162:272–282
Williams PN, Islam MR, Hussain SA et al (2005a) Arsenic absorption by rice. In: Behavior of arsenic in aquifers, soils and plants (conference proceedings), Dhaka
Williams PN, Price AH, Raab A et al (2005b) Variation in arsenic speciation and concentration in paddy rice related to dietary exposure. Environ Sci Technol 39:5531–5540
Williams PN, Raab A, Feldmann J et al (2007) High levels of arsenic in South Central US rice grain: consequences for human dietary exposure. Environ Sci Technol 152:746–749
Wojas S, Clemens S, SkŁodowska A, Antosiewicz DM (2010) Arsenic response of AtPCS1- and CePCS-expressing plants—effects of external As(V) concentration on As-accumulation pattern and NPT metabolism. J Plant Physiol 167(3):169–175
Xu XY, McGrath SP, Zhao FJ (2007) Rapid reduction of arsenate in the medium mediated by plant roots. New Phytol 176(3):590–599
Yamamura S, Amachi S (2014) Microbiology of inorganic arsenic: from metabolism to bioremediation. J Biosci Bioeng 118(1):1–9

Yu Y, Zhang S, Huang H, Luo L, Wen B (2009) Arsenic accumulation and speciation in maize as affected by inoculation with arbuscular mycorrhizal fungus *Glomus mosseae*. J Agric Food Chem 57(9):3695–3701

Zeng D, Zhou S, Ren B, Chen T (2015) Bioaccumulation of antimony and arsenic in vegetables and health risk assessment in the superlarge antimony-mining area, China. J Anal Methods Chem 2015

Zhang J, Zhu YG, Zeng DL, Cheng WD, Qian Q, Duan GL (2008) Mapping quantitative trait loci associated with arsenic accumulation in rice (*Oryza sativa*). New Phytol 177(2):350–356

Zhang WD, Liu DS, Tian JC, He FL (2009) Toxicity and accumulation of arsenic in wheat (*Triticum aestivum* L.) varieties of China. Phyton (Buenos Aires) 78(2):147–154

Zhang C, Xiao X, Zhao Y, Zhou J, Sun B, Liang Y (2021) Patterns of microbial arsenic detoxification genes in low-arsenic continental paddy soils. Environ Res 201:111584

Zhao FJ, McGrath SP, Meharg AA (2010a) Arsenic as a food chain contaminant: mechanisms of plant uptake and metabolism and mitigation strategies. Annu Rev Plant Biol 61:535–559

Zhao FJ, Stroud JL, Eagling T, Dunham SJ, McGrath SP, Shewry PR (2010b) Accumulation, distribution, and speciation of arsenic in wheat grain. Environ Sci Technol 44(14):5464–5468

Zhao Z, Zhang H, Fu Z, Chen H, Lin Y, Yan P, Li W, Xie H, Guo Z, Zhang X, Tang J (2018) Genetic-based dissection of arsenic accumulation in maize using a genome-wide association analysis method. Plant Biotechnol J 16(5):1085–1093

Zhu C, Gore MA, Buckler ES, Yu J (2008) Status and prospects of association mapping in plants. Plant Genome 1:5–20. https://doi.org/10.3835/plantgenome2008.02.0089

# Chapter 10
# Herbal Options for Arsenic Toxicity Mitigation: An Appraisal

**Sanjib Bhattacharya**

**Abstract** Arsenic toxicity, caused mainly by arsenic-contaminated groundwater, is considered as a critical threat to global communal health, as there is no specific and proven conventional therapy for chronic arsenic toxicity i.e., arsenicosis. Therefore, alternative herbal options should be explored for its mitigation. Literature survey reveals several medicinal plants to possess significant protective efficacy against arsenic toxicity in chiefly pre-clinical and few clinical investigations. In this chapter, the medicinal herbs that have arsenic toxicity ameliorative properties are collated as preclinical and clinical evidences which may be useful develop a potential nutraceutical or therapeutic candidate against arsenicosis in humans along with extant therapies.

**Keywords** Arsenic toxicity · Arsenicosis · Medicinal plants · *Spirulina*

## 10.1 Introduction

Arsenic is an element (metalloid) naturally omnipresent in earth. It is found in soil and groundwater from rocks and sediments by their weathering and subsequent percolation. It is also moved to soil and groundwater by different anthropogenic affairs like mining (Behera and Bhattacharya 2016). It is physiologically non-essential and systemic mammalian toxicant. People are subjected to arsenic chiefly via contaminated potable water; skin absorption and inhalation are the minor ways of entry (Shi et al. 2004). Occupational arsenic exposure and regular consumption of arsenic-contaminated potable water for long time by humans precipitates irreversible carcinogenesis of the most body parts/organs; dermatological complications like hyperpigmentation and hyperkeratosis ultimately resulting in skin and epithelial

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tissue cancers; hepatic, renal, respiratory, cardiovascular, gastrointestinal, reproductive (including teratogenesis), neurological complications; thereby imposing morbid health quality (Kapaj et al. 2006; Abdul et al. 2015; Raju 2022). Arsenic is entrenched as human carcinogen according to the international regulatory bodies viz. the U.S. Environmental Protection Agency, the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) (Rafati-Rahimzadeh et al. 2014; Boerleider et al. 2017). 10 μg/L limit or parts per billion (ppb) is endorsed by the WHO for arsenic in drinking water, above which, it may precipitate toxic effects of arsenic within the body. Chronic arsenic toxicity syndrome i.e., arsenicosis due to daily consumption of arsenic-contaminated underground water is a grave global public health menace affecting 50 countries specially inflicting India, Pakistan, Bangladesh, Iran, Myanmar, Czech Republic, China, Thailand, Taiwan, Vietnam, Egypt, Argentina and Chile where arsenic contents in the ground water have been detected several fold inflated than the foregoing prescribed level (Raju 2022).

The harmful consequences of arsenic intrusion in body and their typical treatments were well reported (Abdul et al. 2015). Chelation therapy i.e., administration of metal complexing or chelating agents for arsenic toxicity may be considered as the specified therapy for symptomatic and systemic solace and metabolic arsenic elimination from body by forming a complex with arsenic, thus preventing subsequent health hazard risks like cancers. Chelating agents, viz. dimercaptosuccinic acid (DMSA), D-penicillamine and dimercaptopropane succinate (DMPS) are currently employed to treat acute and sub-chronic arsenic poisoning. Even so, their clinical utility for long-term treatment of chronic arsenic toxicity i.e., arsenicosis has not been established yet (Rafati-Rahimzadeh et al. 2014; Abdul et al. 2015; Boerleider et al. 2017). Complexing agents may not be fit for high-dose and long-term arsenicosis therapy for humans. Currently, there is no clinically proven therapy for long-term use on arsenicosis victims. Therefore, the necessity of unorthodox alternatives for averting arsenic toxicity appear rather obvious.

Several detrimental health complications are reported on account of continuous and long term exposure of arsenic. For that reason, unconventional approaches to restrain heavy arsenic-induced chronic toxicity may be fruitful. Herbal, medicinal and aromatic plants were found to alleviate experimental toxic element/heavy metal or metalloid toxicity (Bhattacharya 2017, 2018a, b, 2023). Right now, there is an urgent necessity to develop innocuous and efficacious herbal-based products against arsenicosis. The use of medicinal plants appears a viable option because of their perceived safety and efficacy profile and relatively lower costs. The natural herbs may normally be consumed as diet, physiologically accepted to the body innately and produce less or no untoward effects hence may overrule the untoward consequences of the typical chelation remedy. Several medicinal plants afforded significant mitigation form experimentally-induced arsenic toxicity chiefly in animals. The object of the present chapter is to collate the apropos pre-clinical and clinically effective herbs from the scientific literature.

## 10.2 Methodology

### *10.2.1 Inclusion Criteria*

Internet-oriented scrutiny of scientific literature was performed by different online databases viz. Google, Scholar Google, Pubmed, Toxnet, Wiley and Science Direct by using keywords and key phrases like—arsenic toxicity amelioration/prevention/protection/alleviation by medicinal plants (common or botanical names) in different combinations. The experimental research articles written in English language found in internet in the last twenty five years were appraised here. The pre-clinical and clinical studies conducted on medicinal plants effective in the obviation of sub-acute and chronic arsenic toxicity were hand-picked.

### *10.2.2 Exclusion Criteria*

Articles other than the language English were not considered. Combinations of medicinal plants with other substances were kept beyond the scope of present endeavor. Environmental remediation effects of medicinal plants i.e., activity of medicinal plants/extracts in removing arsenic and its compounds from the environment (water, soil, etc.) were not within the current scope of compilation and review.

## 10.3 Results

### *10.3.1 Pre-clinical Studies*

Sixty five medicinal plants have been reported to possess experimental arsenic-induced toxicity alleviative effect in animal systems. The details have been enumerated in Table 10.1. The most studied plants include putative higher dietary and medicinal plants. Lower plant (algae) is *Arthospira*/*Spirulina* (Fig. 10.1).

In maximum instances, the crude extracts of dry powdered plant materials by using suitable solvents were employed for the experiments. In few cases like *Camellia sinensis*, *Vitis vinifera*, *Clerodendrum volubile*, *Vernonia amygdalina* certain chemical constituent-enriched extracts/fractions were employed and demonstrated beneficial effects in obviating arsenic-induced collective organ toxicities in animals.

Apart from cells/cell lines, the most common intact animal models were rodents like rats and mice. The common reported parameters include haematological (serum) and major organ (liver, brain, kidney, lung, gonads etc.) biochemistry profiles i.e.,

**Table 10.1** Medicinal plants with pre-clinical arsenic toxicity ameliorative potential

| S. No. | Botanical name | Part/constituents used | Experimental model | Organ(s)/system/cell line involved | References |
|---|---|---|---|---|---|
| 1 | *Withania somnifera* | Root | Rats | Testes, liver, kidney, blood | Kumar et al. (2013, 2015a, b) |
| 2 | *Ipomea aquatica* | Aerial parts | Mice | Liver, kidney, heart, brain and testes | Dua et al. (2015) |
| 3 | *Mentha piperita* | Leaf | Mice | Liver | Sharma et al. (2007) |
| | | Leaf | Rats | Blood, lungs, liver, kidney | Islam et al. (2018) |
| 4 | *Carica papaya* | Fruit | Mice | Testes | Singh and Kumari (2013) |
| 5 | *Phyllanthus emblica* | Leaf | Mice | Liver, kidney and spleen | Sayed et al. (2015) |
| 6 | *Emblica officinalis* | Fruit | Mice | Liver, thymus, spleen, blood | Sharma et al. (2009) and Singh et al. (2013a, b, 2014, 2015, 2018) |
| | | Fruit | Rats | Liver, kidney, blood | Maiti et al. (2014) and Kumar et al. (2015c) |
| | | Fruit | Chicken | Blood | Padmaja et al. (2009) |
| | | Fruit | Japanese quails (*Coturnix coturnix japonica*) | Testes, ovary, liver, kidney, brain, pancreas, heart | Meena et al. (2018) |
| 7 | *Pteris longifolia* | Leaf | Rats | Liver, kidney | Kumar et al. (2015b) |
| 8 | *Triticum aestivum* | Leaf | Rats | Liver, kidney | Lakshmi et al. (2015) |
| 9 | *Azadirachta indica* | Leaf | Rats | Liver | Oyewole (2011) |
| 10 | *Tephrosia purpurea* | Aerial parts | Rats | Liver, kidney, blood, intestine | Gora et al. (2013, 2014) and Baxla et al. (2014) |

(continued)

**Table 10.1** (continued)

| S. No. | Botanical name | Part/constituents used | Experimental model | Organ(s)/system/cell line involved | References |
|---|---|---|---|---|---|
| 11 | *Irvingia gabonensis* | Leaf | Rats | Liver, kidney | Gbadegesin et al. (2014) and Ewere et al. (2019) |
| 12 | *Eupatorium buniifolium* | Aerial parts | – | Renal Vero cells | Soria et al. (2008) |
| 13 | *Mandevilla pentlandiana* | Aerial parts | – | Renal Vero cells | Soria et al. (2008) |
| 14 | *Sebastiania commersoniana* | Aerial parts | – | Renal Vero cells | Soria et al. (2008) |
| 15 | *Heterothalamus alienus* | Aerial parts | – | Renal Vero cells | Soria et al. (2008) |
| 16 | *Boerhavia diffusa* | Aerial parts | – | H9c2 cardiomyocytes | Vineetha et al. (2013) |
| 17 | *Camellia sinensis* | Black and green tea | Mice | Liver | Sinha et al. (2010) |
| | | Green tea | Rat | Liver | Acharyya et al. (2014) |
| | | Green tea | Mice | Liver, kidney | Fatmi et al. (2017a) |
| | | Black and green tea | Rabbit | Blood | Raihan et al. (2009) |
| | | Tannin-rich fraction of green tea | Rats | Liver and kidney | Chandronitha et al. (2010) |
| 18 | *Malus domestica* | Fruit peel | – | H9c2 cardiac myoblast cells | Vineetha et al. (2014) |
| 19 | *Vitis vinifera* | Seed proanthocyanidin extract | Mice | Testes | Li et al. (2015) |
| | | Seed | Rat | Liver | Xinjuan et al. (2011) |
| 20 | *Lantana grisebachii* | Aerial parts | Rats | Blood | Soria et al. (2014) |
| | | Aerial parts | – | Renal Vero cells | Soria et al. (2008) |

(continued)

**Table 10.1** (continued)

| S. No. | Botanical name | Part/constituents used | Experimental model | Organ(s)/system/cell line involved | References |
|---|---|---|---|---|---|
| 21 | *Chlorophytum borivilianum* | Root | Mice | Testes | Sharma and Kumar (2014) |
| 22 | *Phyllanthus fraternus* | Whole plant | – | Chicken liver cell | Verma et al. (2007) |
| 23 | *Trichosanthes dioica* | Root | Rat | Liver, kidney, heart, brain | Bhattacharya and Haldar (2012a, b, 2013) |
| | | Fruit | Rat | Liver, kidney, heart | Bhattacharya and Haldar (2012c) and Bhattacharya et al. (2014) |
| 24 | *Moringa oleifera* | Whole plant | – | Chicken liver cell | Verma et al. (2007) |
| | | Seed | Rat | Liver, kidney | Gupta et al. (2005) |
| | | Leaf | Mice | Heart, liver, kidney, embryo | Sheikh et al. (2014) and Ali et al. (2023) |
| | | Flower | Mice | Embryo | Ali et al. (2023) |
| 25 | *Corchorus olitorius* | Leaves | Rat | Brain, liver, kidney, heart | Das et al. (2010a, b, c) |
| 26 | *Psidium guajava* | Leaves | Rat | Kidney, blood | Roy and Roy (2011) and Tandan et al. (2012) |
| 27 | *Ocimum sanctum* | Leaves | Rat | Liver, kidney | Banu et al. (2009) |
| | | Leaves | Mice | Lungs | Kaushal et al. (2017) |
| 28 | *Allium sativum* | Bulb | Mice | Bone marrow | RoyChoudhury et al. (1996) |
| | | Bulb | Rat | Liver, kidney, ovary, blood | Chowdhury et al. (2008) and Adegboyega and Odunola (2012) |

(continued)

**Table 10.1** (continued)

| S. No. | Botanical name | Part/constituents used | Experimental model | Organ(s)/system/cell line involved | References |
|---|---|---|---|---|---|
| | | Bulb | – | Human malignant melanoma cells (A375), human keratinocyte cells (HaCaT), human normal dermal fibroblast cells | Chowdhury et al. (2008) |
| 29 | *Viscum album* | Leaf | Rats | Blood | Adegboyega and Odunola (2012) |
| 30 | *Eichhornia crassipes* | Root | Rat | Liver, spleen, kidney, lungs, skin | Quayum (2007) |
| 31 | *Zea mays* | Fruit | Rat | Liver, kidney, heart, lungs, skin | Chowdhury et al. (2009) |
| 32 | *Spinacia oleracea* | Aerial parts | Rat | Liver, spleen, kidney, lungs, skin | Umar (2007) |
| 33 | *Bauhinia variegata* | Leaf | Mice | Liver | Biswas and Ghosh (2014) |
| 34 | *Alchornea laxiflora* | Leaf | Rats | Liver | Kingsley et al. (2013) |
| 35 | *Nasturtium officinale* | Aerial parts | Rats | Blood | Zargari et al. (2015) |
| 36 | *Achyranthes aspera* | Roots | Mice | Blood | Sharma and Chaudhary (2016) |
| 37 | *Syzygium jambolanum* | Seeds | Rat skeletal muscle cell line L6, mice | Blood, biochemical | Samadder et al. (2012) |
| 38 | *Hippophae rhamnoides* | Fruits | Mice | Blood, liver | Gupta and Flora (2006a) |
| 39 | *Curcuma aromatica* | Leaf | Rats | Kidney | Saxena et al. (2009) |

(continued)

**Table 10.1** (continued)

| S. No. | Botanical name | Part/constituents used | Experimental model | Organ(s)/system/cell line involved | References |
|---|---|---|---|---|---|
| 40 | *Ageratum conyzoides* | Leaf | Rats | Blood, liver | Ola-Davies and Akinrinde (2016) |
| 41 | *Andrographis paniculata* | Leaf | Mice | Ovary | Damore and Rao (2019) |
| | | Leaf | Rats | Blood, liver, kidney | Owoade et al. (2022) |
| 42 | *Amaranthus hypochondriacus* | Seed | Rats | Blood, liver | Akin-Idowu et al. (2015) |
| 43 | *Curcuma longa* | Rhizome | Calves | Blood | Biswas et al. (2017) |
| | | Rhizome | Rats | Blood, kidney | Bala et al. (2014) |
| 44 | *Zingiber officinale* | Rhizome | Rats | Testes | Morakinyo et al. (2010) |
| | | Rhizome | Calves | Blood | Biswas et al. (2017) |
| 45 | *Centella asiatica* | Aerial parts | Rats | Blood, liver, kidney, brain, testes | Gupta and Flora (2006b) and Goyal et al. (2018) |
| 46 | *Clerodendrum infortunatum* | Leaf | Rats | Blood, kidney | Singh et al. (2020) |
| 47 | *Murraya koenigii* | Leaf | Mice | Liver, kidney | Fatmi et al. (2017b) |
| 48 | *Phyllantus amarus* | Leaf | Rats | Blood, brain | Adeyi et al. (2018) and Hashim et al. (2020) |
| 49 | *Syzygium cumini* | Seed | Rats | Liver, blood | Kumar et al. (2019) |
| | | Leaf | Mice | Blood, spleen, kidney and liver | Barai et al. (2017) |
| 50 | *Tinospora cordifolia* | Stem | Mice | Bone marrow, blood | Ambasta et al. (2017, 2019) |
| | | Stem | Rats | Blood, liver, kidney | Kumar et al. (2020) |

(continued)

**Table 10.1** (continued)

| S. No. | Botanical name | Part/constituents used | Experimental model | Organ(s)/system/cell line involved | References |
|---|---|---|---|---|---|
| 51 | *Arctium lappa* | Root | Rats | Blood, liver | Edison et al. (2014) |
| 52 | *Silybum marianum* | Seeds | Rats | Blood, liver | |
| 53 | *Cucumis sativus* | Seeds | Mice | Liver, kidney | Fatima et al. (2018) |
| 54 | *Brassica oleracea* | Aerial parts | Rats | Liver, kidney, blood | Raeeszadeh et al. (2022) |
| 55 | *Clerodendrum volubile* | Flavonoid enriched extract | Rats | Liver, kidney, blood | Ugbaja et al. (2021) |
| 56 | *Vernonia amygdalina* | Flavonoid enriched extract | Rats | Liver, kidney, blood | |
| 57 | *Asparagus racemosus* | Root | Rats | Liver, kidney, blood | Kumari et al. (2022) |
| 58 | *Carpobrotus deliciousus* | Leaf | Rats | Liver, kidney, blood | Kayode et al. (2023) |
| 59 | *Nigella sativa* | Oil from seed | Rats | Brain, liver | Zaazaa (2014) and Alam et al. (2021) |
| 60 | *Bauhinia acuminata* | Stem bark | Rats | Liver, kidney, heart, lungs, spleen | De et al. (2016) |
| 61 | *Aloe vera* | Gel from stem | Rats | Blood, liver, kidney | Gupta and Flora (2005) |
| | | Juice from stem | Rohu fish (*Labeo rohita*) | Liver, muscle | Zodape (2010) |
| 62 | *Eclipta alba* | Whole plant | White leghorn cockerels | Testes, blood | Mishra and Singh (2019) and Misra et al. (2021) |
| | | Leaf | Rats | Blood, liver, kidney | Odunola et al. (2021) |
| 63 | *Tamarindus indica* | Seed coat | Rats | Blood, liver | Roy et al. (2020) |

(continued)

**Table 10.1** (continued)

| S. No. | Botanical name | Part/constituents used | Experimental model | Organ(s)/system/cell line involved | References |
|---|---|---|---|---|---|
| 64 | *Terminalia arjuna* | Whole plant | – | Chicken liver cell | Verma et al. (2007) |
| | | Stem bark | Rats | Blood, heart, liver | Dutta et al. (2014) |
| | | Stem bark | Mice | Kidney | Khan et al. (2015) |
| | | Stem bark | Buffalo (*Bubalus bubalis*) | Blood | Dash et al. (2016) |
| 65 | *Spirulina*/ *Arthospira* sp. | Whole plant (algae) | Rats, mice | Liver, kidney, blood, testes, lungs, brain | Bhattacharya (2020) |

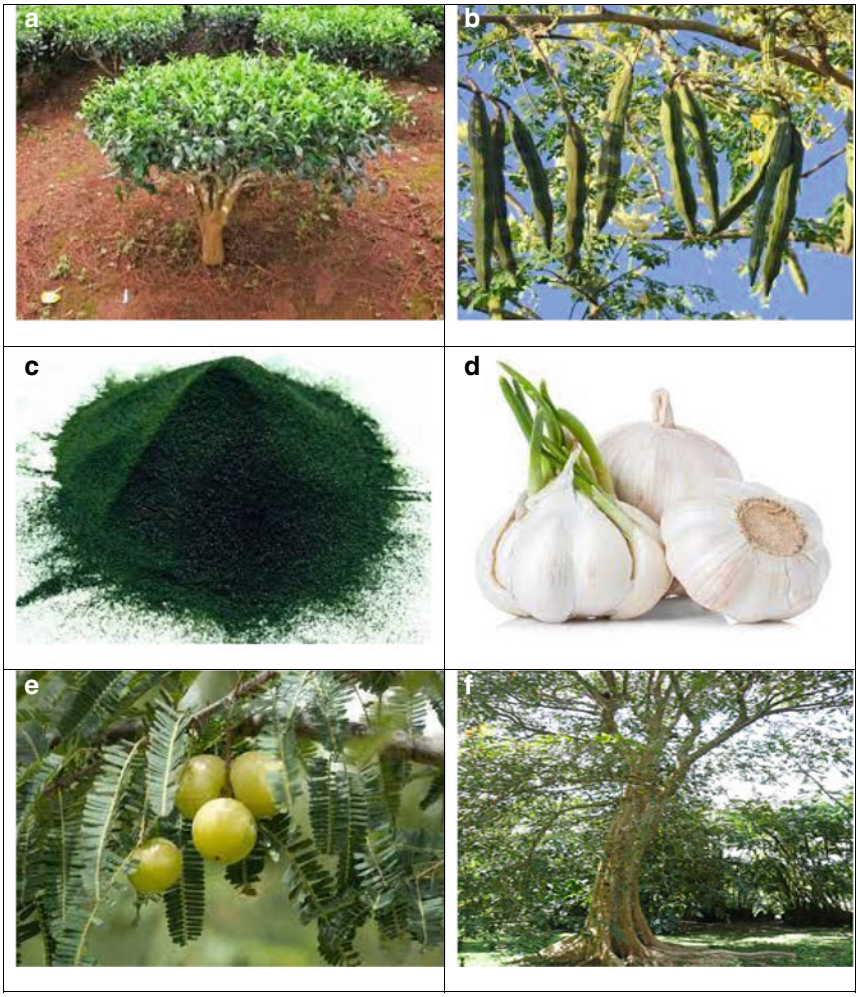


**Fig. 10.1** Some medicinal plants possessing arsenic toxicity ameliorative potential. **a** *Camellia sinensis*, **b** *Moringa oleifera*, **c** *Spirulina* sp., **d** *Allium sativum*, **e** *Emblica officinalis*, **f** *Terminalia arjuna*

bio-markers principally indicating antioxidant status. Tissue histopathological examination of these vital organs and arsenic contents of exposed tissues were also estimated in few studies. Arsenic trioxide ($As_2O_3$) and sodium arsenite ($NaAsO_2$) were generally utilized as toxicant whereas sodium arsenate ($Na_3AsO_4$) was least used.

**Table 10.2** Medicinal plants with clinical arsenic toxicity ameliorative effects

| S. No. | Name | Part/constituent used | References |
|---|---|---|---|
| 1 | *Spirulina/Arthospira* sp. | Whole plant (algae) | Sikder et al. (2000), Khan et al. (2001), Misbahuddin et al. (2006) and Rahman et al. (2006, 2008) |
| 2 | *Allium sativum* | Oil from bulb | Misbahuddin et al. (2013) |
| 3 | *Nigella sativa* | Oil from seed | Bashar et al. (2014) |
| 4 | *Azadirachta indica* | Leaf | Ferdoush and Misbahuddin (2014) |

### *10.3.2 Clinical Studies*

There are eight clinical studies involving four medicinal plants, all of which were performed in Bangladesh (Table 10.2).

## 10.4 Discussion

Toxicity caused by heavy metals inflicts a grave global menace to the habitat and inhabitants. Indiscriminate urbanization and industrialization have exhausted the quality of the environment by introducing different pollutants that are disrupting steady ecosystems, insidiously and irreversibly impacting plants and animals including humans. The long term toxicity induced by toxic heavy metals is considered as a serious silent menace to population and livestock due to their environmental pervasiveness and bio-magnification. In spite of sincere deliberations, total arrest of heavy metal-induced toxicity appear critical from being attained. Arsenic, a cardinal toxicant among all toxic heavy metals, led to various detrimental consequences on multiple organs as well as overall health of cell affecting the overall life quality of humans.

Arsenic and arsenicals are known poison and their toxicity had also been chronicled and recently groundwater arsenic toxicity is regarded a pandemic-like grave public health concern. It precipitates multi-organ dysfunctions based on age, organ, demographic and exposure-related factors (Abdul et al. 2015; Boerleider et al. 2017). The treatment of arsenicosis-induced disorders remains a consequential challenge because of the want of efficacious therapeutic recourses. Adverse effects overrules the pharmacological implications of chelation therapy. Apart from keeping away from arsenic contaminated drinking ground water and occupational arsenic exposure; chelation therapy with certain symptomatic supportive treatments have generally been practised for the management of arsenic toxicity. Till date, there is no evidence-supported specified therapeutic approach for the battle against long-term arsenic toxicity (arsenicosis) in distressed humans. Therapeutic recourses recommended are dietary, multivitamin and beneficial mineral supplements and antioxidant treatment (Rafati-Rahimzadeh et al. 2014; Bhattacharya 2021; Raju 2022). Though,

currently there is considerable argument to advocate any alternative medicine like dietary, medicinal and aromatic plants, natural products or antioxidants in treatment of arsenicosis; nevertheless, generation of oxidative/nitrosative insult by over production of reactive free radicals through the disposition of arsenicals in human body is regarded to become one of the momentous ways of arsenic toxicity in human beings (Shi et al. 2004; Bhattacharya 2021).

Herbs and herbal products historically had a wholesome influence in prevention and cure of different disorders with little or no untoward effects. Present literature scrutiny revealed that, there is sufficient literature available now on effectiveness of medicinal plant crude extracts and fractions thereof against investigational arsenic toxicity and newer reports continually appear. These herbal extracts generally demonstrate concurrent antioxidant potential and thereby exhibit capability in abrogating arsenic-induced oxidative stress. Maximum literature reports neither make any sincere attempt to identify, isolate and characterize their bio-active phytochemical constituents nor speak about their capability in lowering body/organ arsenic content. This may be regarded as the prime setback of almost of these works.

The present literature hunt unveiled that the 65 medicinal plants bearing arsenic toxicity ameliorative effects simultaneously exhibited effective antioxidant property by reversal of arsenic-imposed oxidative impact via multimodal fortification of prevalent endogenous antioxidative defense mechanisms which led to mitigation from arsenic toxicity. Some studied medicinal plants like *Aloe vera*, *Silybum marianum*, *Camellia sinensis*, *Zingiber officinale*, *Withania somnifera*, *Emblica officinalis*, *Curcuma longa*, *Spirulina* sp. etc. have globally been established and consumed as medicinal foods or nutraceuticals and these have duly been reported as naturally occurring antioxidants as well. This implies the favourable effect of antioxidant treatment and firmly substantiates with the advocacy of antioxidant supplementation to human victims. Nonetheless, the observed preclinical benefits of such medicinal herbs require thorough clinical corroboration in human arsenicosis patients.

Although most of these studies captured are pre-clinical, there are few clinical studies on 4 medicinal plants conducted in Bangladesh—the most arsenic affected country. The putative dietary supplement *Spirulina/Arthospira* was reported to be remarkably beneficial in several clinical studies in patients with chronic arsenic toxicity (arsenicosis) complications (Sikder et al. 2000; Khan et al. 2001; Misbahuddin et al. 2006; Rahman et al. 2006, 2008). Oral administration of garlic oil from *Allium sativum* bulb to the arsenicosis patients notably improved arsenic-induced keratosis occurring in their palms and soles (Misbahuddin et al. 2013). Likewise, arsenicosis complications were also ameliorated by oral treatment of *Nigella sativa* seed oil and *Azadirachta indica* leaf extract (Bashar et al. 2014; Ferdoush and Misbahuddin 2014). To the author's knowledge, other relevant clinical studies are presently underway in Bangladesh.

So far, the most investigated medicinal plants in rodents and humans like *Camellia sinensis*, *Moringa oleifera*, *Spirulina/Arthospira* sp., *Allium sativum*, *Nigella sativa*, *Azadirachta indica* etc. need further definitive exploitation at clinical level. Other obviously pre-clinically proven medicinal herbs should be forwarded to clinical stage. These herbs may help in improving arsenicosis complications leading to

disease reversal or may act as palliative or auxiliary therapeutic agents together with conventional therapeutic approaches for arsenicosis.

In the groundwater, arsenic inorganically exists as its pentavalent and trivalent forms. Though both the forms are substantially harmful to human wellbeing, the trivalent arsenic is considered as more toxic (Kapaj et al. 2006; Bhattacharya 2017). In the studies under discussion, the active herbs meliorated trivalent arsenical i.e., arsenic trioxide or sodium arsenite-induced toxicity, implying their plausible prospect for groundwater arsenic toxicity management in humans.

## 10.5 Conclusion

It becomes evident from the explicated preventive effects of the reported pre-clinical and clinical works, medicinal herbs have the sustainable promise for the obviation and treatment of arsenic toxicity. The apropos research may lead to the discovery of any potential therapeutic candidate for clinical management of arsenicosis in humans in future, that may act via mechanisms apart from chelation, viz. modulation of oxidative/nitrosative stress or apoptosis or detoxification. Further mechanism-deducing pre-clinical and conclusively designed clinical trials are necessary for proper substantiation. The pre-clinically chosen medicinal herbs and/or active phytoconstituents thereof should be forwarded to clinical stage alone or together with extant chelating agents. In this course, the herbs may induce synergism, help in disease mitigation and hence may act as adjuvant, complementary agents and thus could aid in restoring the arsenicosis complications in the form of palliative or auxiliary regimen.

Herbal supplementation may thus be considered as the present-day sustainable alternative therapeutic option against poor arsenicosis victims along with extant archetypical therapies like chelation, antioxidant, anti-inflammatory and supportive benevolent treatments. Exhaustive clinical as well as mechanistic probing in this area may pave the way to develop a potential nutraceutical or therapeutic candidate against chronic arsenic toxicity in humans.

## References

Abdul KSM, Jayasinghe SS, Chandana EPS, Jayasumana C, De Silva PMCS (2015) Arsenic and human health effects: a review. Environ Toxicol Pharmacol 40:828–846

Acharyya N, Chattopadhyay S, Maiti S (2014) Chemoprevention against arsenic-induced mutagenic DNA breakage and apoptotic liver damage in rat via antioxidant and SOD1 upregulation by green tea (*Camellia sinensis*) which recovers broken DNA resulted from arsenic-$H_2O_2$ related *in vitro* oxidant stress. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 32:338–361

Adegboyega AM, Odunola OO (2012) The modulatory effects of aqueous extracts of *Viscum album* and garlic on sodium arsenite induced toxicity in Wistar albino rat. J Chem Pharm Res 4:4698–4701

Adeyi OE, Babayemi DO, Adeyi AO, Akinwande OO, Odunewu AA, Amaefule OF, Adetoro GT, Badejo AR (2018) Amelioration of arsenic-induced toxicity by ethanol leaf extract of *Phyllantus amarus* Linn and vitamin C in male albino rats. J Nat Sci Eng Technol 17:83–97

Akin-Idowu PE, Aduloju AO, Odunola OA, Owumi SA, Gbadegesin MA, Adegoke AM (2015) Hepatoprotective effect of *Amaranthus hypochondriacus* seed extract on sodium arsenite-induced toxicity in male Wistar rats. J Med Plants Res 9:731–740

Alam T, Rizwan S, Farooqui Z, Abidi S, Parwez I, Khan F (2021) Oral *Nigella sativa* oil administration alleviates arsenic-induced redox imbalance, DNA damage, and metabolic and histological alterations in rat liver. Environ Sci Pollut Res Int 28:41464–41478

Ali K, Iqbal A, Bukhari SM, Safdar S, Raiz A, Ali W, Hussain A et al (2023) Amelioration potential of *Moringa oleifera* extracts against sodium arsenate induced embryotoxicity and genotoxicity in mouse (*Mus musculus*). Braz J Biol 83:e248022

Ambasta SK, Kumari S, Sinha UK (2017) Anticlastogenicity of *Tinospora cordifolia* stem extract against arsenic genotoxicity in *Mus musculus* bone marrow erythrocytes using micronucleus assay. Int J Pharm Pharm Sci 9:260–264

Ambasta SK, Shashikant, Sinha UK (2019) Genoprotective effects of ethanolic stem extracts of *Tinospora cordifolia* on sodium arsenite-induced DNA damage in Swiss mice lymphocytes by comet assay. Asian J Pharm Clin Res 12:208–212

Bala R, Kumar R, Bano F, Ali M, Kumar A (2014) Restorative effect of *Curcuma longa* on arsenic-induced nephrotoxicity in rats. Innov Pharmaceut Pharmacother 2:486–490

Banu GS, Kumar G, Murugesan AG (2009) Effects of leaves extract of *Ocimum sanctum* L. on arsenic-induced toxicity in Wistar albino rats. Food Chem Toxicol 47:490–495

Barai M, Ahsan N, Paul N, Hossain K, Abdur Rashid M, Kato M, Ohgami N, Azim Akhand A (2017) Amelioration of arsenic-induced toxic effects in mice by dietary supplementation of *Syzygium cumini* leaf extract. Nagoya J Med Sci 79:167–177

Bashar T, Misbahuddin M, Hossain MA (2014) A double-blind, randomize, placebo-control trial to evaluate the effect of *Nigella sativa* on palmer arsenical keratosis patients Bangladesh. J Pharmacol 9:15–21

Baxla SL, Gora RH, Kerketta P, Patnaik S, Roy BK (2014) Hepatoprotective activity of *Tephrosia purpurea* against arsenic induced toxicity in rats. Indian J Pharmacol 46:197–200

Behera B, Bhattacharya S (2016) The importance of assessing heavy metals in medicinal herbs: a quantitative study. TANG [Hum Med] 6:e3

Bhattacharya S (2017) Medicinal plants and natural products in amelioration of arsenic toxicity: a short review. Pharm Biol 55:349–354

Bhattacharya S (2018a) The role of medicinal plants and natural products in melioration of cadmium toxicity. Orient Pharm Exp Med 18:177–186

Bhattacharya S (2018b) Medicinal plants and natural products can play a significant role in mitigation of mercury toxicity. Interdiscip Toxicol 11:247–254

Bhattacharya S (2020) The role of *Spirulina (Arthrospira)* in the mitigation of heavy-metal toxicity: an appraisal. J Environ Pathol Toxicol Oncol 39:149–157

Bhattacharya S (2021) Arsenic toxicity and its remediation by probiotics: an upshot. In: Olsen Y (ed) Probiotics and their role in health and disease, 1st edn. Nova Science Publishers Inc., New York, pp 235–246

Bhattacharya S (2023) A review on experimentally proven medicinal plants and their constituents against fluoride toxicity. J Environ Pathol Toxicol Oncol 42:51–64

Bhattacharya S, Haldar PK (2012a) Ameliorative effect *Trichosanthes dioica* root against experimentally induced arsenic toxicity in male albino rats. Environ Toxicol Pharmacol 33:394–402

Bhattacharya S, Haldar PK (2012b) Ameliorative effect *Trichosanthes dioica* root against arsenic-induced brain toxicity in albino rats. Toxicol Environ Chem 94:769–778

Bhattacharya S, Haldar PK (2012c) *Trichosanthes dioica* fruit ameliorates experimentally induced arsenic toxicity in male albino rats through the alleviation of oxidative stress. Biol Trace Elem Res 148:232–241

Bhattacharya S, Haldar PK (2013) *Trichosanthes dioica* root alleviates arsenic induced myocardial toxicity in rats. J Environ Pathol Toxicol Oncol 32:251–261
Bhattacharya S, Das SK, Haldar PK (2014) Arsenic induced myocardial toxicity in rats: alleviative effect of *Trichosanthes dioica* fruit. J Diet Suppl 11:248–261
Biswas SJ, Ghosh G (2014) Effect of an extract of *Bauhinia variegata* leaves on chronic arsenic intoxication in mice (*Mus musculus*): a preliminary study. CELLMED 4:20.1–20.7
Biswas S, Maji C, Sarkar PK, Sarkar S, Chattopadhyay A, Mandal TK (2017) Ameliorative effect of two ayurvedic herbs on experimentally induced arsenic toxicity in calves. J Ethnopharmacol 197:266–273
Boerleider R, Roeleveld N, Scheepers P (2017) Human biological monitoring of arsenic for exposure assessment. AIMS Environ Sci 4:251–276
Chandronitha C, Ananthi S, Ramakrishnan G, Lakshmisundaram R, Gayathri V, Vasanthi HR (2010) Protective role of tannin-rich fraction of *Camellia sinensis* in tissue arsenic burden in Sprague Dawley rats. Hum Exp Toxicol 29:705–719
Chowdhury R, Dutta A, Chaudhuri SR, Sharma N, Giri AK, Chaudhuri K (2008) *In vitro* and *in vivo* reduction of sodium arsenite induced toxicity by aqueous garlic extract. Food Chem Toxicol 46:740–751
Chowdhury NJA, Misbahuddin M, Rahman MS (2009) Corn extracts lower tissue arsenic level in rat. Bangladesh Med Res Counc Bull 35:21–25
Damore DM, Rao MV (2019) Role of *Andrographis paniculata* on altered steroidogenesis and oxidative impairment in ovary of mice subjected to arsenic intoxication. Int J Pharm Sci Res 10:4501–4506
Das AK, Bag S, Sahu R, Dua TK, Sinha MK, Gangopadhyay M, Zaman K, Dewanjee S (2010a) Protective effect of *Corchorus olitorius* leaves on sodium arsenite-induced toxicity in experimental rats. Food Chem Toxicol 48:326–335
Das AK, Sahu R, Dua TK, Bag S, Gangopadhyay M, Sinha MK, Dewanjee S (2010b) Arsenic-induced myocardial injury: protective role of *Corchorus olitorius* leaves. Food Chem Toxicol 48:1210–1217
Das AK, Dewanjee S, Sahu R, Dua TK, Gangopadhyay M, Sinha MK (2010c) Protective effect of *Corchorus olitorius* leaves against arsenic-induced oxidative stress in rat brain. Environ Toxicol Pharmacol 29:64–69
Dash SK, Nayyar S, Jindal R (2016) Effect of *Terminalia arjuna* bark powder on some diagnostic enzymes in buffalo (*Bubalus bubalis*) ingesting arsenic contaminated water and fodder. Vet World 9:1167–1172
De A, Nath S, Bandyopadhyay SK, Mandal TK, Das AK (2016) Ameliorative effects of *Bauhinia acuminata* L stem bark powder against chronic arsenicosis in rats. Toxicol Environ Health Sci 8:258–262
Dua TK, Dewanjee S, Gangopadhyay G, Khanra R, Zia-Ul-Haq M, Feo VD (2015) Ameliorative effect of water spinach, *Ipomea aquatica* (Convolvulaceae), against experimentally induced arsenic toxicity. J Transl Med 13:81
Dutta M, Chattopadhyay A, Bose G, Ghosh A, Banerjee A, Ghosh AK, Mishra S, Pattari SK, Das T, Bandyopadhyay D (2014) Aqueous bark extract of *Terminalia arjuna* protects against high fat diet aggravated arsenic-induced oxidative stress in rat heart and liver: involvement of antioxidant mechanisms. J Pharm Res 8:1285–1302
Edison AS, Krishnan UM, Pemiah B (2014) Protective role of *Arctium lappa* Linn. against arsenic trioxide using *Silybum marianum* Linn. as standard drug. Asian J Chem 26:3749–3753
Ewere EG, Okolie NP, Eze GI, Jegede DA (2019) *Irvingia gabonensis* leaves mitigate arsenic-induced renal toxicity in Wistar rats. Asian J Biomed Pharm Sci 9:17–25
Fatima N, Fatmi N, Shahzada MZ, Sharma S, Kumar R, Ali M, Kumar A (2018) Ameliorating effect of *Cucumis sativus* (cucumbers) against arsenic induced toxicity in mice. Open J Pathol 8:78–84
Fatmi N, Fatima N, Shahzada MZ, Sharma S, Kumar R et al (2017a) Effect of aqueous extracts of green tea in arsenic induced toxicity in mice. Open J Plant Sci 2:011–014

Fatmi N, Fatima N, Shahzada MZ, Sharma S, Kumar R, Ali MM et al (2017b) Ameliorative effect of *Murraya koenigii* on arsenic induced toxicity in Swiss albino mice. Austin J Pharmacol Ther 5:1097

Ferdoush J, Misbahuddin M (2014) Effect of ethanol extract of leaves of *Azadirachta indica* on palmar arsenical keratosis: a single-blind trial. Bangladesh J Pharmacol 9:279–283

Gbadegesin MA, Adegoke AM, Ewere EG, Odunola OA (2014) Hepatoprotective and anticlastogenic effects of ethanol extract of *Irvingia gabonensis* (IG) leaves in sodium arsenite-induced toxicity in male Wistar rats. Niger J Physiol Sci 29:29–36

Gora RH, Baxla SL, Kerketta P, Toppo R, Kumar N, Roy BK (2013) Ameliorative potential of *Tephrosia purpurea* against arsenic induced toxicity in Wistar rats. Vet World 6:493–496

Gora RH, Kerketta P, Baxla SL, Toppo R, Prasad R, Patra PH, Roy BK (2014) Ameliorative effect of *Tephrosia purpurea* in arsenic-induced nephrotoxicity in rats. Toxicol Int 21:78–83

Goyal A, Singh ND, Banga HS (2018) Ameliorative effect of *Centella asiatica* on induced arsenic toxicity in Wistar rats: pathomorphological study. Indian J Vet Pathol 42:43–50

Gupta R, Flora SJS (2005) Protective value of *Aloe vera* against some toxic effects of arsenic in rats. Phytother Res 19:23–28

Gupta R, Flora SJ (2006a) Protective effects of fruit extracts of *Hippophae rhamnoides* L. against arsenic toxicity in Swiss albino mice. Hum Exp Toxicol 25:285–295

Gupta R, Flora SJS (2006b) Effect of *Centella asiatica* on arsenic induced oxidative stress and metal distribution in rats. J Appl Toxicol 26:213–222

Gupta R, Kannan GM, Sharma M, Flora SJS (2005) Therapeutic effects of *Moringa oleifera* on arsenic-induced toxicity in rats. Environ Toxicol Pharmacol 20:456–464

Hashim A, Ahmed MG, Priya ESS, Shyamjith M (2020) Antianxiety effect of *Phyllanthus amarus* ethanolic extract in arsenic administered Wistar albino rats. Drug Invent Today 13:1105–1110

Islam MM, Khair A, Awal MA, Islam MZ, Haider MG (2018) Prevention of arsenic toxicity with Spirulina and Mentha in rats. Ann Bangladesh Agric 22:29–39

Kapaj S, Peterson H, Liber K, Bhattacharya P (2006) Human health effects from chronic arsenic poisoning—a review. J Environ Sci Health Part A 41:2399–2428

Kaushal S, Garg V, Ul-Ahsan A, Sharma VL, Chopra M (2017) Alleviation of arsenic induced lung toxicity by *Ocimum sanctum* in murine model. Int J Pharm Sci Res 8:4604–4613

Kayode AAA, Jayeola YA, Okumede GF, Hlangothi B, Ogunlaja SA (2023) Leaf pulp of *Carpobrotus deliciousus* attenuate sodium arsenate induced toxicity. Lett Appl Nano BioSci 12:30

Khan MAK, Choudhury SAR, Misbahuddin M, Islam AZMM, Shahjahan M (2001) Effects of Spirulina in the treatment of chronic arsenic poisoning in Bangladesh. Bangladesh J Med Sci 7:223–231

Khan N, Haque M, Haque I, Ali S, Malik MZ, Siddiqui MS, Khan FI (2015) Effect of *Terminalia arjuna* against arsenic-induced renal toxicity in mice. BAOJ Biotech 1:005

Kingsley O, Esosa US, Georgina EO, Sunday JJ, Spencer NCO (2013) Possible reversal of sodium arsenate-induced liver toxicity by hexane leaf extract of *Alchornea laxiflora.* Asian J Med Sci 5:3–8

Kumar A, Ali M, Kumar R, Suman S, Kumar H, Nath A, Singh JK, Kumar D (2013) *Withania somnifera* protects the haematological alterations caused by sodium arsenite in Charles Foster rats. Int J Res Ayurveda Pharm 4:491–494

Kumar A, Kumar R, Rahman MS, Iqubal MA, Anand G, Niraj PK, Ali M (2015a) Phytoremedial effect of *Withania somnifera* against arsenic-induced testicular toxicity in Charles Foster rats. Avicenna J Phytomed 5:355–364

Kumar A, Kumar R, Rahman MS, Iqubal MA, Anand G, Niraj PK, Ali M (2015b) Antidote effects of plants of Himalayan sub-origin against arsenic induced toxicity. Biol Chem Res 2015:99–109

Kumar A, Bala R, Bano F, Kumar R, Ali M (2015c) *Emblica officinalis* protects against sodium arsenite induced hepatotoxicity & nephrotoxicity in rats. Int J Sci 4:47–55

Kumar M, Thakur R, Kumar S (2019) Comparative efficacy of *Syzygium cumini* seed extracts in alleviating arsenic-induced hepatotoxicity and blood cell genotoxicity in Wistar albino rats. Biomed Pharmacol J 12:1329–1338

Kumar V, Akhouri V, Singh SK, Kumar A (2020) Phytoremedial effect of *Tinospora cordifolia* against arsenic induced toxicity in Charles Foster rats. BioMetals 33:379–396

Kumari S, Rani S, Kumar A (2022) Phytoremedial effect of *Asparagus racemosus* on sodium arsenite-induced toxicity in Charles Foster rats. J Appl Nat Sci 14:302–309

Lakshmi BVS, Sudhakar M, Sudha FJ, Gopal MV (2015) Ameliorative effect of *Triticum aestivum* Linn against experimentally induced arsenic toxicity in male albino rats. Pharm Lett 7:202–211

Li SG, Ding YS, Niu Q, Xu SZ, Pang LJ, Ma RL, Jing MX, Feng GL, Liu JM, Guo SX (2015) Grape seed proanthocyanidin extract alleviates arsenic-induced oxidative reproductive toxicity in male mice. Biomed Environ Sci 28:272–280

Maiti S, Chattopadhyay S, Acharyya N, Deb B, Hati AK (2014) *Emblica officinalis* (amla) ameliorates arsenic-induced liver damage via DNA protection by antioxidant systems. Mol Cell Toxicol 10:75–82

Meena ST, Sandip VT, Namrata M, Vinayak PP, Madan VJ (2018) Effect of *Emblica officinalis* in arsenic induced toxicity in Japanese quails (*Coturnix coturnix japonica*). Indian J Poultry Sci 53:12–16

Misbahuddin M, Islam AZMM, Khandker S, Mahmud IA, Islam N, Anjumanara (2006) Efficacy of Spirulina extract plus zinc in patients of chronic arsenic poisoning: a randomized placebo-controlled study. Clin Toxicol 44:135–141

Misbahuddin M, Bashar T, Hossain MA (2013) Effectiveness of garlic oil in the treatment of arsenical palmer keratosis. Bangladesh J Pharmacol 8:22–27

Mishra S, Singh SP (2019) Amelioration of arsenic induced reproductive toxic effects by *Eclipta alba*. J Vet Pharmacol Toxicol 18:85–86

Misra S, Singh SP, Pathak A (2021) Immunomodulation by *Eclipta alba* in arsenic intoxicated cockerels. J Vet Pharmacol Toxicol 20:88–89

Morakinyo AO, Achema PU, Adegoke OA (2010) Effect of *Zingiber officinale* (ginger) on sodium arsenite induced reproductive toxicity in male rats. Afr J Biomed Res 13:39–45

Odunola OA, Fashina NO, Iloba IM, Gbadegeshin MA, Adegoke AM, Olugbami OJ (2021) Antigenotoxic and hepatoprotective activities of ethanol extract of the leaf of *Eclipta alba* in sodium arsenite-induced toxicity. Biokemistri 33:27–38

Ola-Davies OE, Akinrinde AS (2016) Acute sodium arsenite-induced hematological and biochemical changes in Wistar rats: protective effects of ethanol extract of *Ageratum conyzoides*. Pharmacocogn Res 8:S26–S30

Owoade AO, Alausa AO, Adetutu A, Owoade AW (2022) Protective effects of methanolic extract of *Andrographis paniculata* (Burm.f.) Nees leaves against arsenic-induced damage in rats. Bull Natl Res Cent 46:141

Oyewole OI (2011) Ameliorating effect of methanolic leaf extract of *Azadirachta indica* (neem) on arsenic induced oxidative damage in rat liver. Int J Toxicol Appl Pharmacol 1:25–28

Padmaja B, Madhuri D, Anand KA, Anjaneyulu Y (2009) Ameliorative efficacy of *Emblica officinalis* in arsenic induced toxicity in broilers: a haemato-biochemical study. Indian J Vet Pathol 33:43–45

Quayum SL (2007) Effect of water hyacinth root extract on arsenic level in different organs of arsenic-treated rat. Bangladesh J Pharmacol 2:73–80

Raeeszadeh M, Karimi P, Khademi N, Mortazavi P (2022) The effect of broccoli extract in arsenic-induced experimental poisoning on the hematological, biochemical, and electrophoretic parameters of the liver and kidney of rats. Evid-Based Complement Alternat Med 2022:3509706

Rafati-Rahimzadeh M, Rafati-Rahimzadeh M, Kazemi S, Moghadamnia AA (2014) Current approaches of the management of arsenic poisoning: need of the hour. DARU J Pharm Sci 22:46

Rahman MH, Sikder MS, Islam AZMM, Wahab MA (2006) Spirulina as food supplement is effective in arsenicosis. J Pak Assoc Dermatol 16:69–75

Rahman MH, Islam AZMM, Sikder S (2008) Dynamics of Spirulina in promoting health benefits for arsenicosis patients. J Bangladesh Coll Phys Surg 26:14–21

Raihan SZ, Chowdhury AK, Rabbani GH, Marni F, Ali MS, Nahar L, Sarker SD (2009) Effect of aqueous extracts of black and green teas in arsenic-induced toxicity in rabbits. Phytother Res 23:1603–1608

Raju NJ (2022) Arsenic in the geo-environment: a review of sources, geochemical processes, toxicity and removal technologies. Environ Res 203:111782

Roy M, Roy S (2011) Ameliorative potential of *Psidium guajava* in induced arsenic toxicity in Wistar rats. Vet World 4:82–83

Roy M, Roy SS, Roopali B, Ratre HK, Singh N, Singh J, Pathak R (2020) Ameliorative potential of *Tamarindus indica* seed coat against arsenic-induced hepatotoxicity in Wistar rats. J Entomol Zool Stud 8:1125–1129

RoyChoudhury A, Das T, Sharma A, Talukder G (1996) Dietary garlic extract in modifying clastogenic effects of inorganic arsenic in mice: two-generation studies. Mutat Res 359:165–170

Samadder A, Das S, Das J, Paul A, Khuda-Bukhsh AR (2012) Ameliorative effects of *Syzygium jambolanum* extract and its poly (lactic-co-glycolic) acid nano-encapsulated form on arsenic-induced hyperglycemic stress: a multi-parametric evaluation. JAMS J Acupunct Meridian Stud 5:310–318

Saxena PN, Anand S, Saxena N, Bajaj P (2009) Effect of arsenic trioxide on renal functions and its modulation by *Curcuma aromatica* leaf extract in albino rat. J Environ Biol 30:527–531

Sayed S, Ahsan N, Kato M, Ohgami N, Rashid A, Akhand AA (2015) Protective effects of *Phyllanthus emblica* leaf extract on sodium arsenite-mediated adverse effects in mice. Nagoya J Med Sci 77:145–153

Sharma V, Chaudhary U (2016) Antihepatotoxic efficacy of *Achyranthes aspera* roots on sodium arsenate induced hepatic damages in Swiss albino mice. World J Pharm Pharm Sci 5:1360–1374

Sharma G, Kumar M (2014) Amelioration by *Chlorophytum borivilianum* upon arsenic induced oxidative stress in Swiss albino mice. Int J Pharmacol Toxicol 2:62–69

Sharma A, Sharma MK, Kumar M (2007) Protective effect of *Mentha piperita* against arsenic-induced toxicity in liver of Swiss albino mice. Basic Clin Pharmacol Toxicol 100:249–257

Sharma A, Sharma MK, Kumar M (2009) Modulatory role of *Emblica officinalis* fruit extract against arsenic induced oxidative stress in Swiss albino mice. Chem Biol Interact 180:20–30

Sheikh A, Yeasmin F, Agarwal S, Rahman M, Islam K, Hossain E, Hossain S, Karim MR, Nikkon F, Saud ZA, Hossain K (2014) Protective effects of *Moringa oleifera* Lam. leaves against arsenic-induced toxicity in mice. Asian Pac J Trop Biomed 4:S353–S358

Shi H, Shi X, Liu KJ (2004) Oxidative mechanism of arsenic toxicity and carcinogenesis. Mol Cell Biochem 255:67–78

Sikder MS, Islam AZMM, Khan MAK, Huq MA, Choudhury SAR, Misbahuddin M (2000) Effect of Spirulina in the treatment of chronic arsenicosis. Bangladesh J Dermatol Venereal Leprol 17:9–13

Singh N, Kumari D (2013) Amelioration of genotoxicity by papaya extract induced by arsenic contaminated drinking water. Bioscan 8:623–626

Singh MK, Yadav SS, Gupta V, Khattri S (2013a) Immunomodulatory role of *Emblica officinalis* in arsenic induced oxidative damage and apoptosis in thymocytes of mice. BMC Complement Alternat Med 13:193

Singh MK, Dwivedi S, Yadav SS, Sharma P, Khattri S (2013b) Arsenic-induced hepatic toxicity and its attenuation by fruit extract of *Emblica officinalis* (amla) in mice. Indian J Clin Biochem 29:29–37

Singh MK, Yadav SS, Yadav RS, Singh US, Shukla Y, Pant KK et al (2014) Efficacy of crude extract of *Emblica officinalis* (amla) in arsenic-induced oxidative damage and apoptosis in splenocytes of mice. Toxicol Int 21:8–17

Singh MK, Yadav SS, Yadav RS, Chauhan A, Katiyar D, Khattri S (2015) Protective effect of *Emblica officinalis* in arsenic induced biochemical alteration and inflammation in mice. SpringerPlus 4:438

Singh MK, Singh PK, Yadav SS, Singh US, Dwivedi P, Yadav RS (2018) Attenuation of arsenic-induced dyslipidemia by fruit extract of *Emblica officinalis* in mice. Int J Nutr Pharmacol Neurol Dis 8:3–9

Singh P, Prasad R, Gupta V, Kausar H, Nehar S (2020) Nephro-protective effect of *Clerodendrum infortunatum* in arsenic induced sub-acute toxicity in albino rats. Toxicol Int 26:129–136

Sinha D, Roy S, Roy M (2010) Antioxidant potential of tea reduces arsenite induced oxidative stress in Swiss albino mice. Food Chem Toxicol 48:1032–1039

Soria EA, Goleniowski ME, Cantero JJ, Bongiovanni GA (2008) Antioxidant activity of different extracts of Argentinian medicinal plants against arsenic-induced toxicity in renal cells. Hum Exp Toxicol 27:341–346

Soria EA, Quiroga PL, Albrecht C, Ramos, Elizagaray SI, Cantero JJ, Bongiovanni GA (2014) Development of an antioxidant phytoextract of *Lantana grisebachii* with lymphoprotective activity against *in vitro* arsenic toxicity. Adv Pharmacol Sci 2014:416761

Tandan N, Roy M, Roy S (2012) Ameliorative potential of *Psidium guajava* on hemato-biochemical alterations in arsenic-exposed Wistar rats. Toxicol Int 19:121–124

Ugbaja RN, Akinhanmi TF, James AS, Ugwor EI, Babalola AA, Ezenandu EO, Ugbaja VC, Emmanuel EA (2021) Flavonoid-rich fractions from *Clerodendrum volubile* and *Vernonia amygdalina* extenuates arsenic-invoked hepatorenal toxicity via augmentation of the antioxidant system in rats. Clin Nutr Open Sci 35:12–25

Umar BU (2007) Effect of hexane extract of spinach in the removal of arsenic from rat Bangladesh. J Pharmacol 2:27–34

Verma R, Trivedi M, Keshwani H, Choksi P, Sangai N (2007) Ameliorative effect of three medicinal plants (*P. fraternus*, *Terminelia A.*, and *Moringa oleifera*) on arsenic trioxide induced alteration of lipid peroxidation and protein contents in chicken liver homogenate: an *in vitro* study. Acta Pol Pharm Drug Res 63:417–421

Vineetha VP, Prathapan A, Soumya RS, Raghu KG (2013) Arsenic trioxide toxicity in H9c2 myoblasts—damage to cell organelles and possible amelioration with *Boerhavia diffusa.* Cardiovasc Toxicol 13:123–137

Vineetha VP, Girija S, Soumya RS, Raghu KG (2014) Polyphenol-rich apple (*Malus domestica* L.) peel extract attenuates arsenic trioxide induced cardiotoxicity in H9c2 cells via its antioxidant activity. Food Funct 5:502–511

Xinjuan P, Dai Y, Li X, Niu N, Li W, Liu F, Zhao Y, Yu Z (2011) Inhibition of arsenic induced-rat liver injury by grape seed exact through suppression of NADPH oxidase and TGF-β/Smad activation. Toxicol Appl Pharmacol 254:323–331

Zaazaa AM (2014) Protective role of the *Nigella sativa* oil against arsenic-induced neurotoxicity in male rats. World J Pharm Res 3:1624–1636

Zargari F, Ghorbanihaghjo A, Babaei H (2015) Protective effects of hydroalcoholic extract of *Nasturtium officinale* on rat blood cells exposed to arsenic. Iran J Toxicol 9:1331–1335

Zodape GV (2010) Effect of *Aloe vera* juice on toxicity induced by arsenic in *Labeo rohita* (Hamilton). J Appl Nat Sci 2:300–304

# Chapter 11
# Arsenic Uptake and Bioaccumulation in Plants: A Review


**Vandita Anand and Anjana Pandey**

**Abstract** Arsenic is a very dangerous metalloid categorized as a class 1 non-threshold carcinogen. Due to arsenic-contaminated food and drinking water consumption, millions of individuals worldwide experience arsenic poisoning. Even at deficient concentrations, exposure to arsenic can elicit a variety of morphological, physiological, and biochemical alterations in plants. At a physiological level, reactive oxygen species (ROS) overgeneration is caused by arsenic-induced changed biochemistry in the chloroplast, mitochondria, peroxisome, endoplasmic reticulum, and plasma membrane. ROS causes cell damage by dissolving the structure of lipids, proteins, and DNA. As a result, increasing plants' resistance to ROS-induced oxidative stress is an essential technique. Uptake, transportation and accumulation of arsenic in plant cells depend on arsenic transporters. In this chapter, we provide an overview of our current knowledge of arsenic transport in plants, focusing on arsenic absorption, arsenic resistance mechanisms, and arsenic long-distance translocation, particularly the accumulation of arsenic in grains via phloem-mediated transport.

**Keywords** Arsenic toxicity · Arsenate · Arsenite · Methylated as species · Oxidative stress · Reactive oxygen species

## 11.1 Introduction

Arsenic is a non-essential metalloid found in the environment that is extremely dangerous to all plant and animal life. It ranks as the 20th most common and extensively dispersed naturally occurring element on Earth. The average amount of arsenic in continental crusts typically ranges between 2 and 3 mg/kg (Cullen and Reimer 1989). Many peoples are continuously exposed to high levels of arsenic in their environment, which can have detrimental long-term health effects (Taylor

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et al. 2017). Since 3000 BCE, people have employed arsenic for medical purposes and to extract iron from iron ores. For example, Thomas Fowler created a mixture known as "Fowler's solution" in the eighteenth century, an arsenic trioxide ($As_2O_3$) solution based on potassium bicarbonate. Many cutaneous illnesses, including psoriasis, prurigo, eczema, dermatitis, acne, leishmaniasis, and syphilis, have been treated using arsenical chemicals (Neubauer 1947).

Arsenic is a metalloid with atomic number 33 on the modern periodic table, a heavy metal that belongs to the transition group (VI-B) and has an oxidation number ranging from As(III) to As(V). Arsenite (As III), arsenate (As V), monomethylarsonic acid (MMA), dimethyal arsinic acid (DMA), arseno betain, and arseno choline are the main species present in the environment (Tangahu et al. 2011). Trivalent As(III) and pentavalent As(V) species, both of which have unique physicochemical and biological features, are the most stable and prevalent forms in the environment.

### *11.1.1 Arsenic: Health Hazard/Toxicity*

The health hazards of exposure to arsenite and arsenate are well documented by the World Health Organization and the Agency for Toxic Substances and Disease Registry (ATSDR 2013). The United States Environmental Protection Agency (USEPA) has ranked As and its compounds as a Group 1 human carcinogen. These are considered highly lethal for most organisms due to their mutagenic and carcinogenic properties.

Arsine (-3 oxidation state), elemental arsenic (0), arsenite, and arsenate are the most common forms of arsenic in nature. Arsenite and arsenate are the most prevalent of these in nature, and because of their carcinogenic characteristics, they can cause numerous sorts of cellular harm (Bolan et al. 2015). On the other hand, arsenite reacts with thiol and sulfhydryl groups of organic substances, such as proteins and enzymes, found in the human body, making it more poisonous and more mobile (Tsuji et al. 2019). Arsenic is a protoplasmic toxin that manifests toxicity by deactivating crucial enzymes involved in DNA synthesis and repair and the production of cellular energy (Tong et al. 2015). The inactivation of vital enzymes is the main source of arsenic-related toxicity, which might worsen cellular signalling pathways (Jomova et al. 2011). The formation of free radicals causes cell death, aberrant gene expression, and damage of DNA, lipids, and proteins (Tsuji et al. 2019). Phosphorus and pentavalent arsenicals can switch places on many biological processes (Hughes et al. 2011). Recent research has shown that people exposed to arsenic exhibit chromosomal abnormalities and sister chromatid exchange and that the reactive oxygen species created by arsenic compounds can cause skin cancers (Litwin et al. 2013). Following exposure to arsenic, alteration in DNA repair, p53 suppression, amplification of genes and changes in the pattern of DNA methylation are potential carcinogenic processes (Bach et al. 2016).

### *11.1.2 Sources and Concentration of Arsenic in the Environment*

Anthropogenic activities such as mining and agriculture that include chemical pesticides, insecticides, herbicides etc., are potential sources of arsenic pollution (Fayiga and Saha 2016). However, geogenic activities also significantly increase the amount of arsenic in the environment and contribute to its dispersion and mobility in the environment. Widespread use of arsenic-contaminated groundwater through drinking, cooking, and irrigating plants poses a severe hazard to human health in many regions of the world (Taylor et al. 2017). An environmental health hazard is brought on by the rising prevalence of chronic arsenicosis and arsenic poisoning, especially in South Asia.

## 11.2 Pathways of Arsenic Uptake to Plant Roots from the Soil

Certain plants may absorb arsenic from the water via their leaves, terricolous plants typically absorb arsenic through their roots (Wolterbeek and Meer 2002). Arsenate, arsenite, and methylated arsenic i.e., MMA and DMA are the three major forms of arsenic that are accessible to plants in soil. Plant roots preferentially absorb specific arsenic species via various transporters and routes (Table 11.1). A schematic diagram of arsenic uptake and accumulation in plants has been depicted in Fig. 11.1.

### *11.2.1 Uptake of Arsenate*

Arsenate is the predominant arsenic species in aerobic soils and quickly enters plant roots via phosphate (Pht) transporters, since studies have shown that arsenate and phosphate use the same transport channel in higher plants. In plants, a variety of phosphate transporters have been identified. The Pht1 family contains about 100 phosphate transporters, the majority of which are involved in the transport of arsenate in plants.

Two high-affinity Pht1 isoforms in *Arabidopsis thaliana*, AtPht1;1 and AtPht1;4, were initially found to facilitate Pht and arsenate uptake from soils with both low and high phosphorus levels (Shin et al. 2004). AtPht1;5 encourages Pht and arsenate to move from phosphorus sources to sink organs. Loss of AtPht1;5 reduces the harmful effects of arsenate on plants.

Similarly, under arsenate treatment conditions, more lateral roots developed in the mutant type than the wild type (Nagarajan et al. 2011). The overexpression of AtPht1;7 accelerates the accumulation of arsenate, which is expressed only in reproductive tissues of *Arabidopsis* (LeBlanc et al. 2013). Arsenate absorption at the

**Table 11.1** Arsenic transporters in plants

| Plants | NIP family | Arsenic species | Function in Arsenic uptake and transport | References |
|---|---|---|---|---|
| *A. thaliana* | AtPht1;1 | As(V) | Uptake | LeBlanc et al. (2013) |
| | AtPht1;4 | As(V) | Uptake | LeBlanc et al. (2013) |
| | AtPht1;5 | As(V) | Uptake | Nagarajan et al. (2011) |
| | AtPht1;7 | As(V) | Expressed in reproductive tissues | LeBlanc et al. (2013) |
| | AtPht1;9 | As(V) | Expressed in roots | Remy et al. (2012) |
| | AtPht1;8 | As(V) | Expressed in roots | Remy et al. (2012) |
| | AtNIP5;1 | As(III) | Identified as a boric acid transporter essential for boron (B) uptake by roots | Takano et al. (2006) |
| | AtNIP6;1 | As(III) | Highly expressed in roots | Bienert et al. (2008) |
| | AtNIP7;1 | As(III) | Expressed in developing anthers and pollen tissues | Bienert et al. (2008) |
| | AtNIP1;1 | As(III) | Highly expressed in roots | Isayenkov and Maathuis (2008) |
| | AtNIP1;2 | As(III) | Highly expressed in seeds | Kamiya et al. (2009) |
| | AtNIP3;1 | As(III) | Highly expressed in roots | Xu et al. (2015) |
| *O. sativa* | OsPht1;8 | As(V) | Expressed in both the root and shoot tissue | Wu et al. (2011) |
| | OsPht1;1 | As(V) | Expressed in the plasma membrane | Sun et al. (2012) |
| | OsNIP2;1 | As(III) | Predominantly expressed in roots | Bienert et al. (2008) |
| | OsNIP3;2 | As(III) | Highly expressed in anthers and suspension cells | Bienert et al. (2008) |
| *Lotus japonicus* | LjNIP5;1 | As(III) | Transport As(III) across cell membranes | Bienert et al. (2008) |
| | LjNIP6;1 | As(III) | Transport As(III) across cell membranes | Bienert et al. (2008) |

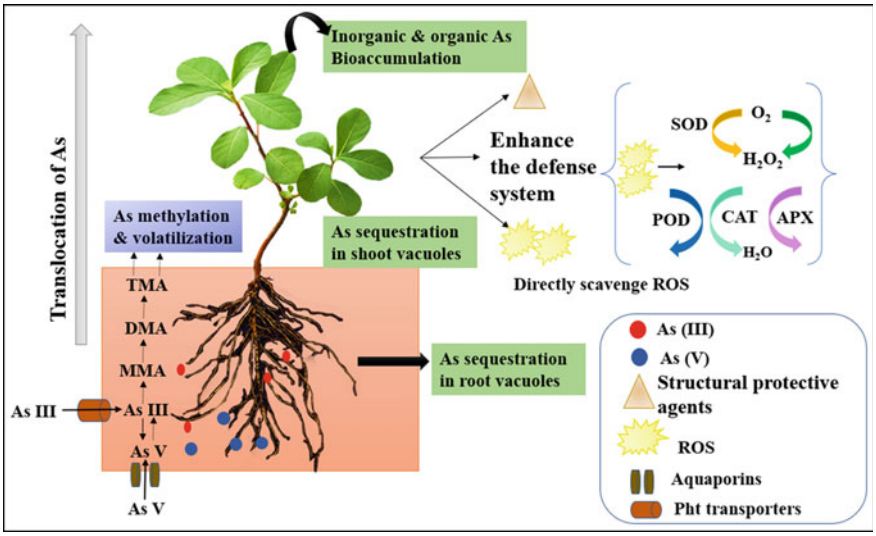


**Fig. 11.1** Schematic illustration of arsenic uptake, translocation, and accumulation in plants

root-soil interface was discovered to be mediated by AtPht1;9, a Pht1 transporter that is mainly expressed in the root and facilitates the acquisition of inorganic Pht in the root during Pht shortage (Remy et al. 2012). In this investigation, AtPht1;8 was also shown to have a similar role in Pht acquisition and arsenate uptake (Remy et al. 2012).

The endoplasmic reticulum (ER)-localized protein AtPHF1 (Pht Transporter Traffic Facilitator 1) influences the location of the Pht1;1 transporter and arsenate tolerance in plants. Recently, it was shown that some WRKY transcription factors were implicated in As(V) inflow. For instance, the plant defence genes WRKY6 and WRKY45 control the expression of AtPht1;1 to further modify arsenate absorption (Wang et al. 2014).

Studies have shown that arsenate absorption by roots via Pht1 transporters occurs in *Oryza sativa*. Independent of Pht supply, OsPht1;8 is expressed in root and shoot tissue and has a strong affinity for Pht and arsenate. Overexpression of OsPht1;8 in rice significantly boosts arsenate absorption and translocation (Wu et al. 2011). The expression of OsPht1;8 is mediated by the transcription factor OsPHR2 (Pi starvation response 2) (Wu et al. 2011). Additionally, arsenate uptake involves OsPht1;1, expressed Pht1 transporter situated in the plasma membrane (Sun et al. 2012). However, as arsenate is the predominant arsenic form in anaerobic conditions, the Pht transport pathway is considered as minor channel for arsenic absorption in flooded soil (Xu et al. 2008).

### *11.2.2 Uptake of Arsenite*

In anaerobic conditions like buried soils, arsenite is the predominant type of arsenic. The understanding of the proteins involved in arsenite absorption in plants has advanced significantly. It has been demonstrated that plant aquaporins, membrane channels that transport water molecules, are particularly significant in arsenite transport (Li et al. 2014). The mechanism of arsenite absorption in plants was poorly understood until recently. Arsenite may be quickly absorbed by plant roots from the environment. Aquaporin channels in plant roots may be able to take up arsenite. The absorption of arsenite by roots in plants is mediated by members of the nodulin 26-like intrinsic protein (NIP) family of plant aquaporins. In *A. thaliana*, NIP5;1 (identified as a boric acid transporter) and NIP6;1 is predominantly expressed in roots. Arsenite absorption is additionally facilitated by the expression of AtNIP7;1 in developing anthers and pollen tissues, AtNIP1;2 in seeds, AtNIP1;1 and AtNIP3;1 in roots, respectively (Bienert et al. 2008; Isayenkov and Maathuis 2008; Kamiya et al. 2009; Xu et al. 2015). In *O. sativa*, NIP2;1 (expressed in roots) and NIP3;2 (expressed in anthers and suspension cells). A key mechanism for arsenite absorption by roots involves the silicon (Si) influx transporter NIP2;1. OsNIP2;1 is located at the distal side of the rice exodermis and endodermis cells to mediate arsenite inflow in a sequential manner (Ma et al. 2008). However, OsNIP1;1 and OsNIP3;1 expression is relatively poor compared to OsNIP2;1 and OsNIP2;2 (OsLsi6), which suggests that they do not have a substantial impact on arsenite absorption by rice roots (Ma et al. 2008). Under the arsenite treatment conditions, OsNIP3;3 expressions were not induced in rice. In order to understand OsNIP3;3's role in rice, more research is necessary (Katsuhara et al. 2014). Aquaporins from the rice plasma membrane intrinsic protein (PIP) family, such as OsPIP2;4, OsPIP2;6, and OsPIP2;7, are likewise permeable to arsenite, and they help plants tolerate arsenite. The overexpression of OsPIP2;4, OsPIP2;6, and OsPIP2;7 in *Arabidopsis* increased arsenite tolerance (Mosa et al. 2012).

### *11.2.3 Uptake of Methylated Arsenic Species*

Soils contain some methylated arsenic species such as MMA and DMA in trace amounts. It accumulates in the soil due to the use of arsenic pesticides and herbicides, as well as arsenic biomethylation by microorganisms (Huang. 2014). At this time, it is uncertain how plant roots absorb MMA and DMA. Plants have been shown to have significant levels of methylated arsenic. In comparison to inorganic As, rice grains accumulate a twofold greater concentration of DMA (Zheng et al. 2013). According to theories, the soil and microbes in the plant rhizosphere are the sources of methylated arsenic species in plants (Jia et al. 2013). The processes underpinning the transport and absorption of methylated arsenic need to be better understood. Rahman et al. (2011) demonstrated that glycerol, carried into plant cells by aquaporins, has

the same entry pathway as MMA and DMA when it enters rice roots. OsLsi1 [the aquaporin NIP2;1 is essential for absorbing undissociated methylated arsenic by rice roots (Li et al. 2007)].

## 11.3 Modulation of Arsenic Uptake and Efflux

The non-essentiality and plant toxicity of arsenic are widely established. The deleterious effects of too much arsenic on plant development and crop productivity have prompted plants to develop a number of defence mechanisms to reduce its toxicity (Verbruggen et al. 2009). In order to relieve arsenic stress in plants, the concentration of arsenic must be reduced, which entails minimising arsenic absorption into plants and maximising arsenic outflow from plants. Various inorganic nutrients may also influence how plants absorb arsenic. Notably the silicon content significantly impacts the absorption and accumulation of both inorganic and methylated arsenic in rice (Liu et al. 2014). A further barrier to As(V) inflow that forms around rice roots is the presence of iron plaques, which are less efficient at preventing As(III) influx due to their predominantly arsenate and weakly arsenite-linked nature (Seyfferth et al. 2010). In several plant species, the efflux of different arsenic species from roots has been detected. Arsenite efflux is mainly carried out by aquaporin channels, including AtNIP5;1, AtNIP6;1, OsNIP2;1, and LjNIP5;1, as well as additional transporters in the aquaporin family (Bienert et al. 2008). Since only 15–25% of the overall membrane efflux occurs through the aquaporin OsLsi1, other arsenite exporters may also exist. Arsenite efflux is mediated by the aquaporin OsLsi1 (Zhao et al. 2010). Under aerobic environments, various Pht transporters are used by plants to take up As(V), and it is possible that suppressing this mechanism is the main factor in plants' ability to tolerate As(V). Studies have demonstrated that mutations in specific Pht transporters reduce the absorption of arsenate by plant roots and increase arsenate resistance (Shin et al. 2004; Remy et al. 2012).

## 11.4 Long-Distance Translocation of Arsenic Accumulation in the Edible Parts of Plants

Arsenic accumulates in edible tissues due to long-distance translocation in plants, particularly in crops, causing major health concerns to people. Plants' ability to tolerate arsenic and the capacity of arsenic hyperaccumulators to accumulate arsenic are influenced by how well arsenic is transported from the roots to the shoots (Verbruggen et al. 2009).

### *11.4.1 Xylem Loading*

The amount of arsenic that accumulates in plant shoots is substantially influenced by the capacity to load arsenic into the xylem. Arsenic is transported from the root to the shoot through xylem tissues and then distributed to other plant tissues. The major arsenic species that moves from the root cortical cells to the xylem vessels appears to be inorganic arsenite (Pickering et al. 2000). Arsenite is the predominant form of arsenic in xylem sap. Several membrane proteins are involved in the loading of arsenic into the xylem. Arsenic may be transported over great distances through the Pht transport route.

In rice, the root uptake and xylem-mediated loading processes use the same routes for arsenite and Si. OsLsi2 is involved in loading arsenite into the xylem of rice roots (Ma et al. 2008). The concentration of arsenite in the xylem sap and rice grains is significantly impacted by the mutation of OsLsi2, while arsenite uptake by the roots is only slightly impacted. This suggests OsLsi2 mediates arsenite efflux toward the xylem (Ma et al. 2008). Tiwari et al. (2014), reported the role of NRAMP (natural resistance-associated macrophage protein) in the loading and accumulation of arsenic in plant shoots through the xylem. OsNRAMP1 expression in Arabidopsis also increases the capacity of plants to withstand As(III). Uncertainty surrounds OsNRAMP1's function in rice arsenic transport. Intriguingly, in the xylem and phloem, methylated arsenic species are more mobile than inorganic arsenic, but the major regulators in these tissues are yet unknown (Li et al. 2007; Ye et al. 2010).

### *11.4.2 Phloem Loading*

The redistribution of arsenic to grains depends on the loading and unloading of phloem. Arsenite concentrations in castor beans (*Ricinus communis*) decline noticeably in the following order: roots > shoots > phloem sap after treatment with 10 mM As(III). Thiol chemicals were present in the phloem sap in significant amounts, but As(III) did not combine with them because the pH was neutral (Ye et al. 2010). In addition, Carey et al. (2011) showed significant differences in the distribution of organic and inorganic arsenic (DMA) in rice grains. Along with strontium, manganese and iron, arsenite collected in the ovular vascular trace (OVT) and DMA diffused over the grain's epidermis and into the endosperm. The embryo, however, did not contain any of the arsenic species.

## 11.5 Physiological Effects of Arsenic on Plants

Arsenic is a protoplasmic toxin that manifests toxicity by deactivating crucial enzymes involved in DNA synthesis and repair as well as the production of cellular energy. The main mechanism of arsenic-related toxicity is the inactivation of vital enzymes, which might worsen cellular signalling pathways. The formation of free radicals causes cell death, aberrant gene expression, and the destruction of DNA, lipids, and proteins (Fig. 11.2) (Tong et al. 2015).

### *11.5.1 Effect of Arsenic on Plant Growth and Nutrient Uptake*

Arsenic exposure to soil is hazardous for both human and environmental health. The presence of arsenic in the soil can interfere with the metabolism of plants, which in turn prevents their growth and development and ultimately causes plant death (Shahid et al. 2015). The disruption of nutrient absorption and nutritional balance is one of the ways that arsenic damages plants (Carbonell et al. 1998). Arsenic may also cause the formation of ROS in plants, damage nucleic acid, chlorophyll, and other components of cell membranes, and impair normal plant growth and development

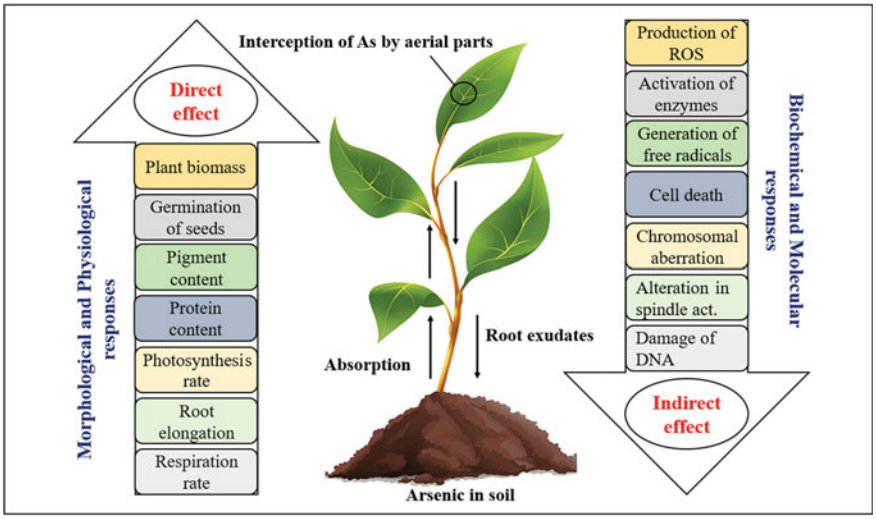


**Fig. 11.2** Arsenic-induced morphological, physiological, biochemical and molecular responses of plants. SOD, superoxide dismutase; POD, peroxidase; CAT, catalase; APX, ascorbate peroxidase; GPX, glutathione peroxidase; GR, glutathione reductase; GPOX, guaiacol peroxidase; DHAR, dehydroascorbate reductase; MDHAR, monodehydroascorbate reductase; GST, glutathione S-transferase; MDA, malondialdehyde and hydrogen peroxide, $H_2O_2$

(Tewari et al. 2002). Arsenic disrupts biochemical and metabolic processes, which at higher concentrations can cause plant death (Imran et al. 2013). The number of leaves, the area of the leaves, and the fresh and dry mass of plants have all been found to be suppressed by arsenic exposure (Nath et al. 2014). Additionally, As resulted in reduced leaf area, wilting, curling, and necrosis of leaf blades (Finnegan and Chen 2012). Under arsenic stress, exposed seedlings of *O. sativa* L. (Vromman et al. 2013) and *Cicer arietinum* L. (Malik et al. 2011) were found to exhibit significant modifications in these plants' typical functioning, including reduced development of roots and shoots. Arsenic disturbs the biochemical and metabolic pathways such as impeded nutrient absorption. *Cicer arietinum* L. seedlings exposed to arsenic stress observed a remarkable decrease in the amounts of a few key amino acids such as Lys, Met, Pro, Thr, Trp, and Val (Malik et al. 2011). According to a previous study, sulphur (S), potassium (K), calcium (Ca), iron (Fe), and copper (Cu) contents in rice roots considerably reduced after arsenic treatment (Singh et al. 2018). According to Wang et al. (2010), arsenite is mostly influenced the P and K contents, whereas arsenate directly impactes the N content.

### *11.5.2 Effect of Arsenic on Chlorophyll Molecules and Photosynthetic Performance*

According to several reports (Nagajyoti et al. 2010; Gusman et al. 2013), arsenic slows down the rate of photosynthesis in plants. According to Duman et al. (2010), arsenic poisoning reduces photosystem I (PSI) and photosystem II (PSII) activity as well as the production of photosynthetic pigments. Under As exposure, PS-II functioning and the rate of carbon dioxide fixation both significantly decreased (Stoeva and Bineva 2003). Arsenic has been found to alter the rates of gas exchange and fluorescence emission by significantly impacting a plant's ability to dissipate heat and perform photochemically (Chandrakar et al. 2016a). These findings, which are mostly similar across research, imply that arsenic may contribute to developing toxic symptoms such as leaf withering and violet colouring (Chandrakar et al. 2016b).

Arsenic stress reduced the synthesis of chlorophyll (Chl) in many plants, including *Zea mays* (Emamverdian et al. 2015), *Trifolium pratense* (Hasanuzzaman et al. 2017), and *Lactuca sativa* (Suneja 2014). According to Upadhyaya et al. (2014), contamination lowered carotenoids and disrupted the chloroplast membrane. Arsenic exposure in chickpea (*C. arietinum*) plants decreased Chl levels, which led to chloroplast deformation (Bhattacharya et al. 2012). Arsenic stress decreased the rate of photosynthesis, stomatal conductance, and PSII effectiveness in soybean. Chl fluorescence and photosynthetic rate in *P. cretica* and *Spinacia oleracea* were decreased by arsenic stress. According to research, arsenic exposure causes microtubules to break down, which hinders the development of stomata and leads to aberrant stomata (Gupta and Bhatnagar 2015). *Leucaena leucocephala* and *P. vittata* leaves have defective chloroplast internal membranes under arsenic stress. Overall, arsenic exposure slows

crop development by modifying root plasmolysis, decreasing photosynthetic parameters such as pigment degradation, rate of $CO_2$ fixation, stomatal conductance, and distorting the integrity of cell membranes.

### *11.5.3 Reactive Oxygen Species (ROS) and Oxidative Stress*

Plants under arsenic stress may experience oxidative stress, which leads to an imbalance between ROS formation and ROS scavenging (Pourrut et al. 2013). The overproduction of ROS negatively impacted various physiological processes, including lipid metabolism, DNA, photosynthesis, respiration, enzyme deactivation, and growth inhibition in stressed plants (Garcia-Caparrós et al. 2021). The ROS are short-lived, unpaired electron-containing oxygen-containing molecules that are highly unstable and chemically reactive. Due to several metabolic processes operating inside a cell, PTEs like arsenic are present in chloroplasts, mitochondria, and peroxisomes, where they are usually hazardous (Shahid et al. 2014).

Numerous investigations have shown that arsenite and arsenate cause the production of ROS (Mishra et al. 2019). Arsenite produces more $O_2$, which is more harmful to plant development than arsenate, which produces more $H_2O_2$ (Coelho et al. 2020). Although leaves produce ROS long before arsenic accumulates in the tissues of leaves, it has been postulated that roots signal arsenic toxicity to leaves, most likely through $H_2O_2$ (Yadav et al. 2021). Li et al. (2007) found that *Triticum aestivum* seedlings had substantial ROS formation in their leaf cells along with rising arsenic levels. In addition to *Zea mays* developing embryos (Mylona et al. 1998), *T. aestivum* L. seedlings (Li et al. 2007; Ghosh et al. 2013), *O. sativa* (Choudhury et al. 2011), *Spinacia oleracea* (Shahid et al. 2013), *Pisum sativum* (Rafiq et al. 2017a), *Vicia faba* (Rafiq et al. 2017b), and seeds of *Anadenanthera peregrina* and *Myracrodruon urundeuva* (Gomes et al. 2013) have all shown to accumulate more ROS.

Malondialdehyde (MDA), a primary byproduct of lipid peroxidation, and membrane leakage are the key indicators of lipid peroxidation caused by ROS (Gupta et al. 2013). Overproduction of ROS causes a decrease in saturated fatty acid and a rise in polyunsaturated fatty acid (PUFA), which enhances membrane permeability (Mishra et al. 2019; Chandrakar et al. 2016b). In addition to altering nitrogenase bases and nucleotide deletion, ROS formation under arsenic stress also alters protein-DNA interaction and may cause DNA breaks (Mucha et al. 2019). By influencing the signalling and vacuolar processing enzymes, ROS causes programmed cell death (Li et al. 2012). Cellular and membrane activities were impeded by lipid peroxidation, a typical harmful impact of arsenic-induced ROS, which was also shown in hyperaccumulating *P. vittata* (Van Breusegem and Dat 2006). Chromosome or microtubule damage in *P. sativum* has been shown under arsenic stress, which inhibited root meristem activity (Dho et al. 2010).

### 11.5.4 *Effect of Arsenic on Antioxidative Enzymatic and Non-enzymatic Antioxidant System*

In response to arsenic, plants produce important ROS-scavenging antioxidant enzymes (Table 11.2) (Rajput et al. 2021). The coordination of antioxidant defence is carried out by the balance of several enzymatic antioxidants, which include the elimination of oxygen radicle (SOD), conversion of $H_2O_2$ into the water and molecular oxygen (CAT), scavenging of $H_2O_2$ in the extracellular space (POD), conjugation of GSH to electrophilic compounds or hydrophobic compounds (GST), preservation of ascorbate pool (MDHAR and DHAR), and conversion of $H_2O_2$ to water using ascorbate as specific electron donor (APX) (Rajput et al. 2021). Numerous studies have examined changes in antioxidant enzyme activity and non-enzymatic antioxidant levels to gain insight into the processes underpinning plants' antioxidant response to arsenic stress. The non-enzymatic antioxidant machinery is composed of GSH, AsA, phenolic substances, sugars, and emergent components (such as anexins and dehydrins) (Soares et al. 2019). The extensive study of arsenic-related non-enzymatic antioxidant accumulation has also been aided by metabolomic techniques (Tripathi et al. 2012).

**Table 11.2** Effects of Arsenic metal on different physiological processes in plants

| S. No | Plant species | Plant organs | Physiological response | References |
|---|---|---|---|---|
| 1 | *Zea mays* | Leaf | Increased SOD, POD, CAT, APX, GPX and GR, MDA and $H_2O_2$ activities | Anjum et al. (2016) |
| 2 | *Zea mays* | Leaf | Increased SOD, GR and decreased CAT, APX, GPOX, MDA and $H_2O_2$ activities | Mallick et al. (2011) |
| 3 | *O. sativa* | Root and shoot | Increased SOD, APX, GPOX and MDA activities | Dave et al. (2013) |
| 4 | *O. sativa* | Root and shoot | Increased SOD, MDA and $H_2O_2$ and decreased CAT activities | Majumder et al. (2019) |
| 5 | *O. sativa* | Leaf | Increased APX, GR and GST and decreased SOD, APX, GPOX and $H_2O_2$ activities | Mallick et al. (2014) |
| 6 | *O. sativa* | Leaf | Increased SOD, CAT and APX activities | Gupta and Ahmad (2014) |
| 7 | *Nicotiana sylvestris and N. tabacum* | Root and leaf | Decreased APX, GST and POD and increased CAT activities in leaf Increased APX and decreased CAT activities in roots | Kofronová et al. (2020) |
| 8 | *Ricinus communis* | Leaf | Increased SOD and GPOX activities | Singh et al. (2021) |
| 9 | *Brassica juncea* | Shoot | Increased SOD, APX, DHAR and MDHAR activities | Srivastava et al. (2010) |

For instance, Bianucci et al. (2017) found that peanut plants exposed to arsenic increased their superoxide dismutase, catalase, and Glutathione S-transferase levels while decreasing their glutathione reductase and guaiacol peroxidase activity and GSH contents in a dose-dependent way. In another study, the activity of superoxide dismutase, peroxidase, and glutathione reductase in *Lemna gibba* increased while the concentration of arsenic increased. In contrast to declining ascorbate peroxidase, catalase activities and chloroplastic pigment levels, anthocyanin concentration increased steadily in these plants (Leao et al. 2013). Arsenate addition in the growth medium of *V. faba* plants resulted in an increased peroxidase activity in leaves, lower peroxidase activity in roots, and initiation of superoxide dismutase and catalase activities in both leaves and roots. Arsenite treatment had an impact on rice, increasing AsA and GSH levels as well as antioxidant activities (Mishra et al. 2011).

### *11.5.5 Effect of Arsenic on the Endogenous Levels of Plant Hormones*

Phytohormones can enhance the antioxidant defence system of plants, which includes both enzymatic and non-enzymatic components for reducing oxidative damage caused by metals (Rohman et al. 2022). For instance, Methyl Jasmonate (MeJA) efficiently reduces oxidative stress as demonstrated by decreased ROS production, increased redox state of AsA and GSH, enhanced enzymatic antioxidant activities, and higher membrane stability in plants post arsenic poisoning (Farooq et al. 2016). One of the essential processes for controlling $H_2O_2$ metabolism in plant cells is the Ascorbate–glutathione cycle, which is increased by phytohormone supplementation under arsenic stress (Kaya et al. 2020). Salicylic acid (SA)-mediated reduced $H_2O_2$, MDA generation, and Electrolyte leakage in arsenic stressed *Z. mays* are only a few examples of oxidative damage caused by ROS that was decreased as a result of the AsA-GSH redox state provided by plant hormones (Kaya et al. 2020). Methyl jasmonate reduces oxidative stress by enhancing antioxidant enzyme activity and reducing arsenic accumulation by regulating arsenic transporters in rice plants and *B. napus* (Farooq et al. 2016).

## 11.6 Conclusions and Future Directions

This chapter provides an overview of how arsenic metal affects plant development and growth. Plants absorb arsenic through their roots, which leads to nutritional imbalance, root damage, and chlorosis of the leaves. Arsenic toxicity also affects chlorophyll production by preventing the function of essential enzymes. Attacking cellular membranes and macromolecules also causes oxidative stress, which slows plant development and causes chlorosis and leaf withering. More investigation is

required to comprehend the interconversion of the arsenic species within the plant system and its location after absorption, which would reveal the entire metabolic system and allow for the development of transgenics. Therefore, it is crucial to comprehend the mechanisms by which arsenic absorption and its detrimental effects on the environment, particularly on plants, might be reduced.

## References

Anjum SA, Tanveer M, Hussain S, Shahzad B, Ashraf U, Fahad S, Hassan W, Jan S, Khan I, Saleem MF (2016) Osmoregulation and antioxidant production in maize under combined cadmium and arsenic stress. Environ Sci Pollut Res Int 23:11864–11875

ATSDR (2013) ATSDR (agency for toxic substances and disease registry). http://www.atsdr.cdc.gov/ substances/toxsubstance.asp?toxid\protect$\relax\protect{\begingroup1\endgroup\@@over4}$3. Accessed 23 Oct 2017

Bach J, Peremart J, Annangi B, Marcos R, Hernandez A (2016) Oxidative DNA damage enhances the carcinogenic potential of in vitro chronic arsenic exposures. Arch Toxicol 90:1893–1905

Bhattacharya S, De Sarkar N, Banerjee P, Banerjee S, Mukherjee S, Chattopadhyay D, Mukhopadhyay A (2012) Effects of arsenic toxicity on germination, seedling growth and peroxidase activity in *C. arietinum.* Int J Agric Food Sci 2:131–137

Bianucci E, Furlan A, Tordable MDC, Hernández LE, Carpena-Ruiz RO, Castro S (2017) Antioxidant responses of peanut roots exposed to realistic groundwater doses of arsenate: identification of glutathione S-transferase as a suitable biomarker for metalloid toxicity. Chemosphere 181:551–561

Bienert GP, Thorsen M, Schussler MD, Nilsson HR, Wagner A, Tamas MJ (2008) A subgroup of plant aquaporins facilitate the bidirectional diffusion of $As(OH)_3$ and $Sb(OH)_3$ across membranes. BMC Biol 6:26

Bolan N, Mahimairaja S, Kunhikrishnan A, Seshadri B, Thangarajan R (2015) Bioavailability and ecotoxicity of arsenic species in solution culture and soil system: implications to remediation. Environ Sci Pollut Res 22:8866–8875

Carbonell AA, Aarabi MA, DeLaune RD, Gambrell RP, Patrick WH (1998) Bioavailability and uptake of arsenic by wetland vegetation: effects on plant growth and nutrition. J Environ Sci Health A Toxic/hazard Subst Environ Eng 33(1):45–66

Carey AM, Norton GJ, Deacon C, Scheckel KG, Lombi E, Punshon T (2011) Phloem transport of arsenic species from flag leaf to grain during grain filling. New Phytol 192:87–98

Chandrakar V, Dubey A, Keshavkant S (2016a) Modulation of antioxidant enzymes by salicylic acid in arsenic exposed Glycine max L. J Soil Sci Plant Nutr 16:662–676

Chandrakar V, Naithani SC, Keshavkant S (2016b) Arsenic-induced metabolic disturbances and their mitigation mechanisms in crop plants: a review. Biologia 71:367–377

Choudhury B, Chowdhury S, Biswas AK (2011) Regulation of growth and metabolism in rice (*O. sativa* L.) by arsenic and its possible reversal by phosphate. J Plant Interact 6:15–24

Coelho DG, de Andrade HM, Marinato CS, Araujo SC, de Matos LP, da Silva VM, de Oliveira JA (2020) Exogenous jasmonic acid enhances oxidative protection of Lemna valdiviana subjected to arsenic. Acta Physiol Plant 42:97

Cullen WR, Reimer KJ (1989) Arsenic speciation in the environment. Chem Rev 89:713–764

Dave R, Tripathi RD, Dwivedi S, Tripathi P, Dixit G, Sharma YK, Trivedi PK, Corpas FJ, Barroso JB, Chakrabarty D (2013) Arsenate and arsenite exposure modulate antioxidants and amino acids in contrasting arsenic accumulating rice (*O. sativa* L.) genotypes. J Hazard Mater 262:1123–1131

Dho S, Camusso W, Mucciarelli M, Fusconi A (2010) Arsenate toxicity on the apices of *P. sativum* L. seedling roots: effects on mitotic activity, chromatin integrity and microtubules. Environ Exp Bot 69:17–23

Duman F, Ozturk F, Aydin Z (2010) Biological responses of duckweed (*Lemna minor* L.) exposed to the inorganic arsenic species As(III) and As(V): effects of concentration and duration of exposure. Ecotoxicology 19:983–993

Emamverdian A, Ding Y, Mokhberdoran F, Xie Y (2015) Heavy metal stress and some mechanisms of plant defense response. Sci World J 2015:756120

Farooq MA, Gill RA, Islam F, Ali B, Liu H, Xu J, He S, Zhou W (2016) Methyl jasmonate regulates antioxidant defense and suppresses arsenic uptake in *Brassica napus* L. Front Plant Sci 7:468

Fayiga A, Saha U (2016) Arsenic contamination, exposure routes and public health, pp 1–11

Finnegan PM, Chen W (2012) Arsenic toxicity: the effects on plant metabolism. Front Physiol 3:182

García-Caparrós P, De Filippis L, Gul A, Hasanuzzaman M, Ozturk M, Altay V, Lao MT (2021) Oxidative stress and antioxidant metabolism under adverse environmental conditions: a review. Bot Rev 87:421–466

Ghosh S, Saha J, Biswas AK (2013) Interactive influence of arsenate and selenate on growth and nitrogen metabolism in wheat (*T. aestivum* L.) seedlings. Acta Physiol Plant 35:1873–1885

Gomes M, Carneiro M, Nogueira C, Soares A, Garcia Q (2013) The system modulating ROS content in germinating seeds of two Brazilian savanna tree species exposed to As and Zn. Acta Physiol Plant 35:1011–1022

Gupta M, Ahmad MA (2014) Arsenate induced differential response in rice genotypes. Ecotoxicol Environ Saf 107:46–54

Gupta P, Bhatnagar AK (2015) Spatial distribution of arsenic in different leaf tissues and its effect on structure and development of stomata and trichomes in mung bean, *Vigna radiata* (L.) Wilczek. Environ Exp Bot 109:12–22

Gupta DK, Inouhe M, Rodríguez-Serrano M, Romero-Puerta MC, Sandalio LM (2013) Oxidative stress and arsenic toxicity: role of NADPH oxidases. Chemosphere 90:1987–1996

Gusman GS, Oliveira JA, Farnese FS, Cambraia J (2013) Arsenate and arsenite: the toxic effects on photosynthesis and growth of lettuce plants. Acta Physiol Plant 35:1201–1209

Hasanuzzaman M, Nahar K, Rahman A, Al Mahmud J, Hossain S, Alam K, Oku H, Fujita M (2017) Actions of biological trace elements in plant abiotic stress tolerance. Essential plant nutrients. Springer, Berlin, pp 213–274

Huang JH (2014) Impact of microorganisms on arsenic biogeochemistry: a review. Water Air Soil Pollut 225:1848

Hughes MF, Beck BD, Chen Y, Lewis AS, Thomas DJ (2011) Arsenic exposure and toxicology: a historical perspective. Toxicol Sci 123:305–332

Imran MA, Khan RM, Ali Z, Mahmood T (2013) Toxicity of arsenic (As) on seed germination of sunflower (*Helianthus annuus* L.). Int J Phys Sci 8:840–847

Isayenkov SV, Maathuis FJM (2008) The *A. thaliana* aquaglyceroporin AtNIP7;1 is a pathway for arsenite uptake. FEBS Lett 582:1625–1628

Jia Y, Huang H, Zhong M, Wang FH, Zhang LM, Zhu YG (2013) Microbial arsenic methylation in soil and rice rhizosphere. Environ Sci Technol 47:3141–3148

Jomova K, Jenisova Z, Feszterova M, Baros S, Liska J, Hudecova D, Rhodes CJ, Valko M (2011) Arsenic: toxicity, oxidative stress and human disease. J Appl Toxicol 31:95–107

Kamiya T, Tanaka M, Mitani N, Ma JF, Maeshima M, Fujiwara T (2009) NIP1;1, an aquaporin homolog, determines the arsenite sensitivity of *A. thaliana.* J Biol Chem 284:2114–2120

Katsuhara M, Sasano S, Horie T, Matsumoto T, Rhee J, Shibasaka M (2014) Functional and molecular characteristics of rice and barley NIP aquaporins transporting water, hydrogen peroxide and arsenite. Plant Biotechnol 31:213–219

Kaya C, Ashraf M, Alyemeni MN, Corpas FJ, Ahmad P (2020) Salicylic acid-induced nitric oxide enhances arsenic toxicity tolerance in maize plants by upregulating the ascorbate-glutathione cycle and glyoxalase system. J Hazard Mater 399:123020

Kofronová M, Hrdinová A, Mašková P, Tremlová J, Soudek P, Petrová Š, Pinkas D, Lipavská H (2020) Multi-component antioxidative system and robust carbohydrate status, the essence of plant arsenic tolerance. Antioxidants 9:283

Leão GA, Oliveira JA, Felipe RTA, Farnese FS, Gusman GS (2013) Anthocyanins, thiols, and antioxidant scavenging enzymes are involved in *L. gibba* tolerance to arsenic. J Plant Interact 9:143–151

LeBlanc MS, McKinney EC, Meagher RB, Smith AP (2013) Hijacking membrane transporters for arsenic phytoextraction. J Biotechnol 163:1–9

Li CX, Feng SL, Yun S, Jiang LN, Lu XY, Hou XL (2007) Effects of arsenic on seed germination and physiological activities of wheat seedlings. J Environ Sci 19:725–732

Li Z, Yue H, Xing D (2012) MAP Kinase 6-mediated activation of vacuolar processing enzyme modulates heat shock-induced programmed cell death in Arabidopsis. New Phytol 195:85–96

Li GW, Santoni V, Maurel C (2014) Plant aquaporins: roles in plant physiology. Biochim Biophs Acta 1840:1574–1582

Litwin I, Bocer T, Dziadkowiec D, Wysocki R (2013) Oxidative Stress and Replication-Independent DNA Breakage Induced by Arsenic in *Saccharomyces cerevisiae*. PLoS Genet 9:1003640

Liu WJ, McGrath SP, Zhao FJ (2014) Silicon has opposite effects on the accumulation of inorganic and methylated arsenic species in rice. Plant Soil 376:423–431

Ma JF, Yamaji N, Mitani N, Xu XY, Su YH, McGrath SP (2008) Transporters of arsenite in rice and their role in arsenic accumulation in rice grain. Proc Natl Acad Sci USA 105:9931–9935

Majumder B, Das S, Mukhopadhyay S, Biswas AK (2019) Identification of arsenic-tolerant and arsenic-sensitive rice (*O. sativa* L.) cultivars on the basis of arsenic accumulation assisted stress perception, morpho-biochemical responses, and alteration in genomic template stability. Protoplasma 256:193–211

Malik JA, Goel S, Sandhir R, Nayyar H (2011) Uptake and distribution of arsenic in chickpea: effects on seed yield and seed composition. Commun Soil Sci Plant Anal 42:1728–1738

Mallick S, Sinam G, Sinha S (2011) Study on arsenate tolerant and sensitive cultivars of *Z. mays* L.: differential detoxification mechanism and effect on nutrients status. Ecotoxicol Environ Saf 74:1316–1324

Mallick S, Kumar N, Sinha S, Dubey AK, Tripathi RD, Srivastav V (2014) $H_2O_2$ pretreated rice seedlings specifically reduce arsenate not arsenite: difference in nutrient uptake and antioxidant defense response in a contrasting pair of rice cultivars. Physiol Mol Biol Plants 20:435–447

Mishra S, Jha AB, Dubey RS (2011) Arsenite treatment induces oxidative stress, upregulates antioxidant system, and causes phytochelatin synthesis in rice seedlings. Protoplasma 248:565–577

Mishra S, Dwivedi S, Mallick S, Tripathi RD (2019) Redox homeostasis in plants under arsenic stress. In: Panda SK, Yamamoto YY (eds) Redox homeostasis in plants: from signalling to stress tolerance. Springer, Singapore, pp 179–198

Mosa KA, Kumar K, Chhikara S, Mcdermott J, Liu Z, Musante C (2012) Members of rice plasma membrane intrinsic proteins subfamily are involved in arsenite permeability and tolerance in plants. Transgen Res 21:1265–1277

Mucha S, Berezowski M, Markowska K (2019) Mechanisms of arsenic toxicity and transport in microorganisms. Adv Microbiol 56:88–89

Mylona PV, Polidoros AN, Scandalios JG (1998) Modulation of antioxidant responses by arsenic in maize. Free Radic Biol Med 25:576–585

Nagajyoti P, Lee K, Sreekanth T (2010) Heavy metals, occurrence and toxicity for plants: a review. Environ Chem Lett 8:199–216

Nagarajan VK, Jain A, Poling MD, Lewis AJ, Raghothama KG, Smith AP (2011) Arabidopsis Pht1;5 mobilizes phosphate between source and sink organs and influences the interaction between phosphate homeostasis and ethylene signaling. Plant Physiol 156:1149–1163

Nath S, Panda P, Mishra S, Dey M, Choudhury S, Sahoo L, Panda SK (2014) Arsenic stress in rice: redox consequences and regulation by iron. Plant Physiol Biochem 80:203–210

Neubauer O (1947) Arsenical cancer: a review. Br J Cancer 1:192–251

Pickering IJ, Prince RC, George MJ, Smith RD, George GN, Salt DE (2000) Reduction and coordination of arsenic in Indian mustard. Plant Physiol 122(4):1171–1178

Pourrut B, Shahid M, Douay F, Dumat C, Pinelli E (2013) Molecular mechanisms involved in lead uptake, toxicity and detoxification in higher plants. Heavy metal stress in plants. Springer, Berlin, pp 121–147

Rafiq M, Shahid M, Abbas G, Shamshad S, Khalid S, Niazi NK, Dumat C (2017a) Comparative effect of calcium and EDTA on arsenic uptake and physiological attributes of *P. sativum*. Int J Phytoremed 19:662–669

Rafiq M, Shahid M, Shamshad S, Khalid S, Niazi NK, Abbas G, Saeed MF, Ali M, Murtaza B (2017b) A comparative study to evaluate efficiency of EDTA and calcium in alleviating arsenic toxicity to germinating and young *V. faba* L. seedlings. J Soils Sedim 14:1–11

Rahman MA, Kadohashi K, Maki T, Hasegawa H (2011) Transport of DMAA and MMAA into rice (*O. sativa* L.) roots. Environ Exp Bot 72:41–46

Rajput VD, Harish Singh RK, Verma KK, Sharma L, Quiroz-Figueroa FR, Meena M, Gour VS, Minkina T, Sushkova S (2021) Recent developments in enzymatic antioxidant defence mechanism in plants with special reference to abiotic stress. Biology 10:267

Remy E, Cabrito TR, Batista RA, Teixeira MC, Sa-Correia I, Duque P (2012) The Pht1;9 and Pht1;8 transporters mediate inorganic phosphate acquisition by the *A. thaliana* root during phosphorus starvation. New Phytol 195:356–371

Rohman MM, Tonny SH, Alam SS, Omy SH, Akhi AH, Raihan HUZ, Akter T, Parvin K, Hasanuzzaman M (2022) Role of phytohormones in antioxidant metabolism in plants under salinity and water stress. In: Hasanuzzaman M, Ahammed GJ, Nahar K (eds) Managing plant production under changing environment. Springer, Singapore, pp 151–191

Seyfferth AL, Webb SM, Andrews JC, Fendorf S (2010) Arsenic localization, speciation, and co-occurrence with iron on rice (*O. sativa* L.) roots having variable Fe coatings. Environ Sci Technol 44:8108–8113

Shahid M, Ferrand E, Schreck E, Dumat C (2013) Behavior and impact of zirconium in the soil–plant system: plant uptake and phytotoxicity. Rev Environ Contam Toxicol 221:107–127

Shahid M, Pinelli E, Pourrut B, Dumat C (2014) Effect of organic ligands on lead-induced oxidative damage and enhanced antioxidant defense in the leaves of *V. faba* plants. J Geochem Explor 144:282–289

Shahid M, Dumat C, Pourrut B, Abbas G, Shahid N, Pinelli E (2015) Role of metal speciation in lead-induced oxidative stress to *V. faba* roots. Russ J Plant Physiol 62:448–454

Shin H, Shin H-S, Dewbre GR, Harrison MJ (2004) Phosphate transport in Arabidopsis: Pht1;1 and Pht1;4 play a major role in phosphate acquisition from both low- and high-phosphate environments. Plant J 39:629–642

Singh R, Upadhyay AK, Singh DP (2018) Regulation of oxidative stress and mineral nutrient status by selenium in arsenic treated crop plant *O. sativa*. Ecotoxicol Environ Saf 148:105–113

Singh A, Tiwari S, Pandey J, Lata C, Singh IK (2021) Role of nanoparticles in crop improvement and abiotic stress management. J Biotechnol 337:57–70

Soares C, Carvalho MEA, Azevedo RA, Fidalgo F (2019) Plants facing oxidative challenges: a little help from the antioxidant networks. Environ Exp Bot 161:4–25

Srivastava S, Srivastava AK, Suprasanna P, D'Souza SF (2010) Comparative antioxidant profiling of tolerant and sensitive varieties of *B. juncea* L. to arsenate and arsenite exposure. Bull Environ Contam Toxicol 84:342–346

Stoeva N, Bineva T (2003) Oxidative changes and photosynthesis in oat plants grown in As-contaminated soil. Bulg J Plant Physiol 29:87–95

Sun SB, Gu M, Cao Y, Huang XP, Zhang X, Ai PH (2012) A constitutive expressed phosphate transporter, OsPht1;1, modulates phosphate uptake and translocation in phosphate-replete rice. Plant Physiol 159:1571–1581

Suneja Y (2014) Physio-biochemical responses and allelic diversity for water deficit tolerance related traits in *Aegilops tauschii* and *Triticum dicoccoides*. Ph.D. Thesis, Punjab Agricultural University, Ludhiana, India

Takano J, Wada M, Ludewig U, Schaaf G, von Wiren N, Fujiwara T (2006) The *Arabidopsis* major intrinsic protein NIP5;1 is essential for efficient boron uptake and plant development under boron limitation. Plant Cell 18:1498–1509

Tangahu BV, Abdullah SRS, Basri H, Idris M, Anuar N, Mukhlisin M (2011) A review on heavy metals (As, Pb, and Hg) uptake by plants through phytoremediation. Int J Chem Eng 939161:1–31

Taylor V, Goodale B, Raab A, Schwerdtle T, Reimer K, Conklin S, Karagas MR, Francesconi KA (2017) Human exposure to organic arsenic species from seafood. Sci Total Environ 580:266–282

Tewari RK, Kumar P, Sharma PN, Bisht SS (2002) Modulation of oxidative stress responsive enzymes by excess cobalt. Plant Sci 162(3):381–388

Tiwari M, Sharma D, Dwivedi S, Singh M, Tripathi RD, Trivedi PK (2014) Expression in Arabidopsis and cellular localization reveal involvement of rice NRAMP, OsNRAMP1, in arsenic transport and tolerance. Plant Cell Environ 37:140–152

Tong D, Ortega J, Kim C, Huang J, Gu L, Li GM (2015) Arsenic inhibits DNA mismatch repair by promoting EGFR expression and PCNA phosphorylation. J Biol Chem 290:14536–14541

Tripathi RD, Tripathi P, Dwivedi S, Dubey S, Chatterjee S, Chakrabarty D, Trivedi PK (2012) Arsenomics: Omics of arsenic metabolism in plants. Front Physiol 3:275

Tsuji JS, Chang ET, Gentry PR, Clewell HJ, Boffetta P, Cohen SM (2019) Dose-response for assessing the cancer risk of inorganic arsenic in drinking water: the scientific basis for use of a threshold approach. Crit Rev Toxicol 49:36–84

Upadhyaya H, Shome S, Roy D, Bhattacharya MK (2014) Arsenic induced changes in growth and physiological responses in *V. radiata* seedling: effect of curcumin interaction. Am J Plant Sci 5:3609–3618

Van Breusegem F, Dat JF (2006) Reactive oxygen species in plant cell death. Plant Physiol 141:384–390

Verbruggen N, Hermans C, Schat H (2009) Mechanisms to cope with arsenic or cadmium excess in plants. Curr Opin Plant Biol 12:364–372

Vromman D, Lutts S, Lefèvre I, Somer L, De Vreese O, Šlejkovec Z, Quinet M (2013) Effects of simultaneous arsenic and iron toxicities on rice (*O. sativa* L.) development, yield-related parameters and As and Fe accumulation in relation to As speciation in the grains. Plant Soil 371:199–217

Wang HB, He HB, Yang GD, Ye CY, Niu BH, Lin WX (2010) Effects of two species of inorganic arsenic on the nutrient physiology of rice seedlings. Acta Physiol Plant 32(2):245–251

Wang H, Xu Q, Kong YH, Chen Y, Duan JY, Wu WH (2014) Arabidopsis WRKY45 transcription factor activates PHOSPHATE TRANSPORTER1;1 expression in response to phosphate starvation. Plant Physiol 164:2020–2029

Wolterbeek HT, Meer AJGM (2002) Transport rate of arsenic, cadmium, copper and zinc in *Potamogeton pectinatus* L.: radiotracer experiments with 76As, 109,115Cd, 64Cu and 65,69mZn. Sci Total Environ 287:13–30

Wu ZC, Ren HY, McGrath SP, Wu P, Zhao FJ (2011) Investigating the contribution of the phosphate transport pathway to arsenic accumulation in rice. Plant Physiol 157:498–508

Xu XY, Mcgrath SP, Meharg AA, Zhao FJ (2008) Growing rice aerobically markedly decreases arsenic accumulation. Environ Sci Technol 42:5574–5579

Xu W, Dai W, Yan H, Li S, Shen H, Chen Y (2015) Arabidopsis NIP3;1 plays an important role in arsenic uptake and root-to-shoot translocation under arsenite stress conditions. Mol Plant 8:722–733

Yadav P, Srivastava S, Patil T, Raghuvanshi R, Srivastava AK, Suprasanna P (2021) Tracking the time-dependent and tissue specific processes of arsenic accumulation and stress responses in rice (*O. sativa* L.). J Hazard Mater 406:124307

Ye WL, Wood BA, Stroud JL, Andralojc PJ, Raab A, McGrath SP (2010) Arsenic speciation in phloem and xylem exudates of castor bean. Plant Physiol 154:1505–1513

Zhao FJ, McGrath SP, Meharg AA (2010) Arsenic as a food chain contaminant: mechanisms of plant uptake and metabolism and mitigation strategies. Annu Rev Plant Biol 61:535–559
Zheng MZ, Li G, Sun GX, Shim H, Cai C (2013) Differential toxicity and accumulation of inorganic and methylated arsenic in rice. Plant Soil 365:227–238

# Chapter 12
# The Role of Plant Growth Promoting Bacteria on Arsenic Removal: A Review of Existing Perspectives


**Aritri Laha, Sudip Sengupta, Jajati Mandal, Kallol Bhattacharyya, and Somnath Bhattacharyya**

**Abstract** Phytobial remediation is a cutting-edge technique that employs bacteria and plants to reduce environmental contamination with arsenic (As). Plant growth-promoting bacteria (PGPB) that aids phytoremediation has recently received much attention for their ability to increase plant growth and metal tolerance while removing As on a massive scale. Here we focus on the PGPB traits that affect plants and how they respond to challenges brought on by As. We'll discuss a few current systems that helped PGPB-facilitated As-stress adaptation and reduced As-availability to plants. Introducing phytoremediation with PGPB assistance requires evaluating how PGPB affects the environment, particularly regarding how it affects local microbes.

**Keywords** Arsenic · PGPB · Bioremediation · Phytoremediation

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## 12.1 Introduction

As a poisonous metalloid, arsenic (As) has raised the alarm on a global scale. This metalloid is also a persistent category 1 human carcinogen; its increased prevalence in the biosphere (Ghosh et al. 2018) concerns environmental and human health (Menon et al. 2020). The arsine ($As^3$), elemental arsenic ($As^0$), arsenite [As(III)], and arsenate [As(V)], as well as dimethylarsinic acid (DMA), monomethylarsonic acid (MMA), trimethylarsine oxide (TMAO), arsenobetaine, and others, may be found in the environment (Upadhyay et al. 2018).

Arsenic pollution is widespread in Europe, Bangladesh, Hungary, Taiwan, India, Malaysia, Vietnam, China, Mexico, Romania, and Pakistan (Abbas et al. 2018). In several areas of India, China, Bangladesh, and Pakistan, "cancer villages" have appeared due to a new study of As contamination in groundwater (Cheng et al. 2019). The groundwater arsenic content is about 50% of aquifers above 2.50 mg/L, which is many orders of magnitude higher than the 0.01 mg/L (WHO recommended range). As a result, a million people suffer from different types of diseases for arsenic poisoning (Fig. 12.1).

The origin of As pollution in the environment includes both anthropogenic (e.g., irrigation water) and natural sources (Fig. 12.2) (e.g., volcanic eruptions). Based on the geographic region, the arsenic content in soil varies from 0.1 to 40.0 mg $kg^{-1}$. These metalloids affect plant growth and efficiency, reducing food output significantly. Due to its physiochemical and molecular properties, the As is toxic to plants (Marinho et al. 2019). Food crops, especially rice grains from rice plants, grow with irrigation water containing a high amount of As, which is a significant source of exposure for people through soil-crop-food transfer.

Many physical and chemical techniques are used for arsenic mitigation, but these are costly and create secondary pollution. So, alternative methods must be needed. Some microorganisms can survive in heavy metal-polluted soil and have been continuously used for bioremediation throughout the past few decades. The basic detoxification of inorganic arsenicals by the *ars* operon; organic arsenical detoxification by As methylation/demethylation; energy-yielding respiratory arsenite oxidation (*arr* operon) and arsenate reduction (*aio*/*arx* operon) are among the arsenic-detoxification processes in microbes (Yan et al. 2019).

These metal-tolerant soil microorganisms may attribute plant growth promotion (PGP) through the secretion of 1-amino cyclopropane-1-carboxylate (ACC) deaminase, indole-3-acetic acid (IAA), and also a few phosphate solubilizers, producing siderophores reduce the metal toxicity. While residing in a metal-polluted rhizosphere, these soil-dwelling microorganisms develop metal resistance systems in their body, survive in stressful environments, and increase plant growth and productivity.

So PGPR-mediated bioremediation phenomenon is an environmentally acceptable method of reducing arsenic toxicity in food crops (Laha et al. 2022). The arsenic tolerance mechanisms in PGPR and the several functions of As-resistant PGPR in reducing arsenic-made phytotoxicity are all thoroughly discussed in this chapter.

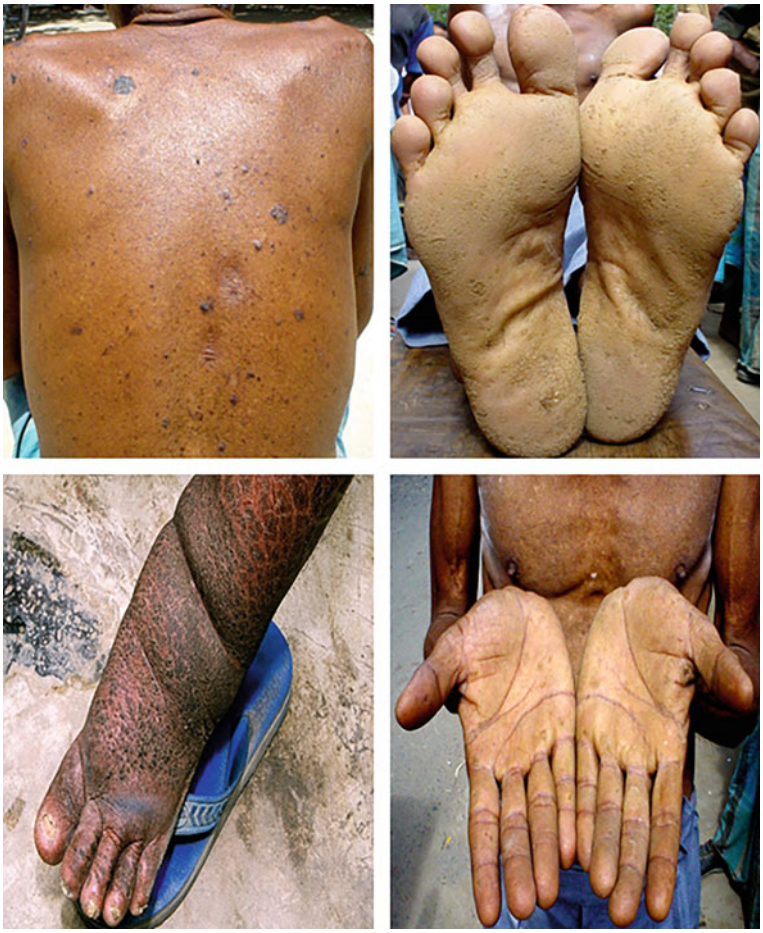

**Fig. 12.1** Arsenocosis (Skin lesions) caused by arsenic

## 12.2 Arsenic in Environment

Arsenic is a poisonous metalloid in group Va of the periodic table. Arsenic has two forms, inorganic and organic form. Both forms are present in the environment. The two most important inorganic forms are arsenate and arsenite. Arsenite is more toxic than arsenate. Organic species of arsenic include methylated forms of arsenic with various degrees of methylation. These are monomethylarsonic acid (MMA), dimethylarsinic acid (DMA), and gaseous variants of arsine (Meharg and Rahman 2003).

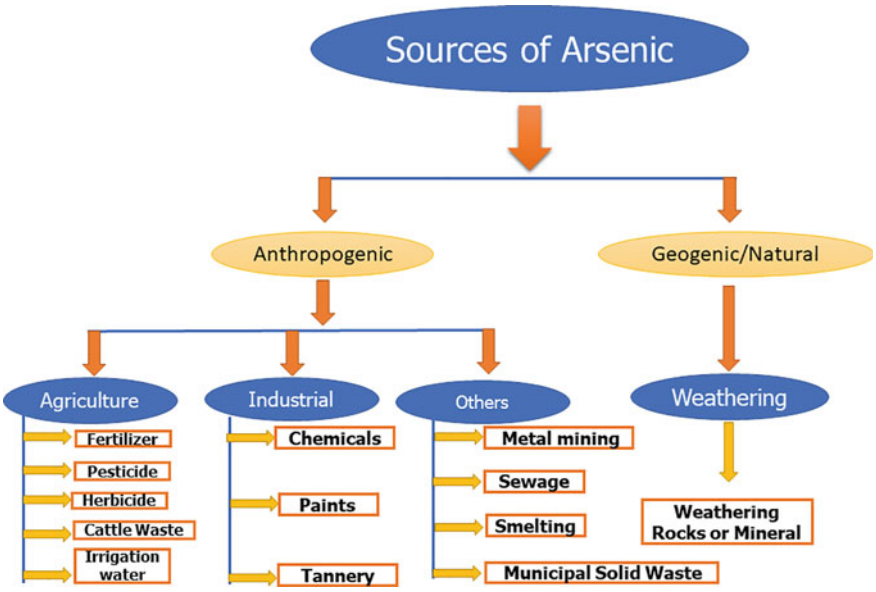


**Fig. 12.2** Origin of arsenic

## 12.3 Identification and Characterization of Arsenic Removal Ability

The arsenic-resistant microbes are identified by calculating their minimum inhibitory concentration (MIC) value against different doses of arsenate and arsenite. The MIC value is the lowest arsenate or arsenite concentration, affecting microbial growth and activities. The value is utilized to compare arsenite or arsenate-tolerant microbial strains. The MIC of arsenic-tolerant bacteria was confirmed and validated using the agar well-diffusion method (Fig. 12.3) (Laha et al. 2021a).

### *12.3.1 Classes of Bacteria and Arsenic Removal Ability*

According to minimum inhibitory concentration (MIC), some bacterial candidates (*Alcaligenes* sp., *Bacillus megaterium, Bacillus subtilis, Arthrobacter* sp., *Variovorax paradoxu, Bacillus megaterium, Acenetobacter* sp.) were reported as arsenic resistant bacteria previously (Bachate et al. 2009; Laha et al. 2021a). The *Burkholderia* sp. can also resist 408 mM of arsenate and 46 mM of arsenite, respectively (Laha et al. 2021a). These all are isolated from contaminated agricultural soils of West Bengal by enrichment culture methods.

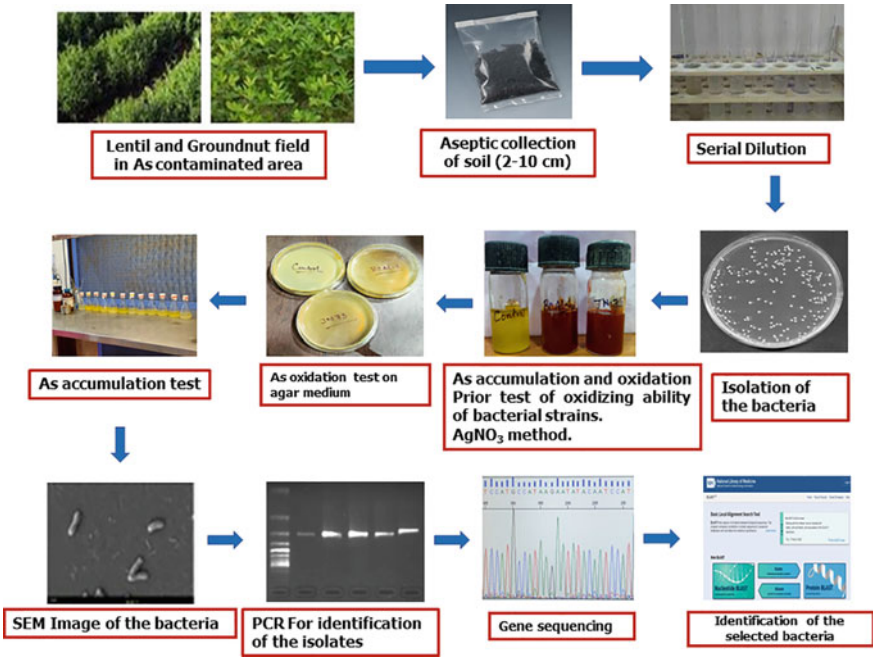


**Fig. 12.3** Identification and characterization of Arsenic removal ability of arsenic tolerant strains

The PGP bacteria have also generated some systems by which they can immobilize, mobilize or transform metals, rendering them less active to resist the uptake of heavy metal ions and survive in metal stress conditions. The *Burkholderia* sp. can live in arsenic, lead, and cadmium-polluted soils, decreasing cadmium translocation and enhancing rice's photosynthesis efficiencies (Jiang et al. 2015). The *Burkholderia cepacia* is also a very good plant growth promoter. These all-arsenic resistant bacterial candidates belong to Proteobacteria, Actinobacteria, and Firmicutes. But in most cases, the arsenic-resistant PGP bacteria belong to Proteobacteria (Laha et al. 2021a).

### *12.3.2 Bioremediation*

Bioremediation is a method where toxic, poisonous heavy metals are extracted from polluted soil and converted into less toxic compounds by the involvement of bacteria. In essence, it includes using bacteria to break down or transform environmental toxins through the processes of their metabolic pathways. Numerous reviewers have documented their methods for surviving in the appearance of heavy metals like arsenic, and their methods for detoxification include redox, intracellular bioaccumulation,

and methylation processes. Numerous chemoautotrophic bacteria (aerobic or anaerobic) can be employed in bioremediation strategies to break down pollutants like As (Laha et al. 2022).

## *12.3.3 Arsenic Resistance Systems in Bacteria*

### 12.3.3.1 As(V) and As(III) Uptake Mechanisms

Arsenic transporter is reported in microbes also. The microorganisms absorb this metal via different non-selective membrane transporters. The arsenate is structurally similar to phosphate, so it is absorbed via phosphate transport systems by inorganic phosphate transport (Pit) and specific transport (Pst). Among these two Pit is a non-specific transport system that transports phosphate more efficiently. The Pst is a unique transporter that transfers phosphate with a higher affinity but less ably. Arsenite (As III) is chemically analog to glycerol and is absorbed via aquaglyceroporin channel GlpF, a candidate of the major intrinsic protein family (Tsai et al. 2009).

### 12.3.3.2 The *ars operon* System

The ***ars operon*** is the most As detoxifying route in microorganisms. They can be found in the chromosome or plasmid of microbes (Tsai et al. 2009), and is organized in different ways, and comprises many gene clusters and bacterial strains. The most common are arsRBC (*Escherichia coli*) and arsRDABC (Fig. 12.4).

ArsR and ArsD, two other significant parts of the *ars* operon, are often regulatory components. The ArsR is a trans-acting repressor protein that responds to arsenite and adversely controls further *ars* operon genes.

The ArsB is an efflux permease that predominantly utilizes membrane potential to remove arsenite from the cell. ArsA is an induced ATPase that also acts as an efflux protein. But ArsAB forms a tightly membrane-bound complex of the ATP-driven arsenite efflux pump, where ArsA functions as a catalytic subunit and ArsB gives the service as a membrane anchor for the catalytic subunit (Tisa and Rosen 1990).

Arsenate is reduced into arsenite by the tiny, monomeric, and cytoplasmic arsenate reductase ArsC, using a three-step nucleophilic attack on cysteine thiols. The two families of arsenate reductases have been documented in prokaryotes (Laha et al. 2022). The primary decontaminating mechanisms through the As-tolerant system are almost indistinguishable in every bacterium.

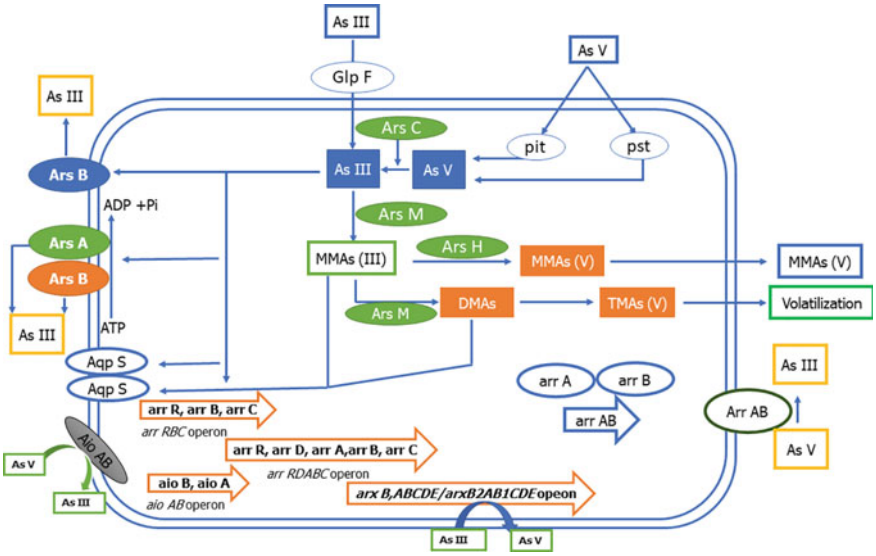


**Fig. 12.4** Arsenic detoxification mechanisms of the microorganisms

### 12.3.3.3 Methylation/Demethylation

Arsenic methylation/demethylation is a significant biotransformation process that further involves As decontamination which is catalyzed by bacterial enzymes. It was long believed that arsenic methylation, followed by volatilization, is an effective detoxifying procedure. However, recent research has shown that some arsenic species formed during this process are more poisonous than inorganic ones. Arsenite S-adenosylmethionine methyltransferase (ArsM) is an enzyme encoded by the *ars*M gene, and is primarily responsible for catalyzing the methylation of arsenite. The S-adenosylmethionine receives methyl groups from the *ars*M and gives them to As(III). The As(III) is methylated in several steps that result in the creation of trimethylarsenite [TMAs(III)], with intermediates such as MAs(III) and DMAs(III). The terminal product trimethylarsenite is not a toxic molecule, and its volatilization can be considered a detoxifying technique. The arsM gene is found in Streptomyces (Mondal et al. 2021).

After arsRDABC and arsM, some PGPR contains aio/arx operon. The AioAB enzyme complex is responsible for catalyzing the reaction in the majority of As(III) oxidizing bacteria. The AioAB complex is also described in the chemolithoautotrophic arsenite oxidizer.

In the arx system, ArxA is a bifunctional enzyme that can both reduce arsenate in vitro and oxidize arsenite in vivo and in vitro. The *arx*A, *arx*B, *arx*b′, *arx*c, *arx*d, and *arx*e all belong to this operon. Although it is claimed that several PGPR can oxidize As(III), the underlying genetic process is still unknown. Other genes in these As(III)-oxidizing PGPR may shed light on the mechanism underlying their capacity

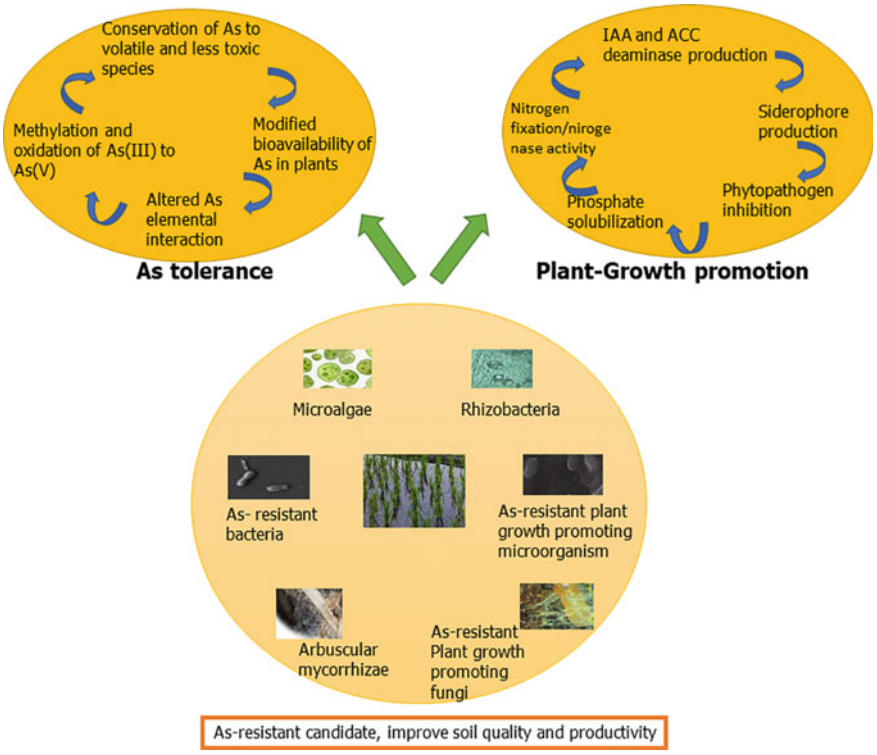


**Fig. 12.5** Mechanisms of microbial bioremediation and plant growth promotion

to oxidize As(III) (Zargar et al. 2010). The mechanisms of microbial bioremediation and plant growth promotion are shown in Fig. 12.5.

## *12.3.4 Arsenic-Resistant PGPR Plays a Multifaceted Role in Reducing Arsenic Phytotoxicity*

### 12.3.4.1 Nutrients Acquisition

Due to PGPR's capacity to fix atmospheric nitrogen, plants can regulate their inability to do so. The nitrogenase enzyme complex is used to reduce $N_2$ into ammonia ($NH_3$) during nitrogen fixation. Both symbiotic and non-symbiotic nitrogen fixation are processes that occur in legumes and other plants (through free-living $N_2$ fixers). The *Rhizobium leguminosarum* is a good example of an arsenic-tolerant nitrogen fixer (Laha et al. 2021b). After nitrogen, phosphorus (P) is likely the nutrient limiting plant growth. When plants are grown in contaminated soil, phosphorus plays a critical function in reducing the toxicity of As. Because they have a structural similarity

with phosphates (Pi), As(V) enters the plant system using the same pathway; as a result, through competitive inhibition, phosphate can effectively suppress As(V) uptake. On the other hand, the As(V) may prevent Pi from entering the plant under Pi-limiting conditions by outcompeting it, which causes Pi deficiency syndromes in plants (Abedin et al. 2002). There are numerous PGPR in this situation that solubilizes phosphorus in arsenic-polluted soil and carries PGPR attributes (*Burkholderia cepacia*, *Burkholderia metallica*, etc.) (Laha et al. 2021a, c, 2022).

Iron mainly exists as the relatively insoluble ferric ($Fe^{3+}$) hydroxide and oxyhydroxide (hard for plants and microbes to digest). Only a small quantity of soluble iron is naturally present in rhizospheric soil, and all creatures inhabiting that region, including plants and bacteria, fight for it (Glick 2012). In heavy metalloid-polluted soil, these things get trickier. As is common knowledge, heavy metals and their metabolites interfere with plant growth, metabolism, and mineral feeding (Laha et al. 2021c). Some As-tolerant and siderophore-producing PGPR include *Bacillus aryabhattai*, *Burkholderia metallica,* etc. (Laha et al. 2021a).

#### 12.3.4.2 Changes in Phytohormones

Phytohormones known as auxins are discovered to be implicated in all significant physiological actions in plants, including the beginning and growth of roots. Indole acetic acid (IAA) participates in a variety of processes, starting with root apical growth, including cell expansion, apical dominance, leaf and fruit abscission, flowering, growth of floral parts, and encouragement of femaleness. Some microbes are also known to create IAA, which is a key factor in the rhizosphere interaction between plants and microbes. Bacterial IAA has also been shown to increase the viability rate of more arsenic-prone rhizobacterial strains, as was the case with *Azospirillum brasilense* Az39, which helped *Bradyrhizobium japonicum* E109 survive in an As-stressed environment (Armendariz et al. 2019).

It is well known that in reaction to various environmental stresses, the plant hormone ethylene is excess produced as "stress ethylene". The synthesis of "stress ethylene" rose in seedlings that had been exposed to as much as (Ghosh et al. 2018). However, it was found that the ethylene rise had been prevented by the application of ACCD, which produced As-tolerant PGPR. A bunch of bacteria is also able to produce ACCD under the arsenic stressed environment, such as *Bacillus* sp., *B. aryabhattai*, *Acinetobacter* sp., *Burkholderia cepacia*, *Burkhoolderia metallica* etc. Due to an underlying IAA and ACCD cross-talk, arsenic-resistant PGPR that is able to produce both IAA and ACCD can considerably reduce stress ethylene levels in plants growing in As-polluted soil environments (Ghosh et al. 2018).

#### 12.3.4.3 Trigger Plant's Antioxidant Defense System

Arsenic exposure in plants produces Reactive oxygen species (ROS), which causes oxidative stress and cellular damage. Due to its propensity to scavenge free radicals,

antioxidant enzymes can control the As-induced overproduction of ROS. To counteract the oxidative damage caused by As, PGPR allows the partial procurement of plant antioxidative enzymatic activity. For example, arsenate treatment decreases SOD and CAT activity in rice seedlings, which were again raised by the application of arsenic-tolerant *B. aryabhattai* by 27.27 and 62.26%, respectively (Ghosh et al. 2018).

#### 12.3.4.4 Recapture of Photosynthetic Activity

The most crucial metabolism for plants and the living earth is undoubtedly photosynthesis. Numerous reports of heavy metal(loid)-induced photosynthetic impairment from different researchers. One of the most detrimental consequences of As-exposure is thought to be a decrease in photosynthetic rate (Gusman et al. 2013).

The use of As-resistant PGPR has been shown to neutralize As's damaging effects on photosynthetic machinery. Generally speaking, it was discovered that bacterial inoculation increased the chlorophyll content in the corresponding host plants. Examples of these PGPR are *Exiguobacterium, Kocuria flava*, *Bacillus flexus* etc., (Srivastava and Singh 2014).

#### 12.3.4.5 Protection from Membrane Deterioration

Arsenic causes oxidative stress by producing ROS, which may then cause polyunsaturated fatty acid (PUFA) peroxidation in membranes, which results in the creation of malonaldehyde (MDA), a by-product of lipid peroxidation. MDA is widely used as a measure of lipid peroxidation, and its presence in high concentrations in As-exposed plants is a sign that free radicals are forming in the cells. Free radicals primarily damage plant cell membranes (Srivastava and Singh 2014). For example, the rice plants treated with 10 and 50 mg $kg^{-1}$ of arsenate showed decreased MDA content following inoculation with *Brevundimonas diminuta* (Singh et al. 2016).

#### 12.3.4.6 Less Accumulated Arsenic in Plants

As-resistance mechanisms in bacteria include the processes of biosorption and bioaccumulation. The major component of biofilm is EPS. Inhibitory As(III) concentrations were observed to enhance biofilm formation in *B. japonicum* and *A. brasilense* (Das and Sarkar 2018). The As-resistant PGPR have also reported the mechanism of biosorption and bioaccumulation, such as *B. aryabhattai*, and *Brevundimonas diminuta* indicating that the presence of these protective systems is widespread among this group of microbes (Ghosh et al. 2018; Laha et al. 2022).

### *12.3.5 Use of Plants to Clean up the Environment*

Even though phytoremediation has been shown to have limitations, encouraging outcomes have been achieved with consistent monitoring, phytoremediation is a method that employs green plants and soil microbes to provide a sustained clean-up solution for some polluted soil (Zhang et al. 2018). The environmental consequences of PGPB-assisted phytoremediation of As must be evaluated before it can be implemented in a field.

The phytoremediation plants fall into three categories: As-tolerant, As-hyperaccumulator, and As-accumulator. The As-tolerant can resist As at a specific limit beneath or at the threshold level. Hyperaccumulator plants may resist and pile up arsenic without displaying any hazardous signs in their above-ground portions. Plants that can pile up arsenic in their roots at low to moderate concentrations are known as As accumulators.

#### 12.3.5.1 Types of as Phytoremediation

Mainly six mechanisms, including phytoextraction, phytostabilization, phytoexclusion, phytostimulation, Phyto filtration, and phytovolatilization, can be used in phytoremediation (Fig. 12.6). But there are other mechanisms for phytoremediation like organic matter, silicon fertilization, mycorrhiza, biochar and iron oxides, phosphorus, and arsenic sequestration by Fe plaque (de Souza et al. 2019). Phytoremediation of Metals Assisted by Plant Growth Promoting Bacteria and the plants involved in ohytoremidiation are listed in Tables 12.1 and 12.2 respectibely.

#### 12.3.5.2 Phytoextraction

The goal of phytoextraction is to abolish contaminants from soil by having plants take them up, move them, and then accumulate them in the section that can be harvested. Then, when the harvestable biomass has been burned, metals are recovered from the ash residue. The *Pteris vittata* L., is the first arsenic hyperaccumulator identified. For detail please see the review of Laha et al. (2022).

#### 12.3.5.3 Phytostabilization

The phytostabilization entails stopping As absorption and accumulation in the rhizosphere zone. This inexpensive procedure is crucial for minimizing the overall bioavailability and biomagnification in the food chain. The *Prosopis juliflora* was found to phytostabilize As in compost-amended pyritic mine tailings, according to Hammond et al. (2018).

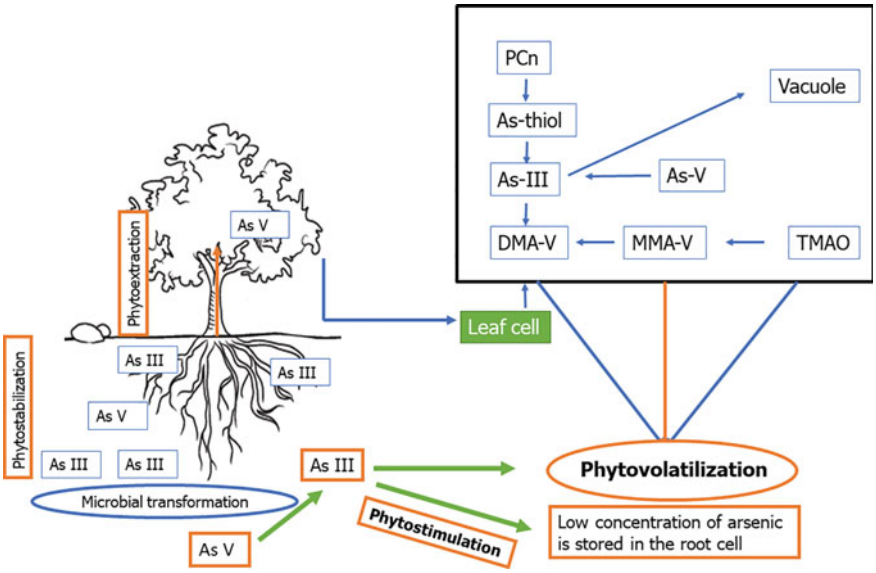


**Fig. 12.6** The phytoremediation mechanisms

### 12.3.5.4 Phytoexclusion

In order to reduce the risk of heavy metal contamination of agricultural products cultivated in contaminated soils, phytoexclusion utilising low heavy metal accumulating cultivars (LACs) is a promising and useful method. It doesn't change cultivation practises, is simple to use, and is affordable (Wang et al. 2021).

In polluted agricultural fields, utilizing non-food crops for phytoextraction is unsuitable. To clean up the contaminated agricultural soils and lessen the arsenic accumulation in rice, a number of agronomic techniques and biotechnologies that have been improved to increase food security and agricultural aptness can be applied. For detail please see the review of Laha et al. (2022).

### 12.3.5.5 Phytofiltration

Rhizofiltration or Phytofiltration is a type of phytoremediation in which wastewater, surface water, and contaminated groundwater are filtered by a dense network of roots to remove toxins or surplus nutrients. The pollutants on the root undergo both absorption and adsorption during the process.

The *P. vittata* and *P. cretica*, are two arsenic hyperaccumulator, were capable to lower arsenic smaller than the drinking water limit of 10 g/L within 24 h. For detail please see the review of Laha et al. (2022).

**Table 12.1** Phytoremediation of metals assisted by plant growth promoting bacteria (PGPB): a summary

| Plant | Plant growth promoting traits | PGPB | As concentration | Effect of PGPB | References |
|---|---|---|---|---|---|
| *Brassica juncea* | IAA production, siderophore, exopolysaccharides, in vitro biofilm formation, phosphate solubilisation and nitrogen fixation | *Actinomycetales* (*Gordonia alkanivorans*), *Betaproteobacteria* (*Cupriavidus necator*) *Bacilli* (*Bacillus megaterium)* isolated from polluted soil | 41.1 mg $kg^{-1}$ exceeded recommendation limits | Indigenous PGPB had a positive effect on plant biomass and assisted phytoextraction strategies | Alka et al. (2020) |
| Rice seedlings | IAA production, siderophore production, and exopolysaccharide (EPS) | *Kocuria flava* and *Bacillus vietnamensis* isolated from mangrove rhizosphere | (> 300 μg/l) As | It promotes growth parameters and decreases As uptake | Alka et al. (2020) |
| *Spirulina Platensis* | Increases in IAA, siderophores, phosphate solubilisation, and ACC deaminase production | *Burkholderia* sp. | | Improved in the growth of plant and metal uptake | Alka et al. (2020) |
| Grapevine | Produce siderophores, solubilize phosphates and fixed N2 | Arsenite resistant bacterial strains which were arsenite resistant bacterial strains | 150 μM (+As) | Decreased arsenite toxic effects, activated antioxidant enzymes | Pinter et al. (2017) |
| *Helianthus annus*var | Phytohormones, Siderophore production, and phosphate solubilisation | *Pseudomonas fluorescens* strain isolated in soil | | Enhanced antioxidant activities, proline, plant yield | Alka et al. (2020) |

(continued)

**Table 12.1** (continued)

| Plant | Plant growth promoting traits | PGPB | As concentration | Effect of PGPB | References |
|---|---|---|---|---|---|
| Plants | Solubilize soil phosphorus, produce siderophore and indole-3-acetic acid (IAA), ACC deaminase | *Pseudomonas jessenii* strain | | Increase plant growth and increases metal uptake | Lozecznik (2018) |
| *Cirsium arvense* | ACC deaminase, IAA and siderophores | *Alphaproteobacteria*, *Betap roteobacteria*, and *Gammaproteobacteria* | (100 mM) As(V) an d (10 mM) As(III) | Improve the phytoremediation process | Alka et al. (2020) |
| Rice | Solubilise phosphate, produce siderophores, and ACC deaminase | *Pseudomonas* sp., *Bacillus* sp., *Paenibacillus* sp., and *Comamonas* sp**.** were isolated from the agricultural soil | 75 μM As(III) or 250 μM As(V) | Improve bioremediation | Das et al. (2016) |
| *Pteris vittata* | Siderophores | *Pseudomonas* sp., *Comamo nas* sp. and *Stenotrophomonas* sp. | 5.04–7.37 mg $L^{-1}$ | Enhance phytoremediation | Alka et al. (2020) |
| *Salix Caprea* | ACCD (Acetylcoenzyme A carboxyl TMA ase carboxyltransferase subunit beta) activity, IAA production, and siderophore release | *Proteobacteria*, *Actinobacteria* and *Bacteroidetes*/*Chlorobi* | | Increase metal uptake | Kuffner et al. (2010) |
| *Triticum aestivum* L | N-fixation and auxin with P solubilising,ACC-deaminase activities, producing siderophore | *Azospirillum* sp. | | Enhance plant growth and alleviate drought stress | Abbas et al. (2018) |
| *Zea mays* | Production of siderophore indole acetic acid, hydrogen cyanide, and ammonia, ACC-deaminase activity | *Chryseobacterium palustre, Sphingobacterium*, *Bacillus*, *Achromobacter*, and *Ralstonia* were isolated from a metal polluted zone | As (5 mg $kg^{-1}$) | Increase plant growth, biomass production, and nutrient status | Alka et al. (2020) |

(continued)

**Table 12.1** (continued)

| Plant | Plant growth promoting traits | PGPB | As concentration | Effect of PGPB | References |
|---|---|---|---|---|---|
| *Atriplex lentiformis* | Plant growth hormones | *A. brasilense* strain and *Bacillus pumilus* strains | 91 mg $kg^{-1}$ | Increase uptake and plant biomass and nutrition | De-Bashan et al. (2010) |
| *Populus deltoids* | Produced siderophores and IAA | *Agrobacterium radiobacter* | 300 mg $kg^{-1}$ | Increase As phytoremediation | Wang et al. (2021) |
| *Brassica juncea* (L.) | IAA, siderophores | *Staphylococcus arlettae* isolated from As contaminated soil | 15 mg $kg^{-1}$ | Increase As accumulation in the root and increased biomass, carotenoid, chlorophyll and protein content | Srivastava et al. (2013) |
| *Panicum virgatum* L | Indole acetic acid production, 1-Amino cyclopropane-1-carboxylic acid deaminase activity, and phosphate solubilisation | *Pseudomonas veronii*, and *Pseudomonas fluorescens were* isolated from Cd polluted soil | | Increase biomass and Increases Cd uptake | Begum et al. (2018) |

**Table 12.2** Plant used in arsenic phytoremediation

| Plant species | Effects | References |
|---|---|---|
| *Pteris vittata* | Significantly reduces As concentration in rice grain by 18–83% | Ye et al. (2011) |
| *Brassica species* | Roots accumulate high levels of As, low quantities of As are detected in the stem and leaves. Uptake of As in the root (67–10, 61% for arsenite) and leaves (65–10%) | Alka et al. (2020) |
| *Arabidopsis thaliana* | *Arabidopsis* reduced arsenate to arsenite in the nutrient solution using a solid-phase extraction (SPE) cartridge | Park et al. (2016) |
| *Glycine max* L. | Soybean grown in soils augmented with phosphate shows a 28.6% arsenic reduction in the toxicity effects | Alka et al. (2020) |
| *Helianthus annuus* L. | Important antioxidants and glutathione present in sunflower leaves exposed to As were decreased by salicylic acid treatment | Alka et al. (2020) |
| *P. calomelanos var. austroamericana* | It accumulates As but takes a longer period of time to be achieved usually required limit for EIL (Ecological Investigation Level) | Alka et al. (2020) |
| *Maize* | Toxicity tests examined the concentrations of arsenite or arsenate reduced | Ding et al. (2011) |
| *Nicotiana tabacum* L. | Both As and Cd accumulation in leaves increases to higher quantities than in roots of *Nicotiana tabacum* | Alka et al. (2020) |
| *Lettuce sativa* L. | The increase in As concentration detected in the leaves was followed by a increase in $H_2O_2$ and malondialdehyde concentrations | Alka et al. (2020) |
| *Pisum sativum* L. | Exogenous Pro application alleviated arsenate toxicity in eggplant seedlings by reducing the accumulation of As | Alka et al. (2020) |
| *Melastoma malabathrum* | Uptake of different metals from polluted soil | Alka et al. (2020) |
| *Solanum melongena* L. | Sodium hydrosulfide enriched arsenate toxicity in pea seedlings | Alka et al. (2020) |

#### 12.3.5.6 Phytovolatilization

Phytovolatilization implies the utilization of plants to volatilise arsenic into atmosphere with or without the cooperation of microbes. Here the plants uptake arsenic from the soil-environment and release it into the atmosphere (Jakob et al. 2010).

#### 12.3.5.7 Phytostimulation

The phytostimulation is a phytoremediation technique that can be used to remediate area contaminated with herbicides. By increasing the venture of the microbial

biomass, phytostimulation lowers the number of organic pollutants that are exuded from the roots of plants. For detail please see the review of Laha et al. (2022).

#### 12.3.5.8 Organic Matter

Arsenic mobility is a complex mixture of several components; organic matter has varying effects on it depending on the variery of compost used, the degree of humification, and pH changes. Conversely, the use of organics reduces the amount of As that is bioavailable in soils and plants, as research on sesame, wheat, maize, and vegetables has shown.

#### 12.3.5.9 Silicon (Si) Fertilization

Rice readily absorbs arsenite through the Si transport system, implying that increased Si availableness can lessen arsenic transfer in the soil-rice system while increasing grain yield.

#### 12.3.5.10 Arsenic Sequestration by Fe (Iron) Plaque

Due to its great capacity to retain As, iron plaque generated on the surface of paddy rice roots and those of other aquatic species resulting from rhizosphere oxygenation may successfully minimize the amount of As that enters rice roots.

#### 12.3.5.11 Water Management

The absorption of arsenic by rice can be significantly decreased under aerobic circumstances, even by 80%, when compared to normal flood irrigation.

#### 12.3.5.12 Phosphorus

A chemical homologue of arsenate, phosphorus (P), or more precisely, pentavalent P, successfully fights with arsenate for binding sites in soils. Competitive anion exchange after P treatment enhanced As bioavailability and plant accumulation. (Hossain et al. 2009).

#### 12.3.5.13 Mycorrhiza

By preferring accumulating P over arsenic, the proper inoculates of arsenic-tolerant mycorrhiza can be a valuable method to increase host tolerance and promote phytostabilization. In an As-stress environment, using mycorrhizal inoculation, like, *Glomus mosseae* increased plant P content by 50–200%.

#### 12.3.5.14 Biochar and Iron Oxides

At a typical ambient pH, biochar with a moderately high cation exchange ability constantly reveals adsorption aptitude toward metal cations but a negligible binding capacity for arsenic species, regardless of the kind of feedstock and pyrolysis. However, when amorphous Fe and biochar were added, most of the As bound to Fe precipitated, significantly lowering the amount of arsenic (Wang and Ma 2015).

#### 12.3.5.15 Indigenous-Resistant Species with Low Translocation Factor (TF)

The finding that trace metals were put down mostly in wooded roots suggested that native *Populus* and *Salix* could be utilized for photostability arsenic-damaged soils. After two years of soil modification (soil blending, ploughing, etc.), 100% survival of native *Populus* and *Salix* was achieved, albeit with 16–92% less tissue biomass than the control (Saxena and Misra 2010).

#### 12.3.5.16 To Mobilise Arsenic, Exudates from the Roots Are Employed

In the rhizosphere, it has been shown that bacteria and root exudates facilitate the solubilization of arsenic. The *P. vittata* produces twice as much diffused organic carbon (DOC) as the fern *Nephrolepis exaltata*, which does not hyperaccumulate. In an As-contaminated soil, organic acids from root exudates mobilized As from intractable As minerals (AlAsO4 and FeAsO4) three times or more than they did for *N. exaltata* (Wang and Ma 2015).

Plants known as hyperaccumulators have the innate ability to hyper accumulate or detoxify in different ways at the molecular, physiological, and biochemical levels. (Laha et al. 2022). Examples of As hyper-accumulators fern species are *Pteris vittata, Pteris longifolia* etc. (Ali et al. 2013). The *Arabidopsis thaliana*, rice, and Indian mustard are also known to accumulate a significant amount of arsenic (Pickering et al. 2000).

### *12.3.6 Phytobial Remediation*

The goal of phytobiological remediation combines the utilization of microorganisms and plants to prevent a number of specific types of contamination. The microbial communities are the key factor of geochemical cycling. They support plant growth and aid in the uptake of harmful heavy metals from the neighbouring ecosystems. In addition to providing nutrients, the rhizosphere microbes (rhizobacteria) have a mutualistic association with plants and help remove toxic metals. These rhizobacteria could therefore be employed to bioremediate metal-contaminated shoreline areas (Goswami et al. 2014; Martins et al. 2008).

### *12.3.7 Plant Growth-Promoting Endophytic Bacteria (PGPE)*

Plant growth-promoting endophytic bacteria (PGPE) and plant growth-promoting rhizospheric bacteria (PGPR) are two types of bacteria that exhibit PGPB features (Afzal et al. 2020). Around the seed surface or plant root, PGPR is present, and PGPE colonizes internal plant tissues (Bilal et al. 2018). The primary mechanisms for the intricate growth promotion process by PGPR are changes in the host plant's physiology and the rhizosphere's microbial stability (Verma et al. 2018). Naturally resistant to high levels of heavy metal pollution, PGPB benefits both soil, and plants. Through their interactions with plants, PGPB and other bacteria contribute to the bioremediation of pollutants by modifying metal mobility and bioavailability and enhancing plant productivity. PGPB can either be endophytic bacteria that colonize inside the plants or free-living bacteria in symbiotic relationships with the plants. The production of compounds such as siderophores, ACC-deaminase by PGPB enhances plant growth in metal stress conditions (Santoyo et al. 2016).

Due to biofilm formation, the PGPB also contains (EPS), a large molecular mass bacterial secretory derivative that can also serve as a hazardous metal(loid) absorber. These comprise mucopolysaccharides, polysaccharides, lipids, proteins, uronic acids, and humic compounds. In addition to phosphate, hydroxyl, and polysaccharide groups, proteins include acetamido, amine, sulfhydryl, carboxyl, and phosphodiester groups, which give EPS a negative charge that encourages metal sequestration (Mondal et al. 2021).

## 12.4 Conclusion and Future Scope

As pollution affects both plants and animals, including humans, it is a serious concern worldwide. An effective way to address environmental arsenic contamination appears to be by bioremediation of such a pervasive pollutant. Remediation has several advantages, including low cost, little environmental harm, and environmental friendliness.

Although recent research is required to assess how environmental factors affect interactions between plant microbes in polluted soils, numerous publications confirm that PGPB plays a critical role in promoting and increasing plant activity. To understand the metal and plant-specified PGPB strains, it is requisite to conduct extensive research on the specific genes and pathways essential for metal tolerance in PGPB. Researchers may be better able to create circumstances and mixtures of hyperaccumulator plants and PGPB for abolishing arsenic and boosting mitigation efforts if they have a molecular understanding of phytobial remediation.

## References

Abbas G, Murtaza B, Bibi I, Shahid M, Niazi NK, Khan MI et al (2018) Arsenic uptake, toxicity, detoxification, and speciation in plants: physiological, biochemical, and molecular aspects. Int J Environ Res Public Health 15(1):59

Afzal MJ, Khan MI, Cheema SA, Hussain S, Anwar-ul-Haq M, Ali MH, Naveed M (2020) Combined application of *Bacillus* sp. MN-54 and phosphorus improved growth and reduced lead uptake by maize in the lead-contaminated soil. Environ Sci Pollut Res 27(35):44528–44539

Ali H, Khan E, Sajad MA (2013) Phytoremediation of heavy metals—concepts and applications. Chemosphere 91(7):869–881

Alka S, Shahir S, Ibrahim N, Chai TT, Bahari ZM, Abd Manan F (2020) The role of plant growth promoting bacteria on arsenic removal: a review of existing perspectives. Environ Technol Innov 17:100602

Armendariz AL, Talano MA, Nicotra MFO, Escudero L, Breser ML, Porporatto C, Agostini E (2019) Impact of double inoculation with *B. japonicum* E109 and *A. brasilense* Az39 on soybean plants grown under arsenic stress. Plant Physiol Biochem 138:26–35

Bachate SP, Cavalca L, Andreoni V (2009) Arsenic-resistant bacteria isolated from agricultural soils of Bangladesh and characterization of arsenate-reducing strains. J Appl Microbiol 107(1):145–156

Begum N, Afzal S, Zhao H, Lou L, Cai Q (2018) Shoot endophytic plant growth-promoting bacteria reduce cadmium toxicity and enhance switchgrass (Panicum virgatum L.) biomass. Acta Physiologiae Plantarum, 40:1–16

Bilal S, Shahzad R, Khan AL, Kang SM, Imran QM, Al-Harrasi A et al (2018) Endophytic microbial consortia of phytohormones-producing fungus Paecilomyces formosus LHL10 and bacteria *Sphingomonas* sp. LK11 to *G. max* L. regulates physio-hormonal changes to attenuate aluminum and zinc stresses. Front Plant Sci 9:1273

Cheng Y, Nathanail CP, Ja'afaru SW (2019) Generic assessment criteria for human health risk management of agricultural land scenario in Jiangsu Province, China. Sci Total Environ 697:134071

Das S, Jean JS, Chou ML, Rathod J, Liu CC (2016) Arsenite-oxidizing bacteria exhibiting plant growth promoting traits isolated from the rhizosphere of Oryza sativa L.: implications for mitigation of arsenic contamination in paddies. J Hazard Mater 302:10–18

Das J, Sarkar P (2018) Remediation of arsenic in mung bean (*Vigna radiata*) with growth enhancement by unique arsenic-resistant bacterium *Acinetobacter lwoffii*. Sci Total Environ 624:1106–1118

De-Bashan LE, Hernandez JP, Bashan Y, Maier RM (2010) Bacillus pumilus ES4: candidate plant growth-promoting bacterium to enhance establishment of plants in mine tailings. Environ Exp Bot 69(3):343–352

Ding D, Li W, Song G, Qi H, Liu J, Tang J (2011) Identification of QTLs for arsenic accumulation in maize (Zea mays L.) using a RIL population. PLoS One 6(10):e25646

de Souza TD, Borges AC, Braga AF, Veloso RW, de Matos AT (2019) Phytoremediation of arsenic-contaminated water by *Lemna valdiviana*: an optimization study. Chemosphere 234:402–408

Ghosh PK, Maiti TK, Pramanik K, Ghosh SK, Mitra S, De TK (2018) The role of arsenic resistant *B. aryabhattai* MCC3374 in promotion of rice seedlings growth and alleviation of arsenic phytotoxicity. Chemosphere 211:407–419

Glick BR (2012) Plant growth-promoting bacteria: mechanisms and applications. Scientifica 2012:401

Goswami D, Dhandhukia P, Patel P, Thakker JN (2014) Screening of PGPR from saline desert of Kutch: growth promotion in *Arachis hypogea* by *Bacillus licheniformis* A2. Microbiol Res 169(1):66–75

Gusman GS, Oliveira JA, Farnese FS, Cambraia J (2013) Arsenate and arsenite: the toxic effects on photosynthesis and growth of lettuce plants. Acta Physiol Plant 35(4):1201–1209

Hammond CM, Root RA, Maier RM, Chorover J (2018) Mechanisms of arsenic sequestration by *P. juliflora* during the phytostabilization of metalliferous mine tailings. Environ Sci Technol 52(3):1156–1164

Hossain MB, Jahiruddin M, Loeppert RH, Panaullah GM, Islam MR, Duxbury JM (2009) The effects of iron plaque and phosphorus on yield and arsenic accumulation in rice. Plant Soil 317(1):167–176

Jakob R, Roth A, Haas K, Krupp EM, Raab A, Smichowski P et al (2010) Atmospheric stability of arsines and the determination of their oxidative products in atmospheric aerosols (PM 10): evidence of the widespread phenomena of biovolatilization of arsenic. J Environ Monit 12(2):409–416

Jiang J, Liu M, Parvez F, Wang B, Wu F, Eunus M et al (2015) Association between arsenic exposure from drinking water and longitudinal change in blood pressure among HEALS cohort participants. Environ Health Perspect 123(8):806–812

Kuffner M, De Maria S, Puschenreiter M, Fallmann K, Wieshammer G, Gorfer M, Strauss J, Rivelli AR, Sessitsch A (2010) Culturable bacteria from Zn-and Cd-accumulating Salix caprea with differential effects on plant growth and heavy metal availability. J Appl Microbiol 108(4):1471–1484

Laha A, Bhattacharyya S, Sengupta S, Bhattacharyya K, GuhaRoy S (2021a) Investigation of arsenic-resistant, arsenite-oxidizing bacteria for plant growth promoting traits isolated from arsenic contaminated soils. Arch Microbiol 203(7):4677–4692

Laha A, Bhattacharyya S, Sengupta S, Bhattacharyya K, GuhaRoy S (2021b) Study on Burkholderia sp: arsenic resistant bacteria isolated from contaminated soil. Appl Ecol Environ Sci 9(2):144–148

Laha A, Bhattacharyya S, Sengupta S, Bhattacharyya K, GuhaRoy S (2021c) *Rhizobium leguminosarum*: a model arsenic resistant, arsenite oxidizing bacterium possessing plant growth promoting attributes. Curr World Environ 16:31

Laha A, Sengupta S, Bhattacharya P, Mandal J, Bhattacharyya S, Bhattacharyya K (2022) Recent advances in the bioremediation of arsenic-contaminated soils: a mini review. World J Microbiol Biotechnol 38(11):1–15

Lozecznik S (2018) Facultative endophytic plant growth promoting bacteria. Google Pat

Marinho BA, Cristóvão RO, Boaventura RA, Vilar VJ (2019) As(III) and Cr(VI) oxyanion removal from water by advanced oxidation/reduction processes: a review. Environ Sci Pollut Res 26(3):2203–2227

Martins FR, Rüther R, Pereira EB, Abreu SL (2008) Solar energy scenarios in Brazil. Part two: photovoltaics applications. Energy Policy 36(8):2865–2877

Meharg AA, Rahman MM (2003) Arsenic contamination of Bangladesh paddy field soils: implications for rice contribution to arsenic consumption. Environ Sci Technol 37(2):229–234

Menon M, Sarkar B, Hufton J, Reynolds C, Reina SV, Young S (2020) Do arsenic levels in rice pose a health risk to the UK population? Ecotoxicol Environ Saf 197:110601

Mondal S, Pramanik K, Ghosh SK, Pal P, Mondal T, Soren T, Maiti TK (2021) Unraveling the role of plant growth-promoting rhizobacteria in the alleviation of arsenic phytotoxicity: a review. Microbiol Res 250:126809

Park JH, Han YS, Seong HJ, Ahn JS, Nam IH (2016) Arsenic uptake and speciation in Arabidopsis thaliana under hydroponic conditions. Chemosphere 154:283–288

Pickering IJ, Prince RC, George MJ, Smith RD, George GN, Salt DE (2000) Reduction and coordination of arsenic in Indian mustard. Plant Physiol 122(4):1171–1178

Pinter IF, Salomon MV, Berli F, Bottini R, Piccoli P (2017) Characterization of the As (III) tolerance conferred by plant growth promoting rhizobacteria to in vitro-grown grapevine. Appl Soil Ecol 109:60–68

Santoyo G, Moreno-Hagelsieb G, del Carmen Orozco-Mosqueda M, Glick BR (2016) Plant growth-promoting bacterial endophytes. Microbiol Res 183:92–99

Saxena P, Misra N (2010) Remediation of heavy metal contaminated tropical land. Soil heavy metals. Springer, Berlin, pp 431–477

Singh AP, Dixit G, Kumar A, Mishra S, Singh PK, Dwivedi S et al (2016) Nitric oxide alleviated arsenic toxicity by modulation of antioxidants and thiol metabolism in rice (*Oryza sativa* L.). Front Plant Sci 6:1272

Srivastava S, Singh N (2014) Mitigation approach of arsenic toxicity in chickpea grown in arsenic amended soil with arsenic tolerant plant growth promoting *Acinetobacter* sp. Ecol Eng 70:146–153

Srivastava S, Verma PC, Chaudhry V, Singh N, Abhilash PC, Kumar KV, Sharma N, Singh N (2013) Influence of inoculation of arsenic-resistant Staphylococcus arlettae on growth and arsenic uptake in Brassica juncea (L.) Czern. Var. R-46. J Hazard Mater 262:1039–1047

Tsai SL, Singh S, Chen W (2009) Arsenic metabolism by microbes in nature and the impact on arsenic remediation. Curr Opin Biotechnol 20(6):659–667

Upadhyay MK, Yadav P, Shukla A, Srivastava S (2018) Utilizing the potential of microorganisms for managing arsenic contamination: a feasible and sustainable approach. Front Environ Sci 6:24

Verma S, Verma PK, Meher AK, Bansiwal AK, Tripathi RD, Chakrabarty D (2018) A novel fungal arsenic methyltransferase, WaarsM reduces grain arsenic accumulation in transgenic rice (*O. sativa* L.). J Hazard Mater 344:626–634

Wang L, Zhang Q, Liao X, Li X, Zheng S, Zhao F (2021) Phytoexclusion of heavy metals using low heavy metal accumulating cultivars: a green technology. J Hazard Mater 413:125427

Wang X, Ma LQ (2015) Recent advances in phytoremediation of arsenic-contaminated soils. In: In-situ remediation of arsenic-contaminated sites. Taylor & Francis Group, pp. 69–86

Yan G, Chen X, Du S, Deng Z, Wang L, Chen S (2019) Genetic mechanisms of arsenic detoxification and metabolism in bacteria. Curr Genet 65(2):329–338

Ye WL, Khan MA, McGrath SP, Zhao FJ (2011) Phytoremediation of arsenic contaminated paddy soils with Pteris vittata markedly reduces arsenic uptake by rice. Environ Pollut 159(12):3739–3743

Zargar K, Hoeft S, Oremland R, Saltikov CW (2010) Identification of a novel arsenite oxidase gene, arxA, in the haloalkaliphilic, arsenite-oxidizing bacterium *Alkalilimnicola ehrlichii* strain MLHE-1. J Bacteriol 192(14):3755–3762

Zhang W, Zhang G, Liu C, Li J, Zheng T, Ma J et al (2018) Enhanced removal of arsenite and arsenate by a multifunctional Fe–Ti–Mn composite oxide: photooxidation, oxidation and adsorption. Water Res 147:264–275

# Chapter 13
# Arsenic Removal from Ground Water by Neem Bio-adsorbents


**Robeena Sarah, Nida Idrees, and Baby Tabassum**

**Abstract** In recent decades, it has been discovered that the presence of Arsenic in water bodies, particularly groundwater, has become a major problem. Arsenic has severe effects on health even at low concentrations in drinking water, thus advances for removing it from polluted water are crucial. For the treatment of As-polluted water, conventional methods like reverse osmosis, ion exchange, and electro-dialysis are often used; however, their use in less developed regions is constrained by their high cost. The use of adsorbents derived from natural resources has been reviewed as an alternative to the expensive procedures for the removal of Arsenic. When it comes to eliminating arsenic from groundwater, Neem bio-adsorbents have shown to be extremely effective and affordable. These adsorbents have a very high arsenic removal capability. Thus, current study concentrates on using bio-adsorbents to adsorb arsenic, which may be a useful approach for arsenic removal from groundwater and mitigation.

**Keywords** Arsenic · Bioadsorbents · Neem · Remediation

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## 13.1 Introduction

**Arsenic (As)** is one of the most hazardous heavy metal found in nature. It has the symbol As, the atomic number 33, and a relative atomic mass of 74.92. Arsenic, which comes from the Greek word arsenikon, which means "potent," has been employed as a tonic and a poison since ancient times. Albertus Magnus, a German alchemist, was the first to record it in 1250. It exists in two common allotropes i.e. yellow and metallic grey. Yellow arsenic is soft and waxy, although the grey form has a metallic look, is important to industry. Arsenic occurs in many mineral forms such as Arsenopyrite, Orpiment, Realgar etc. mainly associated with sulfides and other metals. It is found in organic forms like Methylarsonic acid and Dimethylarsinic acid etc. mainly in fish and shellfish, but the inorganic forms occuring predominately are trivalent arsenite and pentavalent arsenates and they are highly toxic. The trivalent arsenic form, on the other hand, is shown to be more hazardous than the pentavalent arsenic form (Liao et al. 2004). Arsenic can be released into the environment through natural processes such as volcanic activity, weathering of rocks, and erosion. It can also be released by human activities such as mining, agriculture, and industrial processes (Rabbani and Fatmi 2019). One of the most common natural sources of arsenic is volcanic activity. Arsenic is released into the atmosphere through volcanic eruptions and can then be deposited on the Earth's surface through ash fall. This ash can contain high levels of arsenic, which can contaminate nearby water sources and soil. Another natural source of arsenic is the weathering of rocks. As rocks weather, they release minerals and elements into the surrounding environment. Arsenic can be one of these elements found in soil, water, and air (Shukla et al. 2019). Erosion is also a natural process that can release arsenic into the environment. As soil erodes, it carries high levels of arsenic, which can then be deposited into rivers, lakes, and oceans. This can lead to the contamination of water sources and can also contribute to the buildup of arsenic in the soil. Arsenic can also be released into the environment through human activities. Mining is one of the most significant sources of anthropogenic arsenic. When mining for metals such as gold, copper, and lead, large amounts of arsenic can be released into the environment, this can lead to the contamination of water sources and soil and can also contribute to air pollution. Agriculture can also be a source of arsenic. Arsenic is commonly used as a pesticide, and can also be found in some fertilizers. When these products are used, they can release arsenic into the soil, water, and air. This can lead to the contamination of water sources and soil and can also contribute to air pollution (Sahu and Saha 2019). Industrial processes can also release large amounts of arsenic into the environment. For example, burning fossil fuels can release arsenic into the air. This can lead to air pollution and contribute to the buildup of arsenic in soil and water. Arsenic and its derivatives are mostly employed as an alloying agent for lead batteries, but it was also widely utilized as pesticides, herbicides, and insecticides; however, these uses are decreasing (Sabina et al. 2005). In some places of India, arsenic in drinking water is a major problem, and it is emitted by both anthropogenic and natural mechanisms. Arsenic exposure at high levels raises the likelihood of carcinogenic effects and is fatal. Arsenic's toxicological

effects are felt not only by humans, but also by aquatic life forms. The majority of arsenic toxicity research is done in mammalian cells (Li et al. 2017). Arsenic contamination in groundwater has become a major issue of concern worldwide since a large population has been affected over the last two decades. The World Health Organization (WHO) and the European Commission (EC) researched the deadly effects of arsenic on the human body in 1993 and 2003, respectively, and changed the maximum contamination limit (MCL) of arsenic in drinking water from 50 to 10 μg/L (WHO 1993). In recent days the levels of Arsenic has increased several folds in the environment since it is used as a wood preservative, metal industry, thermal power plant, defoliant as well as a pesticide. Arsenic was used as an insecticide, but it was highly toxic since it leads to brain damage among the spray workers who came into contact with the compound. Arsenic toxicity is affected by pH, which is connected to its solubility. Regardless, arsenic is used as a feed additive since it prevents diseases, improves feed efficiency and it increases weight gain in swine and poultry production, thus promoting the growth of chicken. It is, however, essential to note that inorganic arsenic is more harmful and toxic as compared to organic arsenic compounds. The toxicity of Arsenic depends on several factors such as the valence state, inorganic or organic form, and duration of exposure, exposure dose, age, sex and species of the animal (Khan et al. 2016). There are quite several chemicals that can be used for removing Arsenic in water, but so far, these chemicals are not effective. Concerns are being raised about the risks and health hazards due to arsenic contamination of water bodies. In the last two decades, the development of effective technologies that can be used to eradicate arsenic from water has drawn a lot of attention due to the deleterious and high toxic effects of arsenic. Precipitation, coagulation, reverse osmosis, lime softening, ion exchange and adsorption are the various physiochemical techniques that have been applied in an effort to remove arsenic from the aqueous system. The most used technique among these techniques is the adsorption because it is cost effective and effortless. Adsorption is a method for removing chemicals from liquid or gaseous solutions by attracting the substances to the surface of the solid. Solids are often used in commercial applications for wastewater treatment and purification. Examples include synthetic materials (fibres, resins, activated carbon, metal hydrides, membranes) (Seifert et al. 1993; Hering et al. 1996) or natural materials (Lorenzen et al. 1995). However, compared to natural materials, the creation of synthetic materials is more energy- and environmentally-intensive, making them more expensive. There has been an increased tendency to use bio-adsorbents or inactive biological materials among all types of adsorbents (Yeo et al. 2021).

## 13.2 Arsenic Poisoning

### *13.2.1 Causes, Ill-Effects and Treatment Methods*

Arsenic is mostly found in groundwater and arsenic poisoning happens when someone consumes dangerous levels of Arsenic. There are different sources of arsenic exposure since it is found in land, water and air and it is widely distributed in these environments (Fig. 13.1). The inorganic form of Arsenic can cause chronic arsenic poisoning as a result of being exposed to it for a long duration since it is highly toxic. Smoking tobacco, eating contaminated food, industrial processes, irrigation and preserving food using water that is contaminated as well as drinking contaminated water expose people to inorganic arsenic in high levels that are highly toxic. Chronic arsenic poisoning is known as Arsenicosis. Tobacco plant takes Arsenic that is naturally present in the soil; thus, the natural mineral arsenic content of tobacco is exposed to people who smoke tobacco. Also, if lead arsenate insecticide was used to treat the tobacco then there is potential for elevated arsenic exposure. Besides, Arsenic is used as ammunition, wood preservatives, metal adhesives, paper, textiles, processing glass pigments, as well as an alloying agent in industries exposing humans to arsenic poisoning (Li et al. 2017).

Additionally, Arsenic is used in pharmaceuticals in small quantities and pesticides and as well as in the process of tanning hides. Cereals, dairy products, poultry, meat, and fish are ingested by people, they can be sources of arsenic. Although the amount of arsenic in this diet is significantly lower than that found in contaminated groundwater. Arsenic levels in groundwater are present in several nations, including India, China, Chile, Bangladesh, the United States of America, Mexico, and Argentina. India is the world's greatest consumer of groundwater. Arsenic contamination in groundwater has been found in seven Indian states: West Bengal, Jharkhand, Bihar, Uttar Pradesh

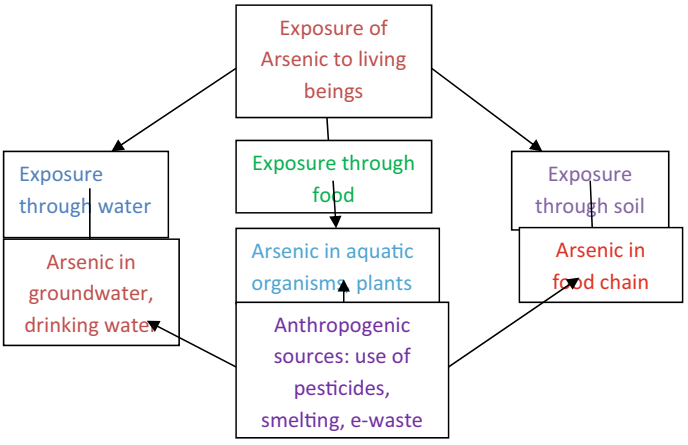


**Fig. 13.1** Various routes of Arsenic contamination

in the Ganga flood plain, Assam, Manipur, and Chhattisgarh. Arsenic pollution levels in 20 districts of Uttar Pradesh are as high as 0.150 mg/l.

Various symptoms experienced due to arsenic poisoning can be chronic, immediate, severe, or acute. Severe diarrhoea, confusion, headaches, drowsiness are some of the signs that may be appeared within thirty minutes after a person swallows arsenic. In case that a person has been exposed to Arsenic for an extended period, fingernail pigmentation might change and the patient may experience convulsions. There are various symptoms that are associated with severe arsenic poisoning (Rasheed et al. 2017). These symptoms include; diarrhea, vomiting, excessive sweating, seizures, stomach cramps, hair loss, cramping muscles, blood in urine, problem in swallowing, excessive salivation, garlicky breath and a metallic taste in the mouth. Long-term arsenic consumption also leads to some complications such as digestive difficulties, diabetes, liver disease and cancer. Also, it can lead to some complications in the nervous system, such as hearing problems and reduced sensation in the limbs.

Arsenic poisoning can also happen in the workplace and workers in industries that face a higher risk of the toxicity, should ensure they take proper safety measures. Some of the industries where arsenic poisoning can happen include; industries that use and produce some pesticides, wood treatment, smelting and glass production. Arsenic may be absorbed into the skin during wood treatment industries and workers may inhale coke emissions in the smelting industries. Besides, Arsenic is found in rice, fish and poultry since Arsenic is in the antibiotics that are used in chicken feed. The poisoning brings many adverse effects on our bodies, with women being the most affected people. First of all, arsenic poisoning has been linked to an increased risk of death, particularly when hazardous levels are exceeded. Toxic chemicals are also thought to impair fertility in both men and women, according to Mukherjee and Dasgupta (2018), who report spontaneously increased abortion rates, low birth rates, and low weight of newly born kids.

Arsenic interferes with ATP synthesis in a number of ways. Lipoic acid, a cofactor for pyruvate dehydrogenase, is inhibited by arsenic at the citric acid cycle level. Arsenate also uncouples oxidative phosphorylation by competing with phosphate, limiting energy-linked NAD+ reduction, mitochondrial respiration, and ATP generation. As a result, the production of hydrogen peroxide rises, potentially leading to the development of reactive oxygen species and oxidative stress. Death occurs as a result of multi-system organ failure caused by metabolic abnormalities (Hughes and Michael 2002).

There are various treatment options, but the treatment to be used depends on the stage and type of arsenic poisoning. Arsenic poisoning can be prevented in a number of ways, which include; considering the depth of wells since the water is likely to have less Arsenic if the well is deeper. Also, it is advisable for people to be careful when harvesting rain water so that the water does not becomes contaminated. It is also essential to chemically examine nearby water sources so that poisonous sources of Arsenic can be identified. Treating drinking water can also be useful in preventing arsenic poisoning. Installing arsenic removal systems and technologies

that can help in reducing arsenic poisoning such as membrane techniques, adsorption, coagulation-precipitation, ion exchange and oxidation (Brahman et al. 2016). Chelation therapy may be used whereby some chemicals such as dimercaprol and dimercaptosuccinic acid are used to isolate arsenic from blood proteins. These techniques can be quite useful in not only removing the arsenic but also in disposing off the removed arsenic appropriately. Also, trying to achieve an optimum arsenic concentration by blending high-arsenic water with low-arsenic water that is acceptable is a technique that can be used to prevent arsenic poisoning. Rainwater can be used as alternatives to groundwater. Additionally, measures should be taken to reduce workplace exposure to arsenic industrial processes. Some of the measures that can be taken include; monitoring early signs for arsenic poisoning in high-risk populations as well as engaging and educating the community on the risks of high arsenic exposure in order to ensure successful interventions (Matta and Gjyli 2016).

Adsorption and ion exchange fixed bed treatment systems are becoming more and more common for the removal of arsenic in small scale treatment systems due to their simplicity, ease of handling, regeneration capacity, and sludge-free operation (Thirunavukkarasu et al. 2003). The creation of a more affordable cleanup technique is required, nonetheless, due to the high expense of existing procedures. The biosorption approach has recently emerged as a new scientific field that may aid in the recovery of heavy metals. The process of biosorption, which is particularly helpful for removing pollutants from industrial effluents, uses cheap dead biomass to sequester hazardous heavy metals (Kratchovil and Volesky 1998). According to one of the early findings on biosorption, it is possible to remove even trace levels of harmful heavy metals from industrial effluents at a very low cost by using accessible biological materials. The ability of these materials to physically retain arsenic ions or molecules is one of their common characteristics. In contrast to alternative approaches employing synthetic membranes and materials requiring large chemical dose, natural adsorbents have higher arsenic removal capacities, are reusable, and have lower costs and environmental impacts (Maiti et al. 2008; Yazdani et al. 2016).

A novel method to get rid of heavy metals when they are present in small amounts is based on the metal-sequestering capabilities of non-viable biomass (Volesky 1990). A more contemporary alternative technology for eliminating contaminants from the environment is Phytoremediation. Due to their natural ability to accumulate heavy metals and breakdown organic molecules, plants are increasingly being used for environmental remediation (Scott 1992; Kumar et al. 1995; Sandhu and Nelson 1980).

## 13.3 Examples of Arsenic Contamination

One of the most well-known examples of naturally occurring arsenic poisoning is the case of Bangladesh. Millions of people are exposed to high levels of arsenic in their drinking water due to the presence of the element in the groundwater. A study by the World Health Organization (WHO) in 2000 estimated that up to 77 million

people in Bangladesh were at risk of arsenic poisoning due to contaminated drinking water. The study found that most of the wells in the country had arsenic levels above the WHO guideline value of 10 μg/l.

The health effects of long-term exposure to arsenic in drinking water in Bangladesh have been well documented. Studies have shown that people living in areas with high levels of arsenic in their drinking water are at an increased risk of developing skin lesions, cancer, and other health problems. A study published in the British Medical Journal in 2002 found that people living in areas with high levels of arsenic in their drinking water had an increased risk of developing skin lesions, lung cancer, and bladder cancer (Smith 2020).

Another example of naturally occurring arsenic poisoning is the case of Chile. Many people living in the Atacama Desert region are exposed to high levels of arsenic in their drinking water due to the element in the soil and rocks. A study conducted by the WHO in 2000 estimated that up to 2 million people in Chile were at risk of arsenic poisoning due to contaminated drinking water (World Health Organization 2019).

The health effects of long-term exposure to arsenic in drinking water in Chile have also been well documented. Studies have shown that people living in the Atacama Desert region with high levels of arsenic in their drinking water are at an increased risk of developing skin lesions, cancer, and other health problems. According to IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2020), people living in the region also had an increased risk of developing skin cancer.

Another example is the case of West Bengal and the neighbouring state of Bihar in India. Like Bangladesh, arsenic in groundwater is a major concern here, where exposure to high levels of arsenic in drinking water leads to skin lesions, cancer and other health problems. According to Smith (2020) in West Bengal and Bihar, people living in areas with high levels of arsenic in their drinking water had an increased risk of developing skin cancer.

In Taiwan, a study published in the journal in 2000 found that people living in areas with high levels of arsenic in the drinking water had an increased risk of skin cancer (Shukla et al. 2019). In addition to these examples, several other cases of naturally occurring arsenic poisoning in humans have been reported around the world, including in Argentina, Mexico, and the United States.

## 13.4 *Azadirachta Indica*(Neem) as Bio-adsorbent of Arsenic

Neem Tree is one of the widely used trees, both medicinal and cosmetic purposes. Neem, also known as *Azadirachta indica* A. Juss, has been used for over 2000 years on the Indian subcontinent as one of the vital multipurpose medicinal plant with a broad range of pharmacological activity. It is also well-known as Indian neem (margosa tree) or Indian lilac and belongs to the Meliaceae family (Girish and Shankara 2008).Compounds present in the neem tree have been known to have

antioxidant, hypoglycemic, anticarcinogenic, antimicrobial, antimalarial, hepatoprotective, nephroprotective etc. properties (Chattopadhyay et al. 1993). It offers a lot of potential in terms of pest control, medicine, and environmental preservation. Insecticides, pesticides, and agrochemicals are all naturally found in neem, are safe for the environment (Brahmachari 2004).

The discovery of the Neem tree as a bio-adsorbent began with a chance observation. In the early 2000s, a group of researchers were studying the medicinal properties of the Neem tree when they noticed that it seemed to have a purifying effect on water. They decided to investigate this further and conducted a series of experiments to test the ability of the Neem tree to remove pollutants and contaminants from water (Sahu and Saha 2019).

The first step in these experiments was to gather samples of Neem leaves, bark, and seeds. These samples were then ground into a powder and added to water contaminated with various pollutants. The researchers then tested the water for the presence of pollutants and contaminants. They found that the Neem powder effectively removed pollutants and contaminants from the water, including heavy metals, pesticides, and other toxic compounds.

This initial discovery was exciting, but the researchers wanted to understand how the Neem tree could remove pollutants and contaminants from water. They began to study the chemical composition of the Neem tree and found that it contains several compounds that can adsorb pollutants and contaminants. These compounds include tannins, flavonoids, and limonoids. Tannins are known for their ability to bind with heavy metals, while flavonoids and limonoids have been shown to have strong antioxidant properties (Shukla et al. 2019).

The researchers also found that the Neem tree has a high surface area-to-volume ratio, which makes it an ideal bio-adsorbent. The high surface area-to-volume ratio means a large amount of surface area is available for the pollutants and contaminants to adhere to. This allows for a high adsorption capacity and makes the Neem tree an efficient bio-adsorbent.

The researchers continued to study the Neem tree as a bio-adsorbent and conducted several other experiments to test its effectiveness. They found that the Neem tree could remove a wide range of pollutants and contaminants from water, including heavy metals such as lead, cadmium, and zinc, as well as pesticides, herbicides, and other toxic compounds (Srivastava 2019). They also found that the Neem tree could remove pollutants and contaminants from water even at low concentrations, making it an effective bio-adsorbent for water purification.

The discovery of the Neem tree as a bio-adsorbent has led to a new field of research. It has the potential to have a significant impact on environmental protection and water purification. The Neem tree is abundant, easy to grow, and can be found in many parts of the world. This makes it a cost-effective and sustainable solution for water purification. Additionally, the Neem tree is a renewable resource that can be grown and harvested repeatedly, making it a more environmentally friendly option than other bio-adsorbents.

The use of the Neem tree as a bio-adsorbent has also been studied for other applications. For instance, it has been found that the Neem tree can also remove

pollutants and contaminants from the air. This is due to the presence of volatile compounds in the Neem tree that can adsorb pollutants and contaminants from the air. This means that the Neem tree has the potential to be used in air purification systems, which can help to improve air quality in urban areas and reduce the impact of air pollution on human health.

The bark of the Neem tree contains compounds such as limonoids and nimbinoids, which have been found to have antimicrobial and anti-inflammatory properties. In addition, the bark is rich in tannins, which are known for their ability to remove heavy metals from water. Studies have shown that the bark of the Neem tree can effectively remove high levels of arsenic from contaminated water, making it a promising bio-adsorbent for treating arsenic-contaminated groundwater.

The Neem tree leaves are also rich in compounds that can be used as bio-adsorbents for cleaning arsenic from groundwater. The leaves contain high flavonoids and tannins, effectively removing heavy metals from water. Studies have shown that Neem leaves can remove up to 80% of arsenic from contaminated water, making them a valuable tool for cleaning contaminated groundwater (Bhakta and Ali 2019).

The roots of the Neem tree are also rich in compounds that can be used as bio-adsorbents for cleaning arsenic from groundwater. The roots contain high levels of flavonoids and tannins, which have been found to be effective at removing heavy metals from water. Studies have shown that Neem roots can remove up to 90% of arsenic from contaminated water, making them a valuable tool for cleaning contaminated groundwater (Srivastava 2019).

The Neem tree flowers also contain compounds that can be used as bio-adsorbents for cleaning arsenic from groundwater. The flowers contain high levels of flavonoids and tannins, which have been found to be effective at removing heavy metals from water. Studies have shown that Neem flowers can remove up to 70% of arsenic from contaminated water, making them a valuable tool for cleaning contaminated groundwater (Rabbani and Fatmi 2019).

Overall, the various parts of the Neem tree are effective bio-adsorbents for cleaning arsenic from groundwater. The bark, leaves, roots, and flowers of the Neem tree all contain compounds that can effectively remove high levels of arsenic from contaminated water. These compounds, such as flavonoids and tannins, work by binding to the arsenic ions and removing them from the water.

Another important aspect of using Neem as a bio-adsorbent is that it is a cost-effective and sustainable solution. Unlike traditional methods of cleaning contaminated water, such as chemical treatment or reverse osmosis, bio-adsorbents like Neem do not require expensive chemicals or energy-intensive processes (Ahuja 2018). Instead, Neem can be grown and harvested locally, reducing the treatment's overall cost and environmental impact.

In addition to cleaning arsenic from groundwater, Neem has also been effectively removing other heavy metals from water, such as lead, cadmium, and mercury. This makes it a versatile bio-adsorbent that can be used for a wide range of water treatment applications.

Another advantage of using Neem as a bio-adsorbent is that it is non-toxic and safe for human consumption. Unlike chemical treatment methods, Neem does not

introduce harmful chemicals into the water, making it safe for drinking and irrigation (Haque 2019).

Sultana (2018) observed the role of *Azadirachta indica* (Neem) dried bark powder for elimination of heavy metal ions from synthetic wastewater. This biosorbent have drawn much attention due to its low cost and also due to its availability all over the world. According to Adeyinka et al. (2007) neem leaves were dried 3 days, cleansed with distilled water, then neem leaves were allowed to air dry. The grinding mill was used to grind the leaves. The sieved powdered neem leaves included particles that ranged in size from 0.25 to 0.5 mm. The purpose of doing this was to enable a shorter diffusion path, allowing the adsorbate (Neem leaves) to enter the effluent deeper and more quickly, increasing the rate of adsorption. $Ni^{2+}$ ions were effectively removed from the synthetic waste water by the grounded neem leaves. The biomaterial neem leaves is effective at removing some heavy metals from industrial wastewater. An effective dose of 1.0 g of bio-adsorbent (Neem leaves) resulted in a removal of $Ni^{2+}$ ions of 68.75%. This method can be used successfully to remove heavy metals from industrial wastewater. Carbonyl, hydroxyl, and amino groups in neem leaveswhich contain lone pairs of electrons may be useful for binding heavy metal ions and therefore, are necessary for the biosorption of cationic contaminants in solution. On the basis of this, the potential of this widely accessible agricultural leaf to treat industrial effluents containing these metal ions was examined (Babarinde 2011).

Furthermore, Neem biomass, a blend of neem leaves and bark, was chosen as a bio-adsorbent to remove the lead metal ion ($Pb^{2+}$) from aqueous solutions because it is inexpensive and environmentally acceptable. A relatively simple method was used to create a neem biomass-based bio-adsorbent with a carboxylic group through activation employing chemical modification with citric acid and NaOH. At 0.9 g/L bio-adsorbent dosage, 50 min of contact duration, pH 6, and initial metal ion concentration of 100 mg/L, the maximum removal of $Pb^{2+}$ ion (97.29%) was observed. The conclusion is that the neem bio-adsorbent can be used as a reliable and affordable substitute for treating wastewater that contains lead(II) ions in water (Hatiya et al. 2022). Moreover, Neem is useful in water purification since it kills harmful germs and makes water safe to drink for aquatic animals and humans.

## 13.5 Advantages of Using the Neem Tree as a Bio-adsorbent of Arsenic

Arsenic is a highly toxic element that can cause serious health problems if ingested or inhaled. One way to reduce people's exposure to arsenic is to use the Neem tree as a bio-adsorbent to remove it from contaminated soil or water. Here are the main advantages of using a bio-adsorbent like the Neem tree for removing arsenic from contaminated water and soil:

- Neem is effective against a wide range of heavy metals, including arsenic.

- Removing arsenic from the environment using Neem will not produce any harmful waste in the process.
- Neem has a long shelf life and does not easily degrade when exposed to light and heat. This greatly increases the lifespan of the product and reduces production costs.
- Neem can absorb heavy metals from water or soil without breaking down. This makes it a highly sustainable product that can remove heavy metals from many different sources. A study found that Neem could remove more than 90% of the arsenic from a water sample contaminated with the metal. This means it is very efficient at absorbing and removing metal from water and soil.
- Neem is a cost-effective solution for removing arsenic from contaminated soil or water. It is a readily available plant that can be easily grown and harvested, making it a cost-effective solution compared to other methods of removing arsenic.
- Neem can also be used in phytoremediation projects to remove environmental pollutants. This means that people can use it to remove arsenic from contaminated areas, making it a sustainable and natural method of removing environmental pollutants.
- Neem also has medicinal properties, making it a valuable plant for multiple uses. Medical practitioners can use it for medicinal purposes and for removing pollutants from the environment at the same time.
- Using Neem as a bio-adsorbent can significantly impact human health by reducing the presence of this toxic element in soil and water. This can help to prevent exposure to arsenic, which can cause serious health problems such as cancer, skin lesions, and neurological damage.

## 13.6 Limitations of the Neem Tree as a Bio-adsorbent

Despite the promising results of using Neem as a bio-adsorbent for cleaning arsenic from groundwater, there are still some limitations to the technology. The efficiency of the Neem tree as a bio-adsorbent for arsenic can vary depending on the specific conditions of the water source. For example, the presence of other contaminants in the water can negatively impact the effectiveness of the Neem tree in removing arsenic. Additionally, the pH level and temperature of the water can also affect the bio-adsorption process.

Another limitation of using the Neem tree as a bio-adsorbent is the cost of obtaining and preparing the Neem tree biomass. Harvesting, drying and grinding the Neem leaves can be time-consuming, making it less practical as a widespread solution for arsenic contamination.

Another limitation of the Neem tree is the availability of the tree in the area where it is needed. The Neem tree is native to the Indian subcontinent and is not found in other areas of the world, so it is not always an option for cleaning arsenic from groundwater in other regions.

Furthermore, the efficiency of the Neem tree as a bio-adsorbent for arsenic also depends on the tree's specific strain. Different strains of the Neem tree can have varying levels of effectiveness in removing arsenic from water, making it difficult to predict the outcome of using the tree as a bio-adsorbent.

In addition, there is a limit to the amount of arsenic the Neem tree can remove. After a certain point, the tree becomes saturated with the contaminant and can no longer effectively remove it from the water. This means the tree needs to be replaced or regenerated before it can be used again, adding to the cost and effort required.

Finally, it is important to note that while the Neem tree can effectively remove arsenic from water, there are more solutions for addressing arsenic contamination in groundwater. The tree can only remove a certain amount of the contaminant, and additional methods, such as filtration and reverse osmosis, may be necessary to clean the water fully.

## 13.7 Technological Replication of the Chemical Components of the Neem Tree

There are several ways in which scientists can replicate the properties of the Neem tree to remove arsenic from groundwater. One of the most promising methods is to use biochar, which is a type of charcoal that is produced from biomass. Biochar is known to have chelating properties similar to those of the Neem tree, and people can use it to remove heavy metals and other toxins from water. Scientists can make biochar from various types of biomass, including wood, straw, and other plant materials. Once the biochar is made, people can add it to groundwater to remove the arsenic.

Another method that scientists can use to replicate the Neem tree's properties is nanotechnology. Nanotechnology is the study of materials at the nanoscale, and it can be used to create materials that have properties similar to those of the Neem tree. For example, researchers have been working on developing nanoparticles that can be used to remove heavy metals and other toxins from water. These nanoparticles can be made from various materials, including metal oxides and other compounds. Once added to the water, they can bind to the arsenic and remove it from the water (Sahu and Saha 2019).

In addition to biochar and nanotechnology, other methods that can be used to replicate the properties of the Neem tree include using absorbents and ion exchange resins. Absorbents are materials that can be used to remove pollutants from water by binding to them. They can be made from various materials, including clay, zeolites, and activated carbon. Ion exchange resins are also used to remove pollutants from water by binding them. They can be made from various materials, including polystyrene and polystyrene crosslinked with divinylbenzene.

## 13.8 Conclusion

Natural adsorbents are effective because they are inexpensive and have good adsorption and desorption properties. Due to their natural ability to accumulate heavy metals and breakdown organic molecules, plants are increasingly being used for environmental remediation. As an adsorbent, they assist in developing technology that is efficient for all types of water polluted from arsenic. Additionally, more studies should be carried out utilizing actual polluted natural water to assess the effectiveness of natural adsorbent in actual circumstances. In the conclusion, neem adsorbents appear to offer a highly affordable and practical solution for the efficient removal of arsenic from groundwater.

## References

Adeyinka A, Liang H, Tina G (2007) Removal of metal ion form waste water with natural waste. School Eng Technol 1–8:33

Ahuja S (2018) Arsenic contamination of groundwater: mechanism, analysis, and remediation, 10th edn. John Wiley & Sons, Hoboken

Babarinde NAA (2011) Kinetic, equilibrium and thermodynamic studies of the biosorption of Pb(II), Cd(II) and Cr(III) by neem leaf. IJIRSE 2:291–306

Bhakta JN, Ali MM (2019) Biosorption of arsenic: an emerging eco-technology of arsenic detoxification in drinking water. Adv Water Sec 30:207–230. https://doi.org/10.1007/978-3-030-21258-2_9

Brahmachari G (2004) Neem-an omnipotent plant: a retrospection. Chem Biochem 5:408–421

Brahman KD, Kazi TG, AfridiHI BJA, Arain SS, Talpur FN, Arain MB (2016) Exposure of children to Arsenic in drinking water in the Tharparkar region of Sindh, Pakistan. Sci Total Environ 544:653–660

Chattopadhyay RR, Chattopadhyay RN, Maitra SN (1993) Possible mechanism of anti-inflammatory activity of *Azadirachta indicaleaf* extract. Indian J Pharmacol 25:99–100

Girish K, Shankara BS (2008) Neem: a green treasure. Electron J Biol 4:102–111

Haque R (2019) Health effects of arsenic contaminated drinking water in West Bengal, India, 5th edn

Hatiya NA, Reshad AS, Negie ZW (2022) Chemical modification of neem (*Azadirachta indica*) biomass as bio-adsorbent for removal of $Pb^{2+}$ ion from aqueous waste water. Adsorp Sci Technol 2022:18. https://doi.org/10.1155/2022/7813513

Hering JG, Chen P-Y, Wilkie JA, Elimelech M, Liang S (1996) Arsenic removal by ferric chloride. J Am Water Work Assoc 88:155–167

Hughes S, Michael F (2002) Arsenic toxicity and potential mechanisms of action. Toxicol Lett 133(1):1–16

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization, and International Agency for Research on Cancer (2020) Some drinking-water disinfectants and contaminants, including arsenic, 9th edn. World Health Organization, New York

Khan S, Rauf R, Muhammad S, Qasim M, Din I (2016) Arsenic and heavy metals health risk assessment through drinking water consumption in the Peshawar District, Pakistan. Hum Ecol Risk Assess 22(3):581–659

Kratchovil D, Volesky B (1998) Advances in the biosorption of heavy metals. TIBTECH 16:291–300

Kumar PBAN, Motto H, Raskin I (1995) The use of plants to remove heavy metals from aqueous streams. Environ Sci Technol 29:1239–1245

Li S, Wang W, Liang F, Zhang WX (2017) Heavy metal removal using nanoscale zero-valent iron (nZVI): theory and application. J Hazard Mater 322:163–171
Liao CM, Tsai JW, Ling MP, Lain HM, Ghou YH, Yang PT (2004) Organ: specific toxicokinetics and dose-reponse of arsenic in tilapia Oreochromis mossambicus. Arch Environ Contam Toxicol 47:502–510
Lorenzen L, van Deventer J, Landi W (1995) Factors affecting the mechanism of the adsorption of arsenic species on activated carbon. Miner Eng 8:557–569
Maiti A, DasGupta S, Basu JK, De S (2008) Batch and column study: adsorption of arsenate using untreated laterite as adsorbent. Ind Eng Chem Res 47:1620–1629
Matta G, Gjyli L (2016) Mercury, lead and arsenic: impact on environment and human health. J Chem Pharm Sci 9(2):718–725
Mukherjee S, Dasgupta R (2018) Surveillance of protozoan infestation in gill and skin of *Channa punctatus* collected from local market of Kolkata. Asian J Biol 14:1–8
Rabbani U, Fatmi Z (2019) Arsenic contamination of drinking water and mitigation in Pakistan: a case of Indus River Basin. Adv Water Sec 58:273–296. https://doi.org/10.1007/978-3-030-21258-2_12
Rasheed H, Kay P, Slack R, Gong YY, Carter A (2017) Human exposure assessment of different arsenic species in household water sources in a high risk arsenic area. Sci Total Environ 584:631–641
Sabina C, Grund S, Hanusch K, Wolf HU (2005) Arsenic and arsenic compounds, ullmann's encyclopedia of industrial chemistry. Wiley-VCH, Weinheim. https://doi.org/10.1002/14356007.a03_113.pub2
Sahu S, Saha D (2019) Groundwater arsenic contamination and availability of safe water for drinking in middle Ganga plain in India. Adv Water Sec 21:1–41. https://doi.org/10.1007/978-3-030-21258-2_1
Sandhu SS, Nelson P (1980) Ionic interferences in the determination of arsenic in water by silver diethyldithiocarbamate method. Anal Chem 50:322–325
Scott CD (1992) Removal of dissolved metal by plant tissues. Biotechnol Bioeng 39:1064–1068
Seifert W, Liu X, Samuelson L (1993) Influence of arsenic adsorption layers on heterointerfaces in GaInAs/InP quantum wellstructures. Appl Phys Lett 62:949–951
Shukla A, Awasthi S, Chauhan R, Srivastava S (2019) The status of arsenic contamination in India. Arsenic Drink Water Food 157:1–12. https://doi.org/10.1007/978-981-13-8587-2_1
Smith BE (2020) Addressing the public health crisis caused by arsenic contamination of drinking water in Bangladesh
Srivastava S (2019) Arsenic in drinking water and food. Springer, New York
Sultana SG (2018) Adsorption of heavy metals from waste water using neem palm and Indian beech trees. Int J ChemTech Res 11(08):238–246
Thirunavukkarasu OS, Viraraghavan T, Subramanian KS (2003) Arsenic removal from drinking water using iron oxide-coated sand. Water Air Soil Pollut 142:95–111
Volesky B (1990) Biosorption of heavy metals. CRC Press, Boca Raton, FL
WHO (1993) Guidelines for drinking water quality. World Health Organization, Geneva, p 41
World Health Organization (2019) Health effects of arsenic in drinking water and food. Arsenic Pollut 44:157–212. https://doi.org/10.1002/9781444308785.ch5
Yazdani MR, Tuutijärvi T, Bhatnagar A, Vahala R (2016) Adsorptive removal of arsenic(V) from aqueous phase by feldspars: kinetics, mechanism, and thermodynamic aspects of adsorption. J Mol Liq 214:149–156
Yeo KFH, Li C, Zhang H, Chen J, Wang W, Dong Y (2021) Arsenic removal from contaminated water using natural adsorbents: a review. Coatings 11(11):1407. https://doi.org/10.3390/coatings11111407

# Chapter 14
# Utilizing Various Potentials for Phytoremediation of Arsenic Contamination—A Feasible Perspective

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**Abstract** Arsenic (As) is a heavy metal having atomic number 33 with both metallic and nonmetallic properties. Typically, the range of its concentrations in unpolluted soil is between 0.2 and 40 ppm, however they have been shown to go as high as 2500 ppm in contaminated soils. Being a poisonous heavy metal, arsenic has contaminated the groundwater in over 75 nations, exposing more than 160 million people, particularly those living in rural areas, to it. This element can be found in the ecosystem having a range of oxidation states, with Arsenic III being much more dangerous than Arsenic V. As a byproduct of agricultural and industrial activities, it is a contaminant found in drinking water, natural soil, and other environmental sources. The buildup of arsenic in the soil is a severe concern to human health since it does not degrade like organic compounds. Most traditional restorative procedures are costlier and damage soil's natural characteristics, making them unsuitable for plant growth. One of the most efficient and affordable cleanup methods ever devised is phytoremediation. In order to characterise phytoremediation systems and address performance issues, many mathematical techniques have been used. Arsenic contamination was much reduced because to the carefully considered and organised application of numerous naturally occurring microphytes, macrophytes, blooming plants, and other well-known plants The ability and methods of the arsenic uptake by duckweeds, hydrilla; water spinach, ferns, cabbage, hyacinth and watercress have been examined in order to assess their potential in phytoremediation technology. In total, 54 cultivable rhizobacteria and 41 root endophytes, mostly belonging to the phylum of Actinobacteria, Bacteroidetes, Proteobacteria and Firmicutes were identified and characterized in order to assess their potential for accumulating metals in

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plants. These traits included the ability to promote plant growth, metal chelation, and/or reduce heavy metal stress. The rate along with depth of contaminant uptake from the soil, concentration in the plant cell, and the extent of contaminant transformation to ordinary cell metabolites can all be used to estimate the plant's capacity for detoxification.

**Keywords** Arsenic · Bacteria · Contaminated · Heavy metal · Phytoremediation

## 14.1 Introduction

Large-scale land contamination has resulted from rising industrialization and rapid urbanization. In terms of pollutants, heavy metals are viewed as posing the greatest menace to the environment and human health (Rajoo et al. 2013). Due to human activities, heavy metals can contaminate the ecosystem. Heavy metal contamination is frequently caused by mining, the manufacturing of fuel, fertilizers used in agriculture, and vehicle emissions (Amin et al. 2013). Heavy metal emissions have peaked at 22,000 metric tonnes per year for Cd, 939,000 for Cu, 135,000 for Zn, and 738,000 for Pb over the past few decennium (Ahmadpour et al. 2012). Arsenic has an atomic weight of 74.9216, specific gravity of 5.73, melting point of 817 °C (28 atm), and sublimes at 613 °C, having a silver-grey colour, brittle and crystalline solid that is denoted by the symbol As. It is the 20th most common element in the crust of the earth and a notoriously hazardous metalloid that may be found in different allotropic colours like yellow, black, and grey. It is a pervasive metalloid with an acceptable standard content of 2 mg $kg^{-1}$ that can be found in all natural media in very low concentrations. It has been introduced to soils in a variety of manner, including about 41% from commercialized refuses, 23% from residues of coal combustion, 14% from atmospheric pollution, 10% from minings, 7% from refineries, 3% from agricultural activities, and 2% from constructions, urbanization and forestland wastes. These collectively discharge beyond a range of $82 \times 10^6$ kg of arsenic into soil each year (Matera and Le Hecho 2001).

Arsenic is the deadliest substance that has had a greater impact on human history than any other, earning it the label of "the king of poison". This metal exists in both organic and inorganic forms having four different oxidation states (− 3, 0, + 3, and + 5). In contrast to the inorganic form of arsenic, which often takes the form of unadulterated metallic forms that are typically linked with non-carbon elements, the organic form of arsenic relates to carbon bases and primarily contains covalently bound arsenic atoms. Arsenic's toxicity is greatly dependent on the chemical state to which the organism is subjected; therefore, its speciation is of great interest. When compared to organic arsenic (Arsenate + 5), inorganic arsenic (Arsenite + 3) is more toxic (Chatterjee et al. 2011). This is mostly because the latter is more soluble. Dimethylarsinic acid (DMAA) and monomethylarsonic acid (MMAA) derivative forms are toxic to a greater degree than their parent compounds (Petrick et al. 2000). Being a poisonous heavy metal, arsenic has contaminated the groundwater in over

75 nations, exposing more than 160 million people, particularly those living in rural areas, to it (Debnath et al. 2016; Seth et al. 2020). Metal-contaminated soil, especially arsenic, is a concern to global environmental ecosystems and human health (Debnath et al. 2017). The WHO's interim recommended limit of 10 g $L^{-1}$ for arsenic was reportedly exceeded by at least 140 million people in 50 different nations. (Ravenscroft et al. 2009). Up to 3 million contaminated sites, many of which contain As, may exist in the European Union, with 250,000 of those in need of immediate remediation (EEA 2007).There are several health risks associated with arsenic exposure for humans. Long-term exposure to skin lesions caused by low concentrations of chemicals, bladder, prostrate and lung cancer, as well as neurological and cardiovascular conditions. Arsenic affects negatively at large concentrations by inhibiting critical functional groups, detaching other metallic ions, or altering biological molecules (Mahimairaja et al. 2005). According to results from the motor-free visual perception test (MVPT) (Siripitayakunkit et al. 2001) and the visual-motor integration test (VMIT), children who drank water with high arsenic levels experienced changes in their visual perception but not in their ability to integrate their visual-motor skills. Melanoma, keratosis, basal cell cancer, and squamous cell carcinoma are all symptoms of long-term arsenic consumption. Melanosis and keratosis are both structural indicators of chronic arsenic exposure. Workers in industrial facilities and those connected to the industries associated with arsenic-containing insecticides, chemicals, and metal smelting, researchers have reported an association between lung cancer and arsenic. Carcinogenesis has been demonstrated in the trivalent (As lll) form of inorganic arsenic (Arsenic WHO 1981).

The term "phytoremediation" is a mixture of Greek words: "Phyto," that refers to a plant, and "remedium," means to remove or correct. Phytoremediation of heavy metals refers to the process of removing heavy metals using microorganisms or plants. It can also be used to remove organic contaminants. Chany first proposed the concept of phytoremediation in 1983, and study on the topic persisted beyond 1990. By adding necessary organic matter and absorbing metal contaminants from the soil, plants naturally improve the fertility of the soil. The planting also prevents erosion and metal leaching. There are several ways to remove metal, however phytoremediation is the most affordable method ever used. Large agricultural areas can be covered with little investment and operating expense. Phytoremediation is sometimes known as "green clean" among the public because it is less dangerous than using other chemicals (Badr et al. 2012). The usage of plants species for decontamination and resulting improvement in quality of soil is known as phytoremediation. It is currently a promising approach. Hyperaccumulator plants are those that take many harmful metals from the soil topography and conserve them in various tissues. As a non-toxic substitute for the currently used physical and chemical remediation techniques, this method continues to receive critical acclaims.

## 14.2 Phytoremediation of Arsenic in Contaminated Soil

Metal phytoremediation, commonly cited as "phytoextraction," includes a range of procedures by which plants can remove, retain, and transfer the contaminants from the soil and water. There are already more than 450 known metallophytes, and most of them exclusively acquire one particular metal (Shah and Nongkynrih 2007). These plants have created methods by which such metals are combined into complexes, then transported into and stored in the vacuole in order to ascertain the concentration of potentially hazardous metals (Shah and Nongkynrih 2007).

The following summarizes the main phytoremediation techniques:

### *14.2.1 Phyto-Desalination*

Halophytic plants are used in inland areas with high salt concentrations in this method of phyto-desalination. These plants are efficient in removing salts from soil. When used on 1 ha of saline soil *Suaeda maritima* and *Sesuvium portulacastrum* can extract 504 and 474 kg of sodium chloride (NaCl) respectively, in a span of four months (Kuang et al. 2004).

### *14.2.2 Rhizo-Degradation*

Rhizo-degradation is the term for the decomposition of organic additives by microbes in the root zone region. Rhizosphere region refers to the 1 mm region surrounding a plant's roots. Plants secrete substances including flavonoids, sugars, and amino acids that promotes micro-organisms activity for the breakdown of organic contaminants. Plants themselves also release enzymes that degrade organic contaminants found in the soil, which helps to increase microbial activity against them.

### *14.2.3 Phytodegradation*

The enzymes that plants produce to decompose the organic materials in the soil include oxygenase and dehalogenase. This process is known as phytodegradation. Plants are sometimes referred to as the "green liver" of the environment. Because heavy metals are not biodegradable, they are excluded in this section and contains the majority of insecticides.

### 14.2.4 Phytovolatilization

It is a process by which pollutants are lifted up by plants from the soil, converted into vapour, and then disseminated into the atmosphere. This approach primarily removes volatile organic pollutants and volatile heavy metal pollutants such as Mercury and Selenium. However, because pollutants are not totally eliminated (transform completely into benign compounds), they are redeposited from the atmosphere to the soil, making it the most contentious phytoremediation technology (Sakakibara et al. 2010). This process involves compounds of arsenic which are methylated and volatile (Frankenberger and Arshad 2002; US EPA 2002).

### 14.2.5 Phyto-Stabilization

Phytostabilization refers to the suppression of certain contaminants' bioavailability or mobility by plants. It is a very efficient technology because it prevents heavy metal ions or other organic contaminants from entering the food web or ground water. Through root absorption, accumulation, or precipitation inside the rhizosphere, plants are utilised to immobilise and physically stabilise pollutants inside the groundwater and soil during the phytostabilization process. Through this procedure, the contaminant's mobility is decreased and considerable erosion or movement of toxins in the water table and atmosphere is prevented. The main drawback of this method is that heavy metals cannot be stopped from moving from one level (biological to abiotic) to the other because they are still in the biota stage, even though it is preferable to prevent their migration (Sakakibara et al. 2010). Bottle sedge (*C. rostrata*), common reed *(P. australis*), Salix and Cottongrass (*Eriophorum*) were all cited by Stoltz and Greger (2006) as being ideal for stabilising and immobilising contaminants in mine tailings.

### 14.2.6 Phyto-Filtration

Phyto-filtration is the process of employing plants to filter harmful contaminants out of surface or groundwater. Caulo-filtration, blasto-filtration, or rhizo-filtration are three main techniques that use, respectively, plant shoots, seedlings, and roots. As pollutants are absorbed by the plants during phyto-filtration, the movement of the pollutants is limited (Sakakibara et al. 2010).

### *14.2.7 Phytoextraction*

The methods used by hyperaccumulators plants to transfer metal pollutants from soil to the plant biomass are also referred as phytoaccumulation or phytomining. The biomass lying aboveground is subsequently reaped to remove contaminants. Bioconcentration is the primary method employed in procedures of phytoextraction. Pollutants are transported from lower to higher biomass through a very efficient metabolic process (Ali et al. 2012) Plants called accumulators and hyperaccumulators are employed in this method. Plants known, as "shot accumulators" are those that have higher shoot arsenic concentrations than the removable portion of arsenic, which is water-solublized, in an arsenic-contaminated media (e.g., *Eriophorum angustifolium*). *C. rostrata*, *Salix phylicifolia*, *P. australis* and *Salix borealis* are instances of root-accumulator plants that have higher content in the root tissues. They also mentioned a plant species, which is a "low-accumulator" and has an intermediate concentration of contaminants in its tissues. *P. vittata* and *P. calomelanos* are two arsenic hyperaccumulators that may absorb in excess of 2000 mg $kg^{-1}$ DM (Gonzaga et al. 2006).

## 14.3 Mechanism of Phytoremediation

Organic carbon-based contaminants that are prevalent in the soil can be released through a variety of processes. It is necessary to degrade the chemical into a non-toxic component in order to remove such contaminants (Meagher 2000). Active transport, which involves particular transporters such carrier proteins, is how the plants absorb the chemicals into their roots (Mokgalaka-Matlala et al. 2008). The "xenobiotic" organic pollutants evolved are human-made with no transportation for their uptake in the biological system are absorbed via diffusion to the extent that their hydrophilic or hydrophobic nature permits (Tu and Ma 2002). There are considerable variances in the uptake by plant species in both shoots and roots according to the type of substances that organic pollutants take up in plant tissues. In contrast to organic pollutants, inorganic contaminants are mineral-based (Bolan et al. 2014). Inorganic pollutants can be totally separated from the ecosystem and transferred, changed into form that is less hazardous, or "stabilized" but are typically not broken down into basic forms. The capability of plants to withstand and accumulate large amount of these toxins is crucial in the phytoremediation process, where they can be used to acquire inorganic chemicals from the soil. Arsenic and other heavy metals can only be converted from one oxidized form to another (Garbisu and Alkorta 2001). Researchers have evaluated bacteria that metabolize As and found that As (III) can be remedied by being oxidized as a contaminant. The most efficient tool for recovering soil poisoned with arsenic may be phytoremediation (Oremland and Stolz 2003).

### *14.3.1 Plants' Defence Mechanisms Against the Soil's Metallic Environment*

Sites that have been polluted by heavy metals can be cleaned up using phytoremediation, which makes use of plants' abilities to absorb and reject metals (Schnoor 2002). According to the methods that plants used to grow on metal-contaminated soils. Baker and Walker (1990) divided plants into three basic groups, according to their ability to grow in contaminated soil: indicators, excluders and accumulators (Prasad 2008). These groups have also demonstrated four distinct conceptual approaches to the relationship between the accumulation of trace elements in plant crops and the escalating levels of total metalloids in the soil.

#### 14.3.1.1 Excluders

Arsenic uptake and transport to the shoots are restricted by arsenic excluders. In contrast to a variable content of arsenic in the soil solution, they may arrest or maintain a lesser, static arsenic content in shoots. They either change arsenic category by repositing metals in plant sections that are non-sensitive, as in the case of *Bidens pilosa*, or they produce intracellular metal binding molecules to withstand the level of metals present (chelators) (Sun et al. 2009). These plants keep significant concentration of heavy metals in the root zone and stop it from moving to the aboveground sections. Therefore, these plants' shoots have a relatively low metal concentration. Their capacity for metal extraction is constrained.

#### 14.3.1.2 Indicators

Metal accumulation in plants is inversely correlated with soil metal concentration. If these plants keep absorbing heavy metals, they will eventually die. They are consequently regarded as metal indicators and play a crucial role in ecology by serving as a reflection of pollution. Due to this, they are also utilised in mining. Indicator plants often reflect metal levels in the soil and can actively absorb trace metals in their aerial tissues. The concentrations of elements in indicators reflect the concentrations externally. *Azolla caroliniana*, *Lemna minor*, *Ranunculus trichophyllus*, and *Ranunculus peltatus* are examples of species that could be used as arsenic indicators (Baker 1981).

#### 14.3.1.3 Accumulators

According to Prasad (2008), accumulation plants take up and move arsenic to the shoots without displaying poisonous symptoms. These plants have enormous potential for metal extraction. In actuality, they store more metal ions in their aerial tissues

than are found in the soil. Bioaccumulation is a term that describes the accumulation. There have been references to "root accumulators," such as *Carex rostrata*, *Eriophorum angustifolium*, and Salix sp., which have roots with higher concentrations of arsenic than shoots (Stoltz and Greger 2006). An extreme kind of accumulators are hyperaccumulator plants (Brooks et al. 1977). Chinese brake fern plant (*Pteris vittata*), is among one of the example of how they may absorb and concentrate toxic arsenic up to a level of 1000 mg $kg^{-1}$ DM and accumulate an excess of 2.3% arsenic in above-ground biomass.

### *14.3.2 Arsenic Hyper-Accumulators*

According to reports, a few of plants hyper-accumulate arsenic, causing their shoots to have an exceptionally high content of 23,000 g arsenic $g^{-1}$. *Pteris vittala* L., a Chinese brake fern, is the first ever known arsenic hyper-accumulator (Ma et al. 2001). The process aggregation of arsenic in brake fern was studied, and the results were helpful in advancing phytoremediation efforts. This paper spurred a surge in similar studies. A distinct method is used by *P. vittata* to absorb arsenate and arsenite (Wang et al. 2010). Arsenic phytoremediation can also be done using a variety of plants, including *Mimosa pudica, Pityrogramma calomelanos*, and many others. *P. calomelanos* accumulates a significant amount of the metal in the foliage but very little in the roots (Visoottiviseth et al. 2002). Indian mustard (*Brassica juncea*), and Sunflower (*Helianthus annuus*) are utilized as hyper-accumulators due to their more biomass and endurance to metals and other inorganic substances (Ebbs et al. 2009).

### *14.3.3 Hyperaccumulation (Phytoextraction): The Basis of Most Effective Phytoremediation Technology*

Hyperaccumulators are plants species that display an exceptional potential to accumulate metals or that accumulate metals in high concentrations in their aerial parts. They demonstrate a metal tolerance trait. A more accurate definition would be that they are plants that accumulate metals at a level that is 100 times more than that of common plants or non-accumulators (Lasat 2000). The term "hyperaccumulator" refers to a group of about 500 species of plants from 45 plant families that have varying levels of bioaccumulation potential. Various elements, including species, the type of heavy metal, the quantity of organic matter in the soil, the pH, the cation exchange capacity, etc., may affect the hyperaccumulation in plants. One metal can be hyperaccumulated by some species, while multiple metals can be hyperaccumulated by others (Lasat 2000).

The finest phytoremediation technology, phytoextraction, has been studied in a large body of literature, but there are still many unanswered concerns that keep ecologists from feeling satisfied. At the completion of the procedure, a heavy biomass high in toxic wastes is created; however, since it is a hazardous waste, it cannot be disposed of in this manner. It becomes imperative to process it further using techniques like pyrolysis, compaction, composting, and then incineration, direct disposal, ashing, and liquid extraction, among other things (Sas-Nowosielska et al. 2004). To maximise the value of the input cost, this stage is essential.

### *14.3.4 Assessment of a Plant's Phytoextraction Capacity*

Four indicators can be used primarily to identify a plant's phytoextraction capacity (Masarovicova and Kraova 2012):

**Accumulating capacity**: Critical threshold estimates of metal concentrations, such as 10 mg $g^{-1}$ (DW) in shoots for Zn, have been used to identify plants as hyperaccumulators (Salt et al. 1995).

BF Index or the bioaccumulation factor: It can be described as the proportion of soil to shoot tissue metal concentration. Metal bioconcentration values in non-accumulator plants are frequently < 1 (Masarovicova and Kraova 2012).

**Translocation factor (TF index)**: It refers to proportion between the heavy metal content in shoots and roots. In order for a phytoextraction to be successful, it must be higher than 1.0 (Mikus et al. 2005).

**Tolerance capability**: Under certain toxic concentrations, hyperaccumulators have such high tolerance to heavy metals that they do not even exhibit apparent indications (Sun et al. 2009).

In comparison to plants that produce less biomass, a high biomass generating plant is anticipated to agglomerate more metals. Therefore, if a crop has a bioaccumulation factor value of 10, it is recommended to utilize a plant with a biomass of 20 t $ha^{-1}$. Even if it produces 10 t of biomass $ha^{-1}$, a plant species with a value of 20 of the same may be produced for clean-up (Peuke and Rennenberg 2005).

### *14.3.5 Metal Detoxifying Mechanisms in Hyperaccumulators*

Plant species that agglomerate hazardous metals at increasing concentrations go through two key processes to mitigate their effects: first, the toxic metals are complexed with organic substances, or bound to them, and second, they are compartmentalized within in the cellular vacuoles.

The various mechanisms of complexation with several elements and groups are provided below:

1. **Complexation with amino acids having SH groups**: Some amino acids, including glutathione and histidine, have functional SH groups that bind to heavy metals in the cytoplasm when they are free and render them inert. Particular examples of this kind of mechanism are Nickel-binding (Kramer 2010).
2. **Complexation with Organic acids**: In the soil, the roots of some plant species release carboxylic acids including citrate, oxaloacetate and malate that have a propensity to attach to heavy metals owing to their carboxylic acid groups and render them non-functional. To stop subsequent metal uptake by plants, heavy metal ions can also be attached to them through the apoplasm of roots. The pH of soils is thought to be altered by organic acid exudation, which has an impact on how readily plants may absorb heavy metals (Alford et al. 2010).
3. **Binding with Phytic acid**: Zinc's proposed/cited method of action involves binding with, a molecule that stores phosphate in *T. caerulescens i.e.* phytic acid (Jain 2007).
4. **Metallothioneins**: These are recently discovered cysteine-rich tiny proteins found in plants. The thiol group (SH-groups) from residues of cysteine, which make up almost 30% of its constituent amino acid residues, allows them to bind heavy metals (Sigel and Sigel 2009).
5. **Binding to phytochelatins**: A class of thiol-SH rich peptides known as phytochelatins is thought to transport hazardous metallic ion from the cytoplasm to the cellular vacuole (Hall 2002). It is acclaimed that phytochelatins chelate Cd for further decontamination (Cobbett 2000).

### *14.3.6 Criteria for Choosing Plants for a Phytoremediation Strategy*

It is crucial to make the appropriate choice when choosing plants in order to use the phytoremediation technology to achieve the intended purposes and goals. Many more qualities should be taken into consideration in addition to the plants' excellent capacity for extracting metal from soil. Firstly, of all the species chosen should have an extreme tolerance for the metal(s) occurring in the contaminated site. The species ought to have a high biomass yield and the ability to expand quickly. For increased accumulation of metals from the soil, plant roots should have a larger surface area. Additionally, it's critical to determine how well-adapted these species are to environmental stresses like salinity, drought, and waterlogging that could harm their capacity to absorb metals, produce biomass, and develop at a faster rate (Sarma 2011).

## 14.4 Phytoremediation of Aquatic Arsenic

Diverse hazardous substances are contaminating freshwater and marine resources because of human activity and natural sources. Therefore, much like with the terrestrial ecosystem, aquatic environment remediation is crucial. Aquatic macrophytes species and other floating plants can easily achieve phytoremediation of the hazardous compounds because the procedure takes biosorption, biomagnification of the dissolved, and bioavailable toxins from waters (Brooks and Robinson 1998). Aquatic plants species, which can be submerged in the water or float on the water's surface, are employed in aquatic phytoremediation systems. While submerged plants gather metals throughout their entire body, buoyant aquatic hyperaccumulative plants absorb or accumulate pollutants through their roots.

According to Hutchinson (1975), who assessed the capacity of aquatic macrophytes species to gather elements or ions from the aquatic environments, proposed the limits of potentially dangerous components within the plants were at least a magnitude more than in the aqueous phase that was supporting them. The implications of trace metal uptake for the disciplines of sewage disposal and bioremediation of contaminants was underlined by Outridge and Noller (1991) along with the tract and rates, absorption and excretion, and environment factors that affect uptake. For the bioremediation of aquatic systems, this is very important. They also examined the aquatic vascular plants' hyperaccumulation of dangerous pollutants. Many literatures have already been generated that discusses numerous biogeochemical factors, procedures, and the absorption of toxic components by a wide range of aquatic macrophytes species in order to evolve an efficient phytoremediation approach.

Aquatic macrophytes species and other microscopic aquatic floating plants have been employed for study on the remediation of natural and sewage that has Cu (II), Cd (II) and Hg (II) contamination (Alam et al. 1995). The aquatic plant *Myriophyllum spicatum* L. is a submerged species that is useful for detoxifying industrial effluent that contains metals (Lesage et al. 2007). Aquatic plants that absorb arsenic from polluted freshwater include *Mentha* spp. and *Rorippa nasturtium-aquaticum* (L.) (Robinson et al. 2006). Because of the promising findings of prior studies on phytoremediation involving usage of aquatic plants, scientists and researchers are keen to carry out more research in this field.

### *14.4.1 Phytoremediation of Arsenic Using Aquatic Macrophytes*

In oxic water, As (V) prevails, and both As (V) and As (III) are forms available for aquatic species (Sizova et al. 2002). Although the kinetics of phosphate interchange among aqueous and adsorbing colloids are similar to those of As (V), phosphate outcompetes As (V) in the competition for exchangeable sites (Mkandawire et al. 2004). Aquatic macrophytes species can therefore be a useful tool for cleaning up

arsenic-affected aquatic environment, and certain species have even been shown to acquire a significant quantity of arsenic from wastewater (Mirza et al. 2010). Among species of Lemnaceae family's the most extensively researched species in bioremediation and ecotoxicology are *Lemna gibba* L. and *Lemna minor* L. (Mkandawire and Dudel 2005).

Table 14.1 lists several illustrations of aquatic hyperaccumulator species.

**Table 14.1** Table summarizes the aquatic plants, which have been studied for phytoremediation of trace elements

| Common name | Scientific name | Trace elements | References |
|---|---|---|---|
| Duckweed | *Lemna gibba* L | As, U, Zn | Mkandawire and Dudel (2005) |
| Lesser duckweed | *Lemna minor* L | As, Zn, Cu, Hg | Robinson et al. (2005), Mishra et al. (2008) |
| Water hyacinth | *Eichhornia crassipes* | As, Fe, Cu, Zn, Pb, Cd, Cr, Ni, Hg | Mishra et al. (2008), Dixit and Dhote (2010) |
| Petries starwort | *Callitriche petriei* | As | Robinson et al. (2005) |
| Butterfly fern | *Salvinia natans*<br>*Salvinia minima* | As, Ni, Cu, Hg(II)<br>As, Pb, Cd, Cr | Rahman et al. (2008c), Sanchez-Galvan et al. (2008) |
| Greater duckweed | *Spirodela polyrhiza L* | As, Hg | Mishra et al. (2008), Rahman et al. (2008b) |
| Water spinach | *Ipomoea aquatica* | As, Cd, Pb, Hg, Cu, Zn | Lee et al. (1991), Wang et al. (2008) |
| Esthwaite waterweed | *Hydrilla verticillata* | As, Pb, Zn, Cr | Lee et al. (1991), Dixit and Dhote (2010) |
| Mosquito fern | *Azolla caroliniana* | As | Zhang et al. (2008) |
| Water fern | *Azolla filiculoides*<br>*Azolla pinnata* | As, Hg, Cd | Rahman et al. (2008a), Zhang et al. (2008) |
| Miriophyllum | *Myriophyllum propinquum* | As | Robinson et al. (2005) |
| Water pepper | *Polygonum hydropiper* | As | Robinson et al. (2005) |
| Alligator weed | *Althernanthera philoxeroides* | As, Pb | Elayan (1999) |
| Water lettuce | *Pistia stratiotes* | As, Cr, Pb, Ag, Cd, Cu, Hg, Ni, Zn | Lee et al. (1991) |

**Abbreviations** *As* arsenic, *U* uranium, *Zn* zinc, *Cu* copper, *Hg* mercury, *Fe* iron, *Pb* lead, *Cd* cadmium, *Cr* chromium, *Ni* nickel, *Ag* silver

### 14.4.2 Mechanisms of Uptake of as in Aquatic Macrophytes

The predominant forms of arsenic in natural water its inorganic forms existing as As (V) and As (III) and the methylated forms (MMAA(V) and DMAA(V)) (Cullen and Reimer 1989). Natural water contains thermodynamically unstable methylarsenic and As (III) chemicals because aquatic organisms like algae convert As (V) to As(III) and then bio transform it into methylated arsenicals (Hellweger and Lall 2004). In freshwater (Kuhn and Sigg 1993) and seawater (Peterson and Carpenter 1983), inorganic arsenic constitutes the majority of the dissolved inorganic arsenic. For the process of uptake of arsenic species in aquatic macrophytes, three different procedures have been proposed: (a) active uptake through $PO_4^-$ transporters, (b) passive uptake through aquaglyceroporins channels, and (c) BY physicochemical adsorption on root surfaces. However, the physicochemical process of adsorption on root surfaces has also been proposed as a potential alternate uptake method for this arsenic species. Plants primarily acquire As (V) through active phosphate uptake transporters (Zhao et al. 2009; Robinson et al. 2006). Through the aquaglyceroporin channels, As (III), DMAA, and MMAA enter the plants passively (Rahman et al. 2011).

1. **Active uptake through phosphate uptake transporters** In the plasmalemma, chemical analogues of phosphate and As (V) fight for uptake carriers (Mkandawire et al. 2004; Debnath et al. 2016). So, it is anticipated that when the phosphate concentration increases, more As (V) will desorbate in the solution (Smith and Read 2008). According to Zhao et al. (2009), plants absorb As (V) using phosphate transporters. For the absorption of As species, aquatic plants likewise employ the same methods. As (V) uptake by *L. gibba* L. and *S. polyrhiza* L. occurs via the phosphate uptake pathway, as demonstrated by Rahman et al. (2007).
2. **Passive uptake through aquaporins/aquaglyceroporins** Physiological studies show that these arsenic compounds are transported in rice by passive uptake processes, even if the exact absorption mechanisms is not yet fully understood for As (III) and methylated arsenicals (DMAA and MMAA) in plant species have not yet been established (Rahman et al. 2011). Two among the three subclasses of water channel proteins (WCPs)—aquaporins and aquaglyceroporins—are transmembrane proteins with particular three-dimensional configurations and pores that allow water, glycerol, other tiny as well as neutral molecules to pass through them (Benga 2009). The glycerol and As (III) molecule competing for uptake in rice (*Oryza sativa* L.) reveals that these arsenic species are transported through the semi- permeable plasma membrane via aquaporins and aquaglyceroporins (Meharg and Jardine 2003).
3. **Physicochemical adsorption on root surfaces** Robinson et al. (2006) have suggested physical and chemical adsorption as a substitute mechanism for As (V) buildup in aquatic plants. This method involves the adsorption and accumulation of arsenic by precipitated Fe oxides/ Fe-plaque on the surfaces of aquatic plants. As and Fe concentrations in aquatic species were found to be positively correlated by Robinson et al. (2006), which is thought to be due to adsorption of arsenic on

iron oxides on plant surfaces. Rahman et al. (2008c) investigated the adsorption of arsenic species on suspended iron $Fe_2O_3/Fe_2O_4$ on *Spirodela polyrhiza* L. roots as well as fronds and discovered a inviolable association between As and Fe concentrations in tissues when the species was subjected to As (V). *Spirodela polyrhiza* L. treated to As (III), DMAA, and MMAA did not show any association between As and Fe in plant tissue.

## 14.5 Potential of Mycorrhizal Fungi in Arsenic Phytoremediation

Since physiochemical remediation solutions are highly extravagant and only suitable for applications on-site, phytoremediation is a feasible substitute for As remediation from affected soils and water (Garg and Singla 2011). Even though the attributes and genes are mainly unrevealed to date, genetically manipulating As hyperaccumulating qualities may aid our attempt in As phytoremediation (Zhu and Rosen 2009). Most focus has been paid to identifying high As shoot accumulators for phytoremediation by above ground harvesting since it is simpler to do so than to do so for high root As accumulators by underground plant harvesting. This is because terrestrial plant parts are easier to collect. Though they might not survive in other locations, all As hyperaccumulating plants shoot require a tropical to subtropical climate to grow. Instead, hyperaccumulators through root could be employed for phytoremediation, particularly in vegetative plants with extensive root parameters in soil surface profiles, even though a procedure for removing the roots is either not yet accessible or unfeasible.

Plant-associated bacteria and AM fungus have each been suggested as having possible roles in the remediation of heavy metals (Garg and Singla 2011; Weyens et al. 2009). But lesser is yet known about the potential role of AM fungus in the tolerating capacity and hyperaccumulation of As (a semimetal element) in their host plants, especially in field settings. Increased As transport through roots to shoots or As buildup in host plant tissues, especially when caused by indigenous isolations (Orlowska et al. 2012). This suggests that mycorrhizal fungus might give their host plants the ability to accumulate As and to tolerate it. Choosing associations of plant with associated fungal species having high As tolerating and accumulation capacity would maximise their prospective for As remediation, especially for phytoextraction and phytostabilization, if these phenomena are generally true (Mendez and Maier 2008). Neither a woody As phytoremediation plant nor another one with high shoot-root As accumulation capability have been discovered as of yet. Therefore, herbaceous shoot hyperaccumulators are the focus of current phytoremediation efforts, while herbaceous root hyperaccumulators are the focus of current phytostabilization strategies.

Even on As-contaminated field locations, diversity of mycorrhiza is strong and mycorrhizal association with shoot for As hyperaccumulation ferns thrives. A research conducted on both As-contaminated and As-uncontaminated areas in China revealed that the prevalent species of *Glomus mosseae*, *G. geosporum*, *G. brohultii*

and *G. microaggregatum* were connected with the As hyperaccumulator *P. vittata* (Wu et al. 2009). In contaminated environments, the high mycorrhizal fungus diversification may have a substantial physiological and ecological impact on the host plants species. Its known root because the aforementioned hyperaccumulative annuals and perennials are mycorrhizae (Brundrett 2009). With the establishment of the mycorrhizal association between plants and fungus species, the insertion of arsenic tolerant mycorrhizae to locations having no, few, or unsuited mycorrhizal fungal association could hasten not just remediation of arsenic but also reclaim soil and restorate vegetation. A shoot/ root hyperaccumulative plant species has a lot of potential for screening and integrating isolates of fungus that improve As tolerance as well as hyperaccumulation. This is because mycorrhizal associations between plants and fungi are formed. There is a lot of potential for screening and combining fungal isolates to intensify As tolerance as well as hyperaccumulation in a shoot or root of plant species. As transfer among mycorrhizal plants species via CMN may offer another flora-based phytoremediation technique by co-growing plants with low As absorption capacity but high biomass output with those with high As uptake capacity but poor biomass production to harvest.

## 14.6 Biotechnological Interventions for Phytoremediation

Although phytotoxicity of heavy metal to plants has slowed down and largely made futile the phytoremediation of hazardous metals and metalloids using plants (Dhankher et al. 2012). There are also naturally occurring heavy metal hyperaccumulators; however, their applicability is constricted to a limited range of geoclimatic conditions, and they lack the essential biomass needed for effective phytoremediation. To increase tolerance of plants and heavy metal buildup through phytoremediation, there are several technological possibilities. Engineering plants for heavy metal and metalloid phytoremediation currently uses three basic biotechnological approaches:

1. **Manipulating the genes and uptake mechanism for metal/metalloid transporters** Through genetic transformation of metal transporter genes, improved tolerances and bioaccumulation of have been achieved in various plant species. Arsenite is transported in plants by the use of proteins known aquaporins, according to recent research findings (Mosa et al. 2012). It has been noted that effective arsenic hyperaccumulators like *Pteris vittata* have an incredibly regularized system for moving arsenic via root to shoot tissues (Xu et al. 2007). The majority of non-hyperaccumulators, in contrast to *P. vittata*, exhibit lower mobility rates, and various plant species exhibit varying mobility rates for arsenic, showing that this is a gene-controlled trait. Despite being a crucial step in the transfer of arsenic from the root to the shoot, its transfer to the vascular tissue is

a poorly understood mechanism. The Lsi2 gene, which encodes an efflux/ transport protein, is crucial for transporting arsenite into the xylem vessels, according to Ma et al. (2006).

2. **Increasing the synthesis of metals and metalloid ligands-Arsenic** (III) can be effectively detoxified by complexing with glutathione (GSH), metallothionein (MTs), or phytochelatins (PCs) which are retained in the vacuoles (Chatterjee et al. 2013). Multidrug resistance protein (MRP) homologs facilitate this process (Lu et al. 1997). One method to boost arsenic phytoremediation may be to increase the deposition or synthesis of PCs, GSH, and/or MTs. *Brassica juncea* tolerance to arsenic was increased by overexpressing PCS, but no discernible increase in arsenic buildup was seen; this may be because the synthesis of PC is simultaneously constrained through the synthesis of GSH (Gasic and Korban 2007).
3. **Transformation of metals and metalloids into a form less hazardous and volatile** There have been various studies on the development of phytoremediation techniques for heavy metals using biotechnological interventions that transform these metals into less harmful and volatile forms. Numerous species, including fungus, bacteria, and mammals, have been found to methylate arsenic. The discovery of methylated arsenic in a diverse domain of plant species, which includes rice grains (Zhu et al. 2008), indicates that the process is the product of endogenous methylation by the flora themselves. The gas trimethylarsine (TMAs (III)), which can be volatilized from the plant, is the last byproduct of this route.

## 14.7 Advantages of Phytoremediation

Being solar-powered, it is a low-cost strategy. The site's vegetation cover makes it easier to minimize erosion of soil and boost soil nourishment (Wei et al. 2005). Along with removing inorganic contaminants, this method can also be employed to remove organic pollutants. Metals collected from plant tissues can be used in biofortification to increase the nutritional content of crops because some heavy metals are essential minerals that may be inadequate in staple food crops. Not to mention that adding greenery to the area would improve its aesthetic appeal (Mayer et al. 2008).

Some naturally existing arsenic hyperaccumulating plants identified with As concentrations in different parts of plant are listed in Table 14.2.

## 14.8 Limitations of Phytoremediation

Because heavy metal poisoning has changed the physicochemical characteristics of these places, the colonisation of many species there becomes slow and challenging. Therefore, care should be used when choosing species that could flourish quickly and effortlessly (Wei et al. 2005). This technique is also time-consuming. The proper

**Table 14.2** Naturally grown arsenic hyperaccumulating plants with arsenic concentrations in different plant parts

| Plant species | Organs | Quantity of As (mg $kg^{-1}$) | References |
|---|---|---|---|
| *Eichhornia crassipes* | Shoot | 909.58 | Delgado et al. (1993) |
| *Pteris vittata* | Frond | 27,000 | Wang et al. (2002) |
| *Lemna gibba* | Shoot | 1021 | Mkandawire and Dudel (2005) |
| *Brassica rapa L. var. pervirdis S* | Shoot | 90.3 | Shaibur and Kawai (2009) |
| *Brassica rapa L. var. pervirdis S* | Root | 4840 | Shaibur and Kawai (2009) |
| *Brassica juncea* | Shoot | 322.1 | Khan et al. (2009) |
| *Brassica juncea* | Root | 210.7 | Khan et al. (2009) |
| *Jussieua repens* | Shoot | 46.50 | Gani molla et al. (2010) |
| *Echinochloa cruss-galli* | Shoot | 67.82 | Gani molla et al. (2010) |
| *Echinochloa cruss-galli* | Root | 61.25 | Gani molla et al. (2010) |
| *Azolla sp.* | Shoot | 27.65 | Gani molla et al. (2010) |
| *Orzya sativa* | Shoot | 9.43 | Gani molla et al. (2010) |
| *Orzya sativa* | Root | 12.10 | Gani molla et al. (2010) |
| *Alternanthera philoxeroides* | Shoot | 67.30 | Gani molla et al. (2010) |
| *Cyperus rotundus* | Shoot | 11.14 | Gani molla et al. (2010) |
| *Monochoria hastata* | Root | 40.78 | Gani molla et al. (2010) |

Abbreviations mg $kg^{-1}$ mg per kilogram

disposal of trash from polluted plants is very important. The number of species of plants that can rehabilitate the soil is insufficient. The contamination might not exist in a physiologically usable form (Lasat 2000).

The inorganic form of arsenic is more difficult to phytoremediate than its organic form. Despite the success of the findings in the pot trials, the removal success in field trials is less effective than anticipated, mostly because of the complications of the soil and the limited acessibility of the contaminants. The interaction of the substances at the sites where both organic as well as inorganic pollutants are present has an effect on the availability of the contaminants. The selection of a suitable combination of flora species that could decompose the organics or stabilise the inorganics while being able to withstand the existence of diversified form of pollutants is crucial to successful on-site rectification when dealing with mixture of impurities (organics and inorganics). To rehabilitate such a site with an aggregation of pollutants, species of plants like *Brassica juncea* and *Helianthus annuus* can be employed. Plant roots have the ability to indirectly break down organic material by exuding root exudates that encourage microbial activity nearby. Additionally, there have been attempts to

directly release catabolic enzymes competent of biotransforming organic compounds (Siciliano et al. 1998).

The proper disposal of the *P. Vittata* biomass gathered during the phytoremediation process is a serious challenge. In order to dispose of contaminated biomass in an appropriate manner and economically viable way, public assistance is essential (Mench et al. 2010). There are several options for the secure disposal of contaminated harvest, including liquid disposal, direct disposal, washing, compaction, pyrolysis, composting, incineration, and washing again (Van Ginneken et al. 2007). However, the residual arsenic in plant biomass that is being thermally processed can release arsenic into the environment directly (Yan et al. 2008) making it dangerous to practise. Sub as well as super-critical water purification procedures, where the accumulation of the arsenic-infected fern fronds was decreased by a percentage of 70–77, may be safer alternatives for the eradication of contaminated biomass (Carrier et al. 2011). The excess amount arsenic is further minimized by sorption on hydrous iron oxides. Once commercialized, these techniques the waste products can be employed as ingredients for antiseptics, herbicide precursors and fragrance which can help make the process profitable.

Due to the steadily expanding anthropogenic activities, heavy metal contamination is becoming a serious issue. The goal of the current analysis is to highlight environmental friendly technology for improving the information and understanding that is related and may be applied to future research. Having an understanding of biochemical and physiological responses facilitates the use of various tactics. One of the excellent prospects for addressing the issue of soil heavy metal contamination stress without causing environmental damage is phytoremediation.

From a scientific perspective, there are still varieties of factors because of its flaws that prevent it from being a huge success. The low productivity of crops provides biotechnology with a chance to use the method of gene engineering to get around the problem. To maximise the process of phytoremediation, special consideration must be given to the usage of biotechnological tools to introduce certain specific genes to promising species with high biomass. From a scientific perspective, there are still varieties of factors because of its flaws that prevent it from being a huge success. Crop production is low, offering gene engineering in biotechnology a possibility to apply the technique to circumvent the issue. The application of biotechnology to incorporate particular genes to potential species with high biomass must be carefully considered in order to maximise the phytoremediation process.

## References

Ahmadpour P, Ahmadpour F, Mahmud TMM, Abdu A, Soleimani M, Tayefeh FH (2012) Phytoremediation of heavy metals: a green technology. Afr J Biotech 11(76):14036–14043

Alam B, Chatterjee AK, Duttagupta S (1995) Bioaccumulation of Cd (II) by water lettuce. Pollut Res 14:59–64

Alford EA, Pilon-Smits EAH, Paschke MW (2010) Metallophytes—a view from the rhizosphere. Plant Soil 337:33–50

Ali H, Naseer M, Anwar Sajad M (2012) Phytoremediation of heavy metals by *Trifolium alexandrinum*. Int J Environ Sci 2:1459–1469

Amin M, Hamidi AA, Mohammed AZ,. Shukor QA, Razip M (2013) Phytoremediation of heavy metals from urban waste leachate by Southern Cattail (*Typha domingensis*). Int J Sci Res Environ Sci 1(4):67–70

Arsenic WHO (1981) Environmental health criteria 18. World Health Organization, Geneva, p 82

Badr N, Fawzy M, Al-Qahtani K (2012) Phytoremediation: an economical solution to heavy-metal-polluted soil and evaluation of plant removal ability. World Appl Sci J 16(9):1292–1301

Baker AJM (1981) Accumulator and excluders—strategies in response of plant to heavy metals. J Plant Nutrition 3v(1–4):643–654

Baker AJM, Walker PL (1990) Ecophysiology of metal uptake by tolerant plants. In: Shaw AJ (ed) Heavy metal tolerance in plants: evolutionary aspects. CRC Press, Boca Raton, pp 155–177

Benga G (2009) Water channel proteins (later called aquaporins) and relatives: past, present, and future. IUBMB Life 61:112–133

Bolan N, Kunhikrishnan A, Thangarajan R, Kumpiene J, Park J, Makino T, Kriham MB, Scheckel K (2014) Remediation of heavy metal(loid)s contaminated soils—to mobilize or to immobilize? J Hazard Mater 266:141–166

Brooks RR, Robinson BH (1998) Aquatic phytoremediation by accumulator plants. In: Brooks RR (ed) Plants that Hyperaccumulate heavy metals: their role in archaeology, microbiology, mineral exploration, phytomining and phytoremediation. CAB International, Wallingford, pp 203–226

Brooks RR, Lee J, Reeves RD, Jaffre T (1977) Detection of nickeliferous rocks by analysis of herbarium specimens of indicator plants. J Geochem Explor 7:49–57. https://doi.org/10.1016/0375-6742(77)90074-7

Brundrett MC (2009) Mycorrhizal associations and other means of nutrition of vascular plants: understanding the global diversity of host plants by resolving conflicting information and developing reliable means of diagnosis. Plant Soil 320:37–77

Carrier M, Loppinet-Serani A, Absalon C, Marias F, Aymonier C, Mench M (2011) Conversion of fern (*Pteris vittata* L.) biomass from a phytoremediation trial in sub-and supercritical water conditions. Biomass Bioenergy 35(2):872–883

Chatterjee M, Sarkar S, Debnath S, Ghosh S, Bhattacharyya S, Sanyal SK (2011) Genetic analysis of arsenic accumulation in grain and straw of rice using recombinant inbred lines. Oryza 48:270–273

Chatterjee M, Sarkar S, Debnath S, Mukherjee A, Chakraborty A, Bhattacharyya S (2013) Genotypic difference in temporal variation of arsenic accumulation and expression of silicon efflux transporter (LSi2) gene in field grown rice. Indian J Genet Plant Breed 73(1):94–97. https://doi.org/10.5958/j.0019-5200.73.1.01

Cobbett CS (2000) Heavy metal detoxification in plants: Phytochelatin biosynthesis and function. Showcase Res 31(4):15–19

Cullen WR, Reimer KJ (1989) Arsenic speciation in the environment. Chem Rev 89:713–764

Debnath S, Bhattacharyya S, Sarkar S, Chatterjee M, (2016) Expression of multidrug and toxic compound extrusion (MATE) genes in response to the presence of arsenic in irrigation water and soil in Rice (*Oryza sativa* L.). Int J Bio-Resour Stress Manag 7(1):88–91. https://doi.org/10.23910/IJBSM/2016.7.1.1488

Debnath S, Bhattacharyya S, Sarkar S, Chatterjee M (2017) Whole genome transcriptional analysis of rice grown in arsenic contaminated field conditions. Trends Biosci 10(2):850–855

Delgado M, Bigeriego M, Guardiola E (1993) Uptake of Zn, Cr and Cd by water hyacinth. Water Res 27:269–272

Dhankher OP, Pilon-Smits EA, Meagher RB, Doty S (2012) Biotechnological approaches for phytoremediation. In: Plant biotechnology and agriculture. Jan 1. Academic Press, pp 309–328

Dixit S, Dhote S (2010) Evaluation of uptake rate of heavy metals by *Eichhornia crassipes* and *Hydrilla verticillata*. Environ Monit Assess 169:367–374

Ebbs S, Hatfield S, Nagarajan V, Blaylock M (2009) A comparison of the dietary arsenic exposures from ingestion of contaminated soil and hyperaccumulating pteris ferns used in a residential

phytoremediation project. Int J Phytorem 12(1):121–132. https://doi.org/10.1080/15226510902861784
EEA (European Environment Agency) (2007) Progress in management of contaminated sites, CSI. 015, DK-1050 Copenhagen K, Denmark
Elayan NMS (1999) Phytoremediation of arsenic and lead from contaminated waters by the emergent aquatic macrophyte *Althernanthera philoxeroides* (alligator weed). Southern University, Louisiana
Frankenberger WT Jr, Arshad M (2002) Volatilisation of arsenic. In: Frankenberger WT (ed) Environmental chemistry of arsenic. Marcel Dekker, New York, pp 363–380
Gani Molla MO, Islam MA, Hasanuzzaman M (2010) Identification of arsenic hyperaccumulating plants for the development of phytomitigation technology. J Phytology 2:41–48
Garbisu C, Alkorta I (2001) Phytoextraction: a costeffective plant-based technology for the removal of metals from the environment. Biores Technol 77:229–236
Garg N, Singla P (2011) Arsenic toxicity in crop plants: physiological effects and tolerance mechanisms. Environ Chem Lett 9:303–321. https://doi.org/10.1007/s10311-011-0313-7
Gasic K, Korban SS (2007) Transgenic Indian mustard (*Brassica juncea*) plants expressing an Arabidopsis phytochelatin synthase (*AtPCS1*) exhibit enhanced As and Cd tolerance. Plant Mol Biol 64(4):361–369
Gonzaga SMI, Santos JAG, Ma LQ (2006) Arsenic phytoextraction and hyperaccumulation by fern species. Scientia Agricola 63(1):90
Hall J (2002) Cellular mechanisms for heavy metal detoxification and tolerance. J Exp Bot 53:1–11. https://doi.org/10.1093/jexbot/53.366.1
Hellweger FL, Lall U (2004) Modeling the effect of algal dynamics on arsenic speciation in lake Biwa. Environ Sci Technol 38:6716–6723
Hutchinson GE (1975) A treatise on limnology. Wiley, London
Jain VK (2007) Stress physiology. In: Fundamentals of plant physiology. S Chand & Company Ltd., Ram Nagar, New Delhi, India. Chapter 23, pp 510–512
Khan I, Ahmad A, Iqbal M (2009) Modulation of antioxidant defence system for arsenic detoxification in Indian mustard. Ecotoxicol Environ Saf 72:626–634
Kramer U (2010) Metal hyperaccumulation in plants. Annu Rev Plant Biol 61:517–534
Kuang Y, Wen D, Zhou G et al (2004) Advances in researches on the phytoremediation of organic contaminants and heavy metals. Chin J Ecol 23:90–96
Kuhn A, Sigg L (1993) Arsenic cycling in eutrophic lake Greifen, Switzerland: influence of seasonal redox processes. Limnol Oceanogr 38:1052–1059
Lasat MM (2000) Phytoextraction of metals from contaminated soil: a review of plant/soil/metal interaction and assessment of pertinent agronomic issues. J Hazard Subst Res 2(5):1–25
Lee CK, Low KS, Hew NS (1991) Accumulation of arsenic by aquatic plants. Sci Total Environ 103:215–227
Lesage E, Mundia C, Rousseau DPL, Van de Moortel AMK, Du Laing G, Meers E, Tack FMG, De Pauw N, Verloo MG (2007) Sorption of Co, Cu, Ni and Zn from industrial effluents by the submerged aquatic macrophyte *Myriophyllum spicatum* L. Ecol Eng 30:320–325
Lu YP, Li ZS, Rea PA (1997) AtMRP1 gene of Arabidopsis encodes a glutathione S-conjugate pump: isolation and functional definition of a plant ATP-binding cassette transporter gene. Proc Natl Acad Sci 94(15):8243–8248
Ma JF, Tamai K, Yamaji N, Mitani N, Konishi S, Katsuhara M, Ishiguro M, Murata Y, Yano M (2006) A silicon transporter in rice. Nature 440(7084):688–691
Ma LQ, Komar KM, Tu C, Zhang W, Cai Y, Kennelley ED (2001) A fern that hyperaccumulates arsenic. Nature 409:579
Mahimairaja S, Bolan NS, Adriano DC, Robinson B (2005) Arsenic contamination and its risk management in complex environmental settings. Adv Agron 86:1–82
Masarovicova E, Kraova K (2012) Plant-heavy metal interaction: phytoremediation, biofortification and nanoparticles. In: Dr Montanaro G (eds) Advances in selected plant physiology

aspects. ISBN: 978-953-51-0557-2. InTech, http://www.intechopen.com/books/advances-inselected-plant-physiology%20aspects/crops-and-medicinal-plants-under-metal-stress
Matera V, Le Hecho I (2001) Arsenic behavior in contaminated soils: mobility and speciation. In: Selim HM, Sparks DM (eds), Heavy metals release in soils. CRC Press, Boca Raton, pp 207–235
Mayer JE, Pfeiffer WH, Beyer P (2008) Biofortified crops to alleviate micronutrient malnutrition. Curr Opin Plant Biol 11:166–170
Meagher RB (2000) Phytoremediation of toxic elemental and organic pollutants. Curr Opin Plant Biol 3:153–162
Meharg AA, Jardine L (2003) Arsenite transport into paddy rice (*Oryza sativa*) roots. New Phytol 157:39–44
Mench M, Lepp N, Bert V, Schwitzguébel JP, Gawronski SW, Schröder P, Vangronsveld J (2010) Successes and limitations of phytotechnologies at field scale: outcomes, assessment and outlook from COST Action 859. J Soils Sediments 10(6):1039–1107
Mendez MO, Maier RM (2008) Phytostabilization of mine tailings in arid and semiarid environments—an emerging remediation technology. Environ Health Perspect 116 (3):278–83
Mikus VK, Drobne D, Regvar M (2005) Zn, Cd and Pb accumulation and arbuscular mycorrhizal colonisation of pennycress *Thlaspi praecox* Wulf. (Brassicaceae) from the vicinity of a lead mine and smelter in Slovenia. Environ Pollut 133:233–242
Mirza N, Mahmood Q, Pervez A, Ahmad R, Farooq R, Shah MM, Azim MR (2010) Phytoremediation potential of *Arundo donax* in arsenic-contaminated synthetic wastewater. Bioresource Technol 101:5815–5819
Mishra V, Upadhyay A, Pathak V, Tripathi B (2008) Phytoremediation of mercury and arsenic from tropical opencast coalmine effluent through naturally occurring aquatic macrophytes. Water Air Soil Pollut 192:303–314
Mkandawire M, Dudel EG (2005) Accumulation of arsenic in *Lemna gibba* L. (duckweed) in tailing waters of two abandoned uranium mining sites in Saxony, Germany. Sci Total Environ 336:81–89
Mkandawire M, Lyubun YV, Kosterin PV, Dudel EG (2004) Toxicity of arsenic species 851 to *Lemna gibba* L. and the influence of phosphate on arsenic bioavailability. Environ Toxicol 19:26–35
Mokgalaka-Matlala NS, Flores-Tavizón E, Castillo-Michel H, Peralta-Videa JR, Gardea-Torresdey JL (2008) Toxicity of arsenic (III) and (V) on plant growth, element uptake and total amylolytic activity of mesquite (*Prosopis Juliflora* x *P. Velutina*). Int J Phytorem 10(1):47–60
Mosa KA, Kumar K, Chhikara S, Mcdermott J, Liu Z, Musante C, White JC, Dhankher OP (2012) Members of rice plasma membrane intrinsic proteins subfamily are involved in arsenite permeability and tolerance in plants. Transgenic Res 21(6):1265–1277
Oremland RS, Stolz JF (2003) The ecology of arsenic. Science 300:939–944
Outridge PM, Noller BN (1991) Accumulation of toxic trace elements by freshwater vascular 874 plants. Rev Environ Contam Toxicol 121:1–63
Orłowska E, Godzik B, Turnau K (2012) Effect of different arbuscular mycorrhizal fungal isolates on growth and arsenic accumulation in *Plantago lanceolata* L. Environ Pollut 168:121–130
Peterson ML, Carpenter R (1983) Biogeochemical processes affecting total arsenic and arsenic species distributions in an intermittently anoxic fjord. Mar Chem 12:295–321
Petrick JS, Ayala-Fierro F, Cullen WR, Carter DE, Vasken AH (2000) Monomethylarsonous acid (MMAIII) is more toxic than arsenite in Chang human hepatocytes. Toxicol Appl Pharmacol 163(2):203–207
Peuke AD, Rennenberg H (2005) Phytoremediation. EMBO Reports, vol 6, no 6, pp 497–501. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1369103
Prasad MNV (2008) Trace element in traditional healing plants-remedies or risk. In: Prasad MNV (ed) Trace elements as contaminants and nutrients: consequences in ecosystems and human health. Wiley, Hoboken
Rahman MA, Hasegawa H, Kitahara K, Maki T, Ueda K, Rahman MM (2008a) The effects of phosphorous on the accumulation of arsenic in water fern (*Azolla pinnata* L.). J Ecotechnol Res 14:21–24

Rahman MA, Hasegawa H, Ueda K, Maki T, Okumura C, Rahman MM (2007) Arsenic accumulation in duckweed (*Spirodela polyrhiza* L.): a good option for phytoremediation. Chemosphere 69:493–499

Rahman MA, Hasegawa H, Ueda K, Maki T, Rahman MM (2008b) Influence of phosphate and iron ions in selective uptake of arsenic species by water fern (*Salvinia natans* L.). Chem Eng J 145:179–184

Rahman MA, Hasegawa H, Ueda K, Maki T, Rahman MM (2008c) Arsenic uptake by aquatic macrophyte *Spirodela polyrhiza* L.: interactions with phosphate and iron. J Hazard Mater 160:356–361

Rahman MA, Kadohashi K, Maki T, Hasegawa H (2011) Transport of DMAA and MMAA into rice (*Oryza sativa* L.) roots. In: Environmental and experimental botany. Corrected Manuscript, In Press

Rajoo KS, Abdu A, Hazandy AH, Karam DS, Shamshuddin J, Jamaluddin AS, Zhen WW (2013) Assessment of heavy metal uptake and translocation by *Aquilaria malaccensis* planted in soils containing sewage sludge. Am J Appl Sci 10(9):952–964

Ravenscroft P, Brammer H, Richards K (2009) Arsenic pollution: a global synthesis. Wiley-Blackwell

Robinson B, Kim N, Marchetti M, Moni C, Schroeter L, van den Dijssel C, Milne G, Clothier B (2006) Arsenic hyperaccumulation by aquatic macrophytes in the Taupo Volcanic Zone, New Zealand. Environ Exp Botany 58:206–215

Robinson B, Marchetti M, Moni C, Schroeter L, van den Dijssel C, Milne G, Bolan N, Mahimairaja S (2005) Arsenic accumulation by aquatic and terrestrial plants. In: Naidu R, Smith E, Owens G, Bhattacharya P, Nadebaum P (eds) Managing arsenic in the environment: from soil to human health. CSIRO, Collingwood, pp 235–247

Schnoor JL (2002) Phytoremediation of soil and groundwater, groundwater remediation technologies analysis center e series; technology evaluation report, TE-02-01; Groundwater Remediation Technologies Analysis Center, Pittsburgh, Pennsylvania

Sakakibara M, Watanabe A, Inoue M, Sano S, Kaise T (2010) Phytoextraction and phyto volatilization of arsenic from As-contaminated soils by *Pteris vittata.* In: Proceedings of the annual international conference on soils, sediments, water and energy, pp 12, 26

Salt DE, Blaylock M, Kumar NPBA, Dushenkov V, Enaley BD, Chet I, Raskin I (1995) Phytoremediat on: a novel strategy for the removal of toxic metals from the environment using plants. Nat Biotechnol 13:468–474

Sanchez-Galvan G, Monroy O, Gomez J, Olguin EJ (2008) Assessment of the hyperaccumulating lead capacity of *Salvinia minima* using bioadsorption and intracellular accumulation factors. Water Air Soil Pollut 194:77–90

Sarma H (2011) Metal Hyperaccumulation in plants: A review focussing on phytoremediation technology. J Environ Sci Technol 4:118–138

Sas-Nowosielska A, Kucharski R, Malkowski E, Pogrzeba M, Kuperberg JM, Krynski K (2004) Phytoextraction crop disposal-an unsolved problem. Environ Pollut 128(3):373–379

Seth S, Debnath S, Chakraborty NR (2020) In silico analysis of functional linkage among arsenic induced MATE genes in rice. Biotechnol Rep 26:e00390. https://doi.org/10.1016/j.btre.2019.e00390

Shah K, Nongkynrih JM (2007) Metal hyperaccumulation and bioremediation. Biol Plant 51(4):618–634

Shaibur MR, Kawai S (2009) Effect of arsenic on visible symptom and arsenic concentration in hydroponic Japanese mustard spinach. Environ Exp Bot 67:65–70

Siciliano SD, Goldie H, Germida JJ (1998) Enzymatic activity in root exudates of Dahurian wild rye (Elymus dauricus) that degrades 2-chlorobenzoic acid. J Agric Food Chem 46(1):5–7

Sigel H, Sigel A (eds) (2009). Metallothioneins and related chelators (metal ions in life sciences). Metal ions in life sciences 5. Cambridge, England: Royal society of chemistry. ISBN 1-84755-899-2

Siripitayakunkit U, Lue S, Choprapawan C (2001) Possible effects of arsenic on visual perception and visual motor integration of children in Thailand. Arsenic Exposure Health Effects IV 4:165–172

Sizova OI, Kochetkov VV, Validov SZ, Boronin AM, Kosterin PV, Lyubun YV (2002) Arsenic-contaminated soils: genetically modified *Pseudomonas* spp. and their arsenic-phytoremediation potential. J Soils Sediments 2:19–23

Smith SE, Read DJ (eds) (2008) Mycorrhizal symbiosis. Academic Press, New York, p 803

Stoltz E, Greger M (2006) Release of metals and arsenic from various mine tailings by *Eriophorum angustifolium.* Plant Soil 289(1–2):199–210

Sun Y, Zhou Q-X, Liu W-T, Wang L (2009) Joint effects of arsenic, cadmium on plant growth and metal bioaccumulation: a potential Cd hyperaccumulator and As-excluder *Bidens pilosa* L. J Hazard Mater 161(2–3):808–814

Tu C, Ma LQ (2002) Effects of arsenic concentrations and forms on arsenic uptake by the hyperaccumulator ladder brake. J Environ Qual 31(2):641–647

US EPA (2002) Arsenic treatment technologies for soil, waste, and water. http://www.clu-in.org/arsenic. 6 Feb 2009

Van Ginneken L, Meers E, Guisson R, Ruttens A, Elst K, Tack FM, Dejonghe W (2007) Phytoremediation for heavy metal-contaminated soils combined with bioenergy production. J Environ Eng Landsc Manag 15(4):227–236

Visoottiviseth P, Francesconi K, Sridokchan W (2002) The potential of Thai indigenous plant species for the phytoremediation of arsenic contaminated land. Environ Pollut 118(3):453–461

Wang J, Zhao FJ, Meharg AA, Raab A, Feldmann J, McGrath SP (2002) Mechanisms of arsenic hyperaccumulation in *Pteris vittata.* Uptake kinetics, interactions with phosphate, and arsenic speciation. Plant Physiol 130:1552–1561

Wang X, Ma LQ, Rathinasabapathi B, Liu Y, Zeng G (2010) Uptake and translocation of arsenite and arsenate by *Pteris vittata* L.: effects of silicon, boron and mercury. Environ Exp Botany 68(2):222–229

Wang KS, Huang LC, Lee HS, Chen PY, Chang SH (2008) Phytoextraction of cadmium by *Ipomoea aquatica* (water spinach) in hydroponic solution: effects of cadmium speciation. Chemosphere 72:666–672

Wei S, Zhou Q, Wang X (2005) Identification of weed plants excluding the uptake of heavy metals. Environ Int 31:829–834

Weyens N, van der Lelie D, Taghavi S, Vangronsveld J (2009) Phytoremediation: plant-endophyte partnerships take the challenge. Curr Opin Biotechnol 43:9413–9418

Wu TY, Mohammad AW, Jahim JM, Anuar N (2009) A holistic approach to managing palm oil mill effluent (POME): Biotechnological advances in the sustainable reuse of POME. Biotechnol Adv 27(1):40–52

Xu XY, McGrath SP, Zhao FJ (2007) Rapid reduction of arsenate in the medium mediated by plant roots. New Phytol 176(3):590–599

Yan XL, Chen TB, Liao XY, Huang ZC, Pan JR, Hu TD, Xie H (2008) Arsenic transformation and volatilization during incineration of the hyperaccumulator *Pteris vittata* L. Environ Sci Technol 42(5):1479–1484

Zhang X, Lin AJ, Zhao FJ, Xu GZ, Duan GL, Zhu YG (2008) Arsenic accumulation by the aquatic fern *Azolla*: Comparison of arsenate uptake, speciation and efflux by *Azolla caroliniana* and *Azolla filiculoides*. Environ Pollut 156:1149–1155

Zhao FJ, Ma JF, Meharg AA, McGrath SP (2009) Arsenic uptake and metabolism in plants. New Phytol 181:777–794

Zhu YG, Rosen BP (2009) Perspectives for genetic engineering for the phytoremediation of arsenic-contaminated environments: from imagination to reality? Curr Opin Biotechnol 20:220–224

Zhu YG, Sun GX, Lei M, Teng M, Liu YX, Chen NC, Wang LH, Carey AM, Deacon C, Raab A, Meharg AA (2008) High percentage inorganic arsenic content of mining impacted and nonimpacted Chinese rice. Environ Sci Technol 42(13):5008–5013

# Chapter 15
# Mycoremediation of Arsenic: An Overview


**Shraddha Rai and Vivek Kumar Singh**

**Abstract** Arsenic (As) removal from polluted environment (soil or water) seems essential as As has been proved as a potential toxic pollutant that poses health risk and environmental contamination. Many forms of As are available in the environment which are based on the $p^H$ and redox potential. Two oxidation states of inorganic As i.e. $As^{3+}$ and $As^{5+}$ exist at normal $p^H$. Transformation of $As^{3+}$ oxidation form to a less toxic form $As^{5+}$ is the basis for As remediation from a particular source. A range of simple to sophisticated remediation technologies are available for As removal from the polluted environment. Implementation of the suitable As remediation technology depends on its source, distribution and chemical forms. There are several strategies for As removal from the contaminated soil and water among which microfungi have been proved as appropriate low-cost adsorbents for remediation of heavy metal ion. The sorption capacity of cationic heavy metal of microfungi has been found to be promising. The study of interaction between hazardous heavy metals such as As, Cd, Cu, Hg, Pb and Zn and soil fungi has been of biological interest for a long time. Soil fungi play significant part in the removal of As through its interchange between various forms. The present review portrays an overview about remediation potential of fungi with constraints and future perspectives.

**Keywords** Arsenic · Mycoremediation · Biosorption · Bioaccumulation · Biovolatilization

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## 15.1 Introduction

Metal pollutants have been a place in the human life since the evolution of modern civilization. However, global metal pollution has increased fast since the starting of the industrialization resulting main health and environmental issues (Fig. 15.1) (Kabata-Pendias and Pendias 2001; Azevedo et al. 2005; Sharma et al. 2007; Hughes et al. 2011; Saha and Rahman 2020). Among the several metal pollutants, arsenic (As) is assessed as a major environmental contaminant. Because of its chronic and epidemic effects on humans, As toxicity has attracted increased attention of researchers (Abernathy et al. 1999; Nassar 2020). As present in various chemical forms and contaminates terrestrial, marine and freshwater environments (National Research Council 2001). As has been proved as a significant soil contaminant due to the application of As-based fertilizers and pesticides, geological functioning, anthropogenic activities, improper management of industrial and municipal wastes, and irrigation with As-polluted water (Breckle 1991; Abedin et al. 2002; Requejo and Tena 2005; Hughes et al. 2011; Roy et al. 2014). Widespread ground water contamination by As has become a serious global problem (Abedin et al. 2002; Ahsan et al. 2010; Abbas and Cheema 2014; Dey et al. 2014).

In the environment, As is available in both forms (inorganic and organic) and in various valence or oxidation states. Organic As is less toxic than inorganic form for plants, animals and humans (Meharg and Hartley-Whitaker 2002). It was studied that the reason behind As pollution in the groundwater of South and South-East Asia was the leakage of As from solid phases in anaerobic environment (Polizzotto et al. 2008). Arsenate ($As^{+5}$) and Arsenite ($As^{+3}$) are the two main inorganic forms of As present in the soil which are interchangeable according to the redox condition of the soil (Tripathi et al. 2007; Beiyuan et al. 2017). Arsenate ($As^{+5}$) is the predominant inorganic form in the aerated soils, hence most of the phytotoxic studies are concerned with it (Gunes et al. 2008). However, Arsenite ($As^{+3}$) is prevalent in reducing environmental conditions like paddy soils in flooded condition (Xu et al. 2008). In the plants, $As^{+3}$ is absorbrd by plants through aquaporins while $As^{+5}$ through carrier-mediated phosphate translocation mechanism (Tripathi et al. 2007). Phytotoxicity mechanisms and expression of cocerned genes and enzymes of two As species vary in plants (Ahsan et al. 2010). $As^{+5}$ causes root membrane damage, inhibition of cellular activities, oxidative stress, and ultimately cell death, while $As^{+3}$ which is more phytotoxic than $As^{+5}$ causes retardation in root and shoot length, fresh weight, dry weight etc. (Gunes et al. 2008; Sahu et al. 2012).

Based on the redox potential and $p^H$, different forms of As is present in the environment such as $As^{3+}$ and $As^{5+}$ oxidation states are prevalent at normal $p^H$ values (Ng et al., 2004). Transformation from $As^{3+}$ to less toxic form $As^{5+}$ is the basis for removal of arsenic from a particular area. A range of simple to sophisticated technologies are available for the remediation of As from contaminated environments (soil and water). Implementation of any suitable remediation technology is based on the source and level, rout and distribution, and chemical forms of As (Ferguson 1990; Bhattacharya et al. 2002; Ng et al. 2004; Srivastava et al. 2011). There are


**Fig. 15.1** Toxic effects of arsenic on humans and crop plants

several strategies for the removal of As from the contaminated environments which could be arranged in three groups like physical, chemical and biological (Mahimairaja et al. 2005).

Among various techniques, bioremediation is a natural method to remove As contamination from the soil and make it suitable for plants and animals. Bioremediation technology depends on the stabilization, degradation or volatilization of contaminats from the environment by applying microorganism (Andrews et al. 2000; Bhattacharya et al. 2002). Different As forms can be removed through several microbial processes such as As mobilization and immobilization by sorption, As oxidation and reduction, biomethylation and complexation, among which microbial oxidation of As is supposed to be the most suitable process to immobilize the dissolved As (Bundschuh and Hollander 2014; Ghosh et al.2014). In addition, phytoremediation (plant-based ecofriendly technology) performs well for the removal of As from contaminated environments by using plants and microorganisms (Rocovich and West

1975; Salt et al. 1995; Pickering et al. 2000; Raskin and Ensley 2000; Lasat 2002; Cherian and Oliveira 2005; Peuke and Rennenberg 2005; Dickinson et al. 2009; Mishra et al. 2011; Behera 2014).

Microfungi have been studied as promising less costlier ecofriendly adsorbents for the removal of heavy metal ions from the environment (Kapoor and Viraraghavan 1995). At pH range of 3–10, negative surface charge of fungi exists normally (Huang et al. 1988). Fungi show a great sorption potential for cationic heavy metal (Akthar et al. 1996; Kapoor et al. 1999; Sag 2001). The remediation of toxic heavy metals by using fungi has been of environmental and scientific interests. The presence of fungi in soils and toxic heavy metal polluted sediments with As, Cd, Cu, Hg, Pb and Zn have been studied extensively. About 33 genera of soil fungi were isolated and identified through routine culture methods from polluted soils (Simonovicova and Frankova 2001).

## 15.2 Possible Remedial Technologies for Arsenic Removal

Remediation of As from the soil or water can be done by applying a range of appropiate methods. Implementation of any suitable remedial technology solely depends on the source of contamination, level of contaminant, rout and distribution of contaminant, and chemical forms and oxidation states of contaminant like As for possible removal and sustainable development (Bhattacharya et al. 2002; Ng et al. 2004; Srivastava et al. 2011).

### *15.2.1 Soil Remediation Techniques*

Presence of As in soil is because of natural or anthropogenic activities. There are various methods for remediation As from the contaminated which could be grouped into three approaches i.e. physical, chemical and biological (Mahimairaja et al. 2005). In the physical methods, the concentration of As in the soil could be minimized by combination of both contaminated and uncontaminated soil together resulting in an acceptable level of As dilution (Mahimairaja et al. 2005). Soil washing is another technique which is included in physical methods whereby As polluted soil will be washed by using various concentrations of sulphuric acid, nitric acid, phosphoric acid, hydrogen bromide, some chelating agents and humic substances (Mahimairaja et al. 2005; Tsang and Hartley 2014). The efficiency of the washing solution depends on soil characteristics, the concentration and chemical forms of As present in the soil and washing conditions (Im et al. 2014). Meanwhile, element can immobilise soluble arsenites in sludges and has been successfully applied to stabilize As-rich sludges which may be appropriate method for treating sludges produced from precipitative As removal units (Sullivan et al. 2010). Remediation of As from soil can also be done by chemical fixation method. Chemical fixation is considered as one of the best

removal techniques, as it suspends and mobilizes As in the soil. Chemical fixation of As in soil can be carried out by adding some chemical additives such as lime, ferric hydroxide and ferrous sulphate. In chemical fixation, As in soil binds well with ferrous compounds and is converted into ferric arsenate. The conversion into stable phases is beneficial for the stabilization process. Electroremediation is another As removal technique by applying direct current (DC) through electromigration, electroosmosis or electrophoresis.

### *15.2.2 Water Remediation Techniques*

There are various As removal techniques from water which help in minimizing high As level to minimum detection level of 1–2 μg/l As. Now a days sustainable, eco-friendly, cost effective and efficient remedial technologies are promising for As removal (Ng et al. 2004). There are some common As removal methods from contaminated water such as adsorption, oxidation, ion exchange, lime treatment, chemical precipitation, chemical coagulation, bioremediation, phytoremediation and hybrid membrane technique (Bhattacharya et al. 2002; Ng et al. 2004).

## 15.3 Biological Remediation

Plants and microbes have potential for As removal in soil (Valls and Lorenzo 2002; Ahmed et al. 2005, 2006; Arenas-Lago et al. 2019). Bioremediation is a microbe-based process which is basically used to treat the polluted soil and degrade the pollutants through the changing of physical and biological environmental conditions to stimulate the microbial growth. Bioconversion of inorganic As to organic As compounds through microbial process is the simplest and ecofriendly As removal method (Bhattacharya et al. 2002). Bioremediation technology process includes degradation, stabilization or volatilization of pollutants from contaminated sites by the application of microorganisms (fungi and bacteria) (Andrews et al. 2000; Bhattacharya et al. 2002; Dhuldhaj et al. 2013; Alcántara-Martínez et al. 2018; Awasthi et al. 2018). As can be removed from contaminated sites by various microbial processes like oxidation, reduction, mobilization and immobilization, sorption, complexation and biomethylation (Das et al. 2016). Oxidation of arsenite As (III) to arsenate As (V) by the application of microorganisms is assessed as one of the most effective methods to immobilize As from dissolved state (Oremland and Stolz 2005; Bundschuh and Hollander 2014; Ghosh et al. 2014; Tiwari et al. 2016). Oxidation and biomethylation by microbes are the important processes for As removal. Oxidation has been assessed effective in As-polluted aerated water (Osborne and Ehrlich 1976; Ahmann et al. 1997). Remediation of As through biomethylation by fungi was assessed both in both aerobic and anaerobic environments (Cox and Alexander

1973a, b, c; Andrews et al. 2000). Biomethylation rate is based on certain environmental conditions like $p^H$, temperature and redox potential (Fergussan 1990; Wallschlager and London 2008). Generally, methylation of As is occured under nitrogen or phosphate-deficient condition, however, nitrate and sulphate concentrations can be minimized by some bacterial metabolic processes (Bhattacharya et al. 2002; Luongo and Ma 2005). Biomethylation through filamentous fungi has been studied extensively (Huysmans and Frankenberger 1991; Andrews et al. 2000). Several bioremediators like *Candida humicola, Gliocladium roseum, Scopuariopsis brevicaulis, Penicillium* spp., *Aspergillus niger, Bacillus arsenoxydans* and *Pseudomonas putida* are known for their remediation potential (Ferguson and Gavis 1972; Dhuldhaj et al. 2013). *Glomus mosseae* and *Glomus caldonium* isolated from As-contaminated mine-spent soil are highly resistant to As pollution. Different As-resistant fungi like *Penicillium janthinellum, Fusarium oxysporium* and *Trichoderma asperellum* were frequently used for As remediation (Su et al. 2011).

## 15.4 Remediation Potential of Fungi (Mycoremediation)

Microfungi have been proved as effective ecofriendly and low-cost adsorbents for the removal of heavy metals from the contaminated environment (Kapoor and Viraraghavan 1995). At pH range of 3–10, fungi possess negative charge at the surface normally (Huang et al. 1988). Researches have proved that microfungi have excellent remediation potential (Akthar et al. 1996; Kapoor et al. 1999; Sag 2001). Soil fungi are normally available in the environments contaminated with toxic heavy metals such as As, Cd, Cu, Hg, Pb and Zn have been broadly studied. About 33 genera of soil fungi were isolated and identified from these contaminated soils by using routine culturing methods (Simonovicova and Frankova 2001). *Penicillium* and *Aspergillus* spp. were realized as very efficient metal tolerant species showing increased growth even at high heavy metal concentrations (2000 mg $l^{-1}$) (Valix et al. 2001). Solubilization, transformation, and uptake of metal species are important characteristics of soil fungi as potential bioremediators. These capabilities of soil fungi are important portion of their metabolism in natural and artificial (laboratory and industrial) conditions (Visoottiviseth and Panviroj 2001). It has been observed that fungi can tolerate, biosorb and detoxify toxic metals through various mechanisms like active uptake, valence transformation and intra and extracellular precipitation (Zafar et al. 2007). Wastewaters polluted with metal(loid)s can be effectively remediated through fungal biosorption (Pumpel and Schinner 1993; Volesky et al. 1993; Ceribasi and Yetis 2001; Cernansky et al. 2007a, b).

As pollution of soil can be remediated through interchange between toxic and non-toxic forms, and soluble and insoluble forms by soil fungi which shows their remediation potential. As is biomethylated to mono methylarsonic acid (MMAA), dimethylarsinic acid (DMAA) and trimethylarsine oxide (TMAO) by fungi (Gadd 1993, 2004; Turpeinen et al. 2002). Qin et al. (2006) have also observed that As can be volatilized into gaseous arsines through several microbial activities. It was

also observed that as much as $2.1 \times 10^7$ kg of As could be removed from land to the atmosphere through microbial volatilization process annually. Various fungal species like *Aspergillus glaucum*, *Candida humicola*, *Gliocladium roseum*, *Penicillium gladioli*, *Fusarium* spp. and *Scopulariopsis brevicaulis* were found potential bioremediators to transform As into volatile trimethylarsine through reductive methylation process from the environments contaminated with inorganic and methylated As species (Cullen and Reimer 1989; Su et al. 2011) (Table 15.1).

In nineteenth century, there were several poisoning incidents in England and Germany ocurred by a volatile and toxic methylarsine gas which promoted the importance of fungal metabolism towards As remediation. The toxic trimethylarsine gas was assessed with a characteristic garlic-like odour where victims lived (Challenger 1945). Production of toxic trimethylarsine gas was noticed by the activity of fungi developing on wallpaper containing arsenical pigments such as Scheele's green and Schweinfiirter green. After that, several fungal species have been isolated and identified as potential agents for As volatilization (Cox and Alexander 1973a). Trimethylarsine can be produced by *Penicillium brevicaule* (*Scopulariopsis brevicaulis*) fungus when cultured on bread crumbs having either methylarsonic acid (MAA) or dimethylarsinic acid (DMA). Challenger (1945) proposed a biochemical

**Table 15.1** Reported soil fungi in arsenic bioremediation

| Fungi | Mechanism | References |
|---|---|---|
| *Penicillium* sp. | Methylarsonic and dimethylarsinic acid methylation to trimethylarsine | Huysmans and Frankenberger (1991) |
| *Aspergillus* sp. | As biosorption | Pokhrel and Viraraghavan (2006) |
| *Fusarium oxysporum* | As(V) accumulation and methylation into dimethylarsine | Granchinho et al. (2002) |
| *Saccharomyces cerevisiae* | As biosorption | Volesky et al. (1993) |
| *Zygosaccharomyces* sp. | As biosorption | Murugesan et al. (2006) |
| *Trichoderma viride* | As biosorption | Mukherjee and Gopal (1996) |
| *Scopulariopsis brevicalue* | As(V) methylation to arsine | Andrews et al. (2000) |
| *Ulocladium* sp. | As(V) methylation to arsine | Edvantoro et al. (2004) |
| *Sphaerotilus* sp. | Iron oxidization and thus arsenic precipitation | Pellegrin et al. (1999) |
| *Pichia sp.* | As biosorption | Murugesan et al. (2006) |
| *Ralstonia eutropha* | As biosorption | Mondal et al. (2008) |
| *Mucor rouxii* | As biosorption | Satari and Keikhosro (2018) |
| *Candida humicola* | Monomethylarsenic acid to trimethylarsine | Huysmans and Frankenberger (1991) |
| *Gliocladium roseum* | Monomethylarsenic acid to trimethylarsine | Tamaki and Frankenberger (1992) |
| *Rhizopus arrhizus* | As biosorption | Gadd (2004) |

assay for trimethylarsine production. Three different fungal species such as *Candida humicola*, *Gliocladium roseum* and *Penicillium* sp., have been proved capable for transforming MAA and DMA into trimethylarsine (Cox and Alexander 1973a, b).

The following equation shows trimethylarsine formation through fungal methylation:

$$\text{MAA} \sim \text{DMA} \rightarrow \text{trimethylarsine oxide} \sim \text{trimethylarsine}$$

As-methylating fungi such as *Penicillium janthinellum*, *Fusarium oxysporum*, and *Trichoderma asperellum* can transform dimethylarsinic acid [DMA(V)] into As(V) and As(III) through methylation. As methylation involves the transformation of aqueous or solid inorganic As into gaseous arsines. Obviously, gaseous arsines are more mobile than aqueous As form. It was studied that aqueous forms of trivalent and pentavalent methyl As have less mobilization capacity due to their lower adsorption affinity (Mukai et al. 1986; Lafferty and Loeppert 2005; Huang and Matzner 2006). Intracellular methylation occurs in *Penicillium janthinellum*, *Fusarium oxysporum* and *Trichoderma asperellum* (Su et al. 2012). Generally, As biomethylation involves transformation of inorganic forms to organic forms such as MMA, DMA, TMAO, MMA (III), DMA (III) or sometime arsines as gaseous forms (Sanders 1979; Takamatsu et al. 1982; Oremland and Stolz 2003). Among different effective fungal strains, *Trichoderma* is genetically very diverse having many capabilities with agricultural as well as environmental significance. Researches shows that *Trichoderma* is very tolerant to various recalcitrant pollutants like heavy metals, polyaromatic hydrocarbons and pesticides (Azevedo et al. 2000; Harman et al. 2004a; Chulaksananukul 2008; Ahamed and Vermette 2009; Contrras-Carnejo et al. 2009; Lorito et al. 2010). Genus *Trichoderma* is a soil inhabiting telomorphic filamentous fungus which belongs to Hypocreales order of the Ascomycota division. Along with several capabilities like plant growth promotion, soil fertilization, disease suppressiveness and composting capacities, *Trichoderma* has been proved as a potential biocontrol agent in agriculture (Chulalaksananukul 2008; Contreras-cornejo et al. 2009; Lorito et al. 2010). Several strains of the genus *Trichoderma* show high biodegradation capability and possess soil colonization and fertilization capacities (Harman et al. 2004a, b; Lorito et al. 2010). The strategies for remediation of heavy metals and other inorganic contaminants adopted by *Trichoderma* can be grouped in following four categories.

### *15.4.1 Biosorption*

The capacity of organisms to uptake and accumulate heavy metals from contaminated soil and wastewater by physico-chemical or metabolism-mediated processes is called biosorption. Biosorption includes metabolism-independent association with negatively charged free groups present in various biopolymers which finally integrated to the cell wall of microorganisms (Volesky et al. 1993; Gomes et al. 1998; Errasquin

and Vazquez 2003; Cernansky et al. 2007a, b; Ting and Choong 2009). Heavy metal biosorption by fungi was proved as an another important removal option for heavy metal-polluted wastewater (Kapoor and Viraraghavan 1995; Say et al. 2003).

### *15.4.2 Bioaccumulation*

Bioaccumulation is an active and energy-dependent metal remediation process by living cells (Benson et al. 1981; Alguacil and Merino 1998; Gomes et al. 1998; Errasquin and Vazquez 2003; Ting and Choong 2009). Several heavy metals such as As, Cd, Cu and Zn can be removed by certain species of *Trichoderma* in vitro through bioaccumulation process (Errasquin and Vazquez 2003; Zeng et al. 2010).

### *15.4.3 Biovolatilization*

Biovolatilization is an enzyme-dependent transformation of inorganic and organic forms into volatile forms of metal(loid)s through intracellular biomethylation (Mukhopadhyay et al. 2002). *Tricoderma asperellum* and *Tricoderma viridae* were assessed as potential As remediator from contaminated liquid environment by biovolatilization process (Urik et al. 2007; Zeng et al. 2010; Srivastava et al. 2011).

### *15.4.4 Phytobial Remediation*

Phytobial remediation is also known as microbe-assisted phytoremediation which is employed for bioremediation of pollutants by the application of plants and microbes (Watanbe 1997; Wenzel et al. 1999; Schmoger et al. 2000; Loureiro et al. 2006; Khan et al. 2009; Farnese et al. 2014). *Trichoderma*-plant association has the ability to remove the polluted sites because such association possess metal detoxifying abilities which combined with other physiological processes like capacity to degrade inorganic environmental contaminants (Cao et al. 2004).

## 15.5 Future Prospects and Challenges

Recently the remediation potential of fungal strains to break down various toxic metal contaminants present in soil and water have assessed very useful. It is not important that fungal strains are native or externally introduced to the contaminated sites but the process of remediation of environmental contaminants is significant and critical for explaining mycoremediation. However, despite being the microbes dominating

biomass in soil, fungi have not yet been significantly explored for remediation of such environmental contaminants. Much critical studies need to be carried out on the application of fungi in mycoremediation. Further, the use of mycoremediation technology at large level will certainly need more research works to set the methods for future studies. Once the proper research and development gets established such technology will be fruitful at the local, state and federal levels but it requires appropiate funding and also the time to do so. Extensive researches should be carried out to prove such strategy for successful remediation of toxic heavy metals like As from the environment. Scientists think that this technology is supposed to be easier, faster and cheaper than other remediation technologies once it is established commercially. The application of fungi for mycoremediation would allow industries to offer cost-effective, safe products to As-affected population. If the remediation ability of fungal strains is further used with modern thechnologies it will certainly be a great strategy to get rid of As contamination from the polluted environments (soil and water).

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## References

Abbas M, Cheema KJ (2014) Correlation studies of arsenic level in drinking water and hair samples of females in District Sheikhupura, Pakistan. Int J Current Microbiol Appl Sci 3(8):1077–1085

Abedin MJ, Feldmann J, Meharg AA (2002) Uptake kinetics of arsenic species in rice plants. Plant Physiol 128:1120–1128

Abernathy CO, Liu Y, Longfellow D et al (1999) Arsenic health effects, mechanisms of actions, and research issues. Environ Health Perspect 107:593–597

Ahamed A, Vermette P (2009) Effect of culture medium composition on *Trichoderma reesei's* morphology and cellulase production. Biores Technol 100:5979–5987

Ahmann D, Krumholz LR, Hemond HF, Lovley DR, Morel FMM (1997) Microbial mobilization of arsenic from sediments of the Aberjona watershed. Environ Sci Technol 31(10):2923–2930

Ahmed MF, Ahuja S, Alauddin M, Hug SJ, Lloyd JR, Pfaff A et al (2006) Ensuring safe drinking water in Bangladesh. Science 314:1687–1688

Ahmed I, Hayat S, Pichtel J (eds) (2005) Heavy metal contamination of soil: problems and remedies. Science Publishers, Inc, Enfield

Ahsan N, Lee DG, Kim KH et al (2010) Analysis of arsenic stress-induced differentially expressed proteins in rice leaves by two-dimensional gel electrophoresis coupled with mass spectrometry. Chemosphere 78:224–231

Akthar MN, Sastry KS, Mohan PM (1996) Mechanism of metal ion biosorption by fungal biomass. Biometals 9:21–28

Alcántara-Martínez N, Figueroa-Martínez F, Rivera-Cabrera F, Gutiérrez-Sánchez G, Volke-Sepúlveda T (2018) An endophytic strain of *Methylobacterium* sp. increases arsenate tolerance in *Acacia farnesiana (L.)* Willd: a proteomic approach. Sci Total Environ 625:762–774. https://doi.org/10.1016/j.scitotenv.2017.12.314

Alguacil FJ, Merino Y (1998) Biotratamiento de contaminantes de origen inorga´nico. Rev Metal Madrid 34:428–436

Andrews P, Cullen WR, Polishchuk E (2000) Arsenic and antimony biomethylation by *Scopulariopsis brevicaulis*: interaction of arsenic and antimony compounds. Environ Sci Technol 34(11):2249–2253

Arenas-Lago D, Abreu MM, Couce LA, Vega FA (2019) Is nanoremediation an effective tool to reduce the bioavailable As, Pb and Sb contents in mine soils from Iberian Pyrite Belt? Catena 176:362–371

Awasthi S, Chauhan R, Dwivedi S, Srivastava S, Srivastava S, Tripathi RD (2018) A consortium of alga (*Chlorella vulgaris*) and bacterium (*Pseudomonas putida*) for amelioration of arsenic toxicity in rice: a promising and feasible approach. Environ Exp Bot 150:115–126. https://doi.org/10.1016/j.envexpbot.2018.03.00

Azevedo AMC, de Marco JLD, Felix CR (2000) Characterization of an amylase produced by a *Trichoderma harzianum* isolate with antagonistic activity against *Crinipellis perniciosa*, the causal agent of witches' broom of cocoa. FEMS Microbiol Lett 188:171–175

Azevedo H, Gomes C, Fernandes J et al (2005) Cadmium effects on sunflower growth and photosynthesis. J Plant Nutr 28:2211–2220

Behera KK (2014) Phytoremediation, transgenic plants and microbes. Sustain Agric Rev 13:65–85

Beiyuan J, Li JS, Tsang DCW, Wang L, Poon CS, Li XD, Fendorf S (2017) Fate of arsenic before and after chemical-enhanced washing of an arsenic-containing soil in Hong Kong. Sci Total Environ 599–600, 679–688

Benson LM, Porter EK, Peterson PJ (1981) Arsenic accumulation, tolerance and genotypic variation in plants on arsenical mine wastes in SW England. J Plant Nutr 3:655–666

Bhattacharya P, Jacks G, Frisbie SH, Smith E, Naidu R, Sarkar B (2002) Arsenic in the environment: a global perspective. In: Sarkar B (ed) Heavy metals in the environment. Marcel Dekker. Inc., New York, pp 147–215

Breckle CW (1991) Growth under heavy metals. In: Waisel Y, Eshel A, Kafkafi U (eds) Plant roots: the hidden half. Marcel Dekker, New York, pp 351–373

Bundschuh J, Hollander H (2014) In-situ remediation of arsenic contaminated sites. IWA Publishers

Cao X, Ma LQ, Tu C (2004) Antioxidative responses to arsenic in the arsenic hyperaccumulator Chinese brake fern (*Pteris vittata* L.). Environ Pollut 128:317–325

Ceribasi IH, Yetis U (2001) Biosorption of Ni (II) and Pb (II) by *Phanerochaete chrysosporium* from a binary metal system—kinetics. Water S A 27:15–20

Cernansky S, Urik M, Sevc J, Littera P, Hiller E (2007a) Biosorption of arsenic and cadmium from aqueous solutions. Afr J Biotechnol 6:1932–1934

Cernansky S, Urık M, Sevc J, Khun M (2007b) Biosorption and biovolatilization of arsenic by heat-resistant fungi. Env Sci Pollut Res 14:31–35

Challenger F (1945) Biological Methylation. Chem Rcv 36(315–361):1985

Cherian S, Oliveira MM (2005) Transgenic plants in phytoremediation: recent advances and new possibilities. Environ Sci Technol 39:9377–9390

Chulalaksananukul W (2008) Construction of cellulase hyperproducers of *Trichoderma reesei* by genetic techniques. Sci Forum 100

Contreras-Cornejo HA, Macias-Rodriguez L, Cortes-Penagos C, Lopez-Bucio J (2009) *Trichoderma virens*, a plant beneficial fungus, enhances biomass production and promotes lateral root growth through an auxin-dependent mechanism in Arabidopsis. Plant Physiol 149:1579–1592

Cox DP, Alexander D (1973a) Effect of phosphate and other anions on trimethylarsine formation by *Candida humicola.* Appl Microbiol 25(3):408–413

Cox DP, Alexander M (1973b) Effect of phosphate and other anions on trimethylarsine formation by Candida humh'ola. Appl Microbiol 25:408–413

Cox DP, Alexander M (1973c) Production of trimethylarsine ga+,; fi'om various arsenic compounds by three sewage fungi. Bull Environ Contam Toxicoi 9:84–88

Cullen WR, Reimer KJ (1989) Arsenic-speciation in the environment. Chem Rev 89:713–763

Das S, Jean JS, Chou ML, Rathod J, Liu CC (2016) Arsenite-oxidizing bacteria exhibiting plant growth promoting traits isolated from the rhizosphere of *Oryza sativa* L.: implications for

mitigation of arsenic contamination in paddies. J Hazard Mater 302:10–18. https://doi.org/10.1016/j.jhazmat.2015.09.044
Dey TK, Banerjee P, Bakshi M, Kar A, Ghosh S (2014) Groundwater arsenic contamination in West Bengal: current scenario, effects and probable ways of mitigation. Int Lett Nat Sci 8(1):45–58
Dhuldhaj UP, Yadav IC, Singh S, Sharma NK (2013) Microbial interactions inthe arsenic cycle: adoptive strategies andapplications inenvironmental management. Rev Environ Contam T 224:1–38
Dickinson NM, Baker AJM, Doronila A, Laidlaw S, Reeves RD (2009) Phytoremediation of inorganics: realism and synergies. Int J Phytoremediat 11:97–114
Edvantoro BB, Naidu R, Megharaj M, Merrington G, Singleton I (2004) Microbial formation of volatile arsenic in cattle dip site soils contaminated with arsenic and DDT. Appl Soil Ecol 25:207–217
Errasquin EL, Vazquez C (2003) Tolerance and uptake of heavy metals by *Trichoderma atroviride* isolated from sludge. Chemosphere 50:137–143
Farnese FS, Oliveira JA, Farnese MS, Gusman GS, Silveira NM, Siman LI (2014) Uptake of arsenic by plants: effects on mineral nutrition, growth and antioxidant capacity. IDESIA (chile) 32(1):99–106
Ferguson JF, Gavis J (1972) A review of the arsenic cycle in natural waters. Water Res 6:1259–1274
Fergusson JE (1990) The heavy elements: chemistry, environmental impact and health effects. Pergamon Press, Oxford, p 614
Gadd GM (1993) Interactions of fungi with toxic metals. New Phytol 124:25–60
Gadd GM (2004) Microbial influence on metal mobility and application for bioremediation. Geoderma 122:109–119
Ghosh D, Bhadury P, Routh J (2014) Diversity of arsenite oxidising bacterial communities in arsenic rich deltaic aquifers in West Bengal, India. Front Microbiol 602:1–14. https://doi.org/10.3389/fmicb.,00602
Gomes NCM, Mendonca-Hagler L, Savvaidis I (1998) Metal bioremediation by microorganisms. Rev Microbiol 29:85–92
Granchinho SCR, Franz CM, Polishchuk E, Cullen WR, Reimer KJ (2002) Transformation of arsenic (V) by the fungus Fusarium oxysporum melonis isolated from the alga Fucus gardneri. Appl Organomet Chem 16:721–726
Gunes A, Pilbeam DJ, Inal A (2008) Effect of arsenic-phosphorus interaction on arsenic-induced oxidative stress in chickpea plants. Plant Soil 314:211–220
Harman GE, Lorito M, Lynch JM (2004) Uses of *Trichoderma* spp. to remediate soil and water pollution. Adv Appl Microbiol 56:313–330
Huang JH, Matzner E (2006) Dynamics of organic and inorganic arsenic in the solution phase of an acidic fen in Germany. Geochim Cosmochim Acta 70(8):2023–2033
Huang CP, Westman D, Quirk K, Huang JP (1988) The removal of Cadmium (II) from dilute aqueous solutions by fungal adsorbent. Water Sci Technol 20(11/12):369–376
Hughes MF, Beck BD, Chen Y, Lewis AS, Thomas DJ (2011) Arsenic exposure and toxicology: a historical perspective. Toxicol Sci 123(2):305–332
Huysmans KD, Frankenberger WT (1991) Evolution of trimethylarsine by a Penicilliumsp. isolated from agricultural evaporation pond water. Sci Total Environ 105:13–28
Im J, Kim YJ, Yang K, Nam K (2014). Applicability of soil washing with neutral phosphate for remediation of arsenic-contaimninated soil at the former Janghang smelter site. J Soil Groundw Environ 19:45–51
Kabata-Pendias A, Pendias H (2001) Trace elements ion soils and plants, 3rd edn. CRC Press, Boca Raton
Kapoor A, Viraraghavan T (1995) Fungi biosorption-an alternative treatment option for heavy metal bearing wastewaters: a review. Biores Technol 53:195–206
Kapoor A, Viraraghavan T, Cullimore DR (1999) Removal of heavy metals using the fungus *Aspergillus niger*. Bioresource Technol 70:95–104

Khan I, Ahmad A, Iqbal M (2009) Modulation of antioxidant defence system for arsenic detoxification in Indian mustard. Ecotoxicol Environ Saf 72:626–634
Lafferty BJ, Loeppert RH (2005) Methyl arsenic adsorption and desorption behavior on iron oxides. Environ Sci Technol 39(7):2120–2127
Lasat MM (2002) Phytoextraction of toxic metals: a review of biological mechanisms. J Environ Qual 31:109–120
Lorito M, Woo SL, Harman GE, Monte E (2010) Translational research on Trichoderma: from 'Omics to the field. Ann Rev Phytopathol 48:395–417
Loureiro S, Santos C, Pinto G et al (2006) Toxicity assessment of two soils from Jales Mine (Portugal) using plants: growth and biochemical parameters. Arch Environ Contam Toxicol 50:182–190
Luongo T, Ma LQ (2005) Characteristics of arsenic accumulation by Pteris and non-Pteris ferns. Plant Soi, l 277:117
Mahimairaja S, Bolan NS, Adriano DC, Robinson B (2005) Arsenic contamination and its risk management in complex environmental settings. Adv Agron 86:1–82
Mondal P, Majumder CB, Mohanty B (2008) Treatment of arsenic contaminated water in a batch reactor by using Ralstonia eutropha MTCC 2487 and granular activated carbon. J Hazard Mater 153(1–2):588–599
Meharg AA, Hartley-Whitaker J (2002) Arsenic uptake and metabolism in arsenic resistant and non-resistant plant species. New Phytol 154:29–43
Mishra S, Jha AB, Dubey RS (2011) Arsenite treatment induces oxidative stress, upregulates antioxidant system, and causes phytochelatin synthesis in rice seedlings. Protoplasma 248:565–577
Mukai H, Ambe Y, Muku T, Takeshita K, Fukuma T (1986) Seasonal variation of methylarsenic compounds in airborne participate matter. Nature 324(6094):239–241
Mukherjee I, Gopal M (1996) Degradation of chlorpyrifos by two soil fungi Aspergillus niger and Trichoderma viride. Toxicol Environ Chem 57:145–151
Mukhopadhyay R, Rosen BP, Phung LT, Silver S (2002) Microbial arsenic: from geocycles to genes and enzymes. FEMS Microbiol Rev 26:311–325
Murugesan K, Nam I, Kim Y, Chang Y (2006) Decolourization of reactive dyes by a thermostable laccase produced by Ganoderma lucidum in solid state culture. Enzyme Microb Technol 40:1662–1672
Nassar M (2020) In vitro mitigation of arsenic-induced toxicity by reduced glutathione in rat pulpal cells. Euro Endod J. https://doi.org/10.14744/eej.2020.26878
National Research Council (2001) Arsenic in drinking water. National Academy Press, Washington, p 244
Ng KS, Ujang Z, Le-Clech P (2004) Arsenic removal technologies for drinking water treatment. Rev Environ Sci Biotechnol 3:43–53
Oremland RS, Stolz JF (2005) Arsenic microbes and contaminated aquifers. Trends Microbiol 13:45–49. https://doi.org/10.1016/j.tim.2004.12.002
Osborne FH, Ehrlich HL (1976) Oxidation of arsenite by a soil isolated of alcaligenes. J Appl Bacterio l(41):295–305
Pellegrin V, Juretschko S, Wagner M, Cottenceau G (1999) Morphological and biochemical properties of a Sphaerotilus sp. isolated from paper mill slimes. Appl Environ Microbiol 65(1):156–162
Peuke H, Rennenberg H (2005) Phytoremediation. EMBO Rep 6(6):497–501
Pickering IJ, Prince RC, George MJ et al (2000) Reduction and coordination of arsenic in Indian mustard. Plant Physiol 122:1171–1177
Pokhrel D, Viraraghavan T (2006) Arsenic removal from an aqueous solution by a modified fungal biomass. Water Res 40(3):549–552
Polizzotto M, Kocar BD, Benner SG et al (2008) Near-surface wetland sediments as a source of arsenic release to ground water in Asia. Nature 454:505–508

Pumpel T, Schinner F (1993) Native fungal pellets as biosorbent for heavy metals. FEMS Microbiol Rev 11:159–164

Qin J, Rosen BP, Zhang Y, Wang G, Franke S, Rensing C (2006) Arsenic detoxification and evolution of trimethylarsine gas by a microbial Arsenite S-adenosylmethionine methyltransferase. PNAS 103:2075–2080

Raskin I, Ensley D (2000) Phytoremediation of toxicmetals: using plants to clean up the environment. Wiley, New York

Requejo R, Tena M (2005) Proteome analysis of maize roots reveals that oxidative stress is a main contributing factor to plant arsenic toxicity. Phytochemistry 66:1519–1528

Rocovich SE, West DA (1975) Arsenic tolerance in populations of the grass Andropogon scoparius. Science 188:187–188

Roy M, Mukherjee A, Mukherjee S, Biswas J (2014) Arsenic: an alarming global concern. Int J Curr Microbiol App Sci 3(10):34–47

Sag Y (2001) Biosorption of heavy metals by fungal biomass and modeling of fungal biosorption: a review. Sep Purif Methods 30(1):1–48

Saha N, Rahman MS (2020) Groundwater hydrogeochemistry and probabilistic health risk assessment through exposure to arsenic contaminated groundwater of Meghna floodplain, central-east Bangladesh. Ecotoxicol Environ Saf 206:111349

Sahu GK, Upadhyay S, Sahoo BB (2012) Mercury-induced phytotoxicity and oxidative stress in wheat (*Triticum aestivum* L.) plants. Physiol Mol Biol Plants 18(1):21–31

Salt DE, Blaylock M, Kumar NPBA, Dushenkov V, Ensley BD, Chet I, Raskin I (1995) Phytoremediation: a novel strategy for the removal of toxic metals from the environment using plants. Biotechnology 13:468–474

Satari B, Keikhosro K (2018) Mucoralean fungi for sustainable production of bioethanol and biologically active molecules. Appl Microbiol Biotechnol 102(3):1097

Sanders JG (1979) Microbial role in the demethylation and oxidation of methylated arsenicals in seawater. Chemosphere 8(3):135–137

Say R, Yilmaz N, Denizli A (2003) Bisorption of cadmium, lead, mercury, and arsenic ions by the fungus penicillium purpur-ogenum. Sep Sci Technol 38(9):2039–2053

Schmoger ME, Oven M, Grill E (2000) Detoxification of arsenic by phytochelatins in plants. Plant Physiol 122:793–801

Sharma RK, Agrawal M, Marshall F (2007) Heavy metal contamination of soil and vegetables in suburban areas of Varanasi, India. Ecotoxicol Environ Saf 66:258–266

Simonovicova A, Frankova E (2001) Soil micro fungi in toxic and heavy metal environment. Ekol Bratislava 20:242–249

Srivastava PK, Vaish A, Dwivedi S, Chakrabarty D, Singh N, Tripathi RD (2011) Biological removal of arsenic pollution by soil fungi. Sci Total Environ 409:2430–2442

Su SM, Zeng XB, Bai LY, Li LF, Duan R (2011) Arsenic biotransformation by arsenic-resistant fungi *Trichoderma asperellum* SM-12F1, *Penicillium janthinellum* SM-12F4, and *Fusarium oxysporum* CZ-8F1. Sci Total Environ 409:5057e5062

Su SM, Zeng XB, Li LF, Duan R, Bai LY, Li AG, Jiang S (2012) Arsenate reduction and methylation in the cells of *Trichoderma asperellum* SM-12F1, *Penicillium janthinellum* SM-12F4, and *Fusarium oxysporum* CZ-8F1 investigated with X-ray absorption near edge structure. J Hazard Mater 243:364–367

Sullivan C, Tyrer M, Cheeseman CR, Graham NJD (2010) Disposal of water treatment wastes containing arsenic—a review. Sci Total Environ 408(8):1770–1778

Takamatsu T, Aoki H, Yoshida T (1982) Determination of arsenate, arsenite, monomethylarsonate, and dimethylarsinate in soil polluted with arsenic. Soil Sci 133(4):239–246

Tamaki S, Frankenberger WT (1992) Environmental biochemistry of arsenic. In: Ware GW (ed) Reviews of environmental contamination and toxicology, reviews of environmental contamination and toxicology vol 124. Springer, New York, NY

Ting ASY, Choong CC (2009) Bioaccumulation and biosorption efficacy of *Trichoderma* isolates SP2F1 in removing copper (Cu II) from aqueous solutions. World J Microbiol Biotechnol 25:1431–1437

Tiwari S, Sarangi BK, Thul ST (2016) Identification of arsenic resistant endophytic bacteria from *Pteris vittate* roots and characterization for arsenic remediation application. J Environ Manage 180:359–365

Tripathi RD, Srivastava S, Mishra S et al (2007) Arsenic hazards: strategies for tolerance and remediation by plants. Trends Biotechnol 25:158–165

Tsang DC, Hartley NR (2014) Metal distribution and spectroscopic analysis after soil washing with chelating agenets and humic substances. Envrion. Sci. Pollut. R 21:3987–3995

Turpeinen R, Mari PK, Timo K (2002) Role of microbes in controlling the speciation of arsenic and production of arsines in contaminated soils. Sci Total Environ 285:133–145

Urik M, Cernansky S, Sevc J, Simonovicova A, Littera P (2007) Biovolatilization of arsenic by different fungal strains. Water Air Soil Poll 186:337–342

Valix M, Tang JY, Malik R (2001) Heavy metal tolerance of fungi. Miner Eng 14:499–505

Valls M, Lorenzo VD (2002) Exploiting the genetic and biochemical capacities of bacteria for the remediation of heavymetal pollution. FEMS Microbiol Rev 26(4):327–338

Visoottiviseth P, Panviroj N (2001) Selection of fungi capable of removing toxic arsenic compounds from liquid medium. Sci. Asia 27:83–92

Volesky B, May H, Holan ZR (1993) Cd (II) biosorption by *Saccharomyces cerevisiae*. Biotechnol Bioeng 41:826–829

Wallschlager D, London J (2008) Determination of methylated arsenic–sulfur compounds in groundwater. Environ Sci Technol 42(1):228–234

Watanbe ME (1997) Phytoremediation on the brink of commercialization. Environ Sci Technol 31:182–186

Wenzel WW, Adriano DC, Salt D, Smith R (1999) Phytoremediation: a plant-microbe based remediation system. In: Adriano DC et al (eds) Bioremediation of contaminated soils. American Society of Agronomy, Madison, pp 457–508

Xu XY, McGrath SP, Meharg AA, Zhao FJ (2008) Growing rice aerobically markedly decreases arsenic accumulation. Environ Sci Technol 42:5574–5579

Zafar S, Aqil F, Ahmad I (2007) Metal tolerance and biosorption potential of filamentous fungi isolated from metal contaminated agricultural soil. Biores Technol 98:2557–2561

Zeng X, Su S, Jiang X, Li L, Bai L, Zhang Y (2010) Capability of pentavalent arsenic bioaccumulation and biovolatilization of three fungal strains under laboratory conditions. Clean Soil Air Water 38:238–241

# Chapter 16
# Biomarker and Arsenic


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**Abstract** Arsenic exposure may lead to severe health problems for human beings. It affects both males and females non-selectively. The primary signs of arsenic exposure include nausea, abdominal pain, vomiting, and muscular discomfort while chronic exposure may lead to raindrop pigmentation, keratosis, gastrointestinal imbalances, neurological disorder, and cancer. Raindrop pigmentation is the first sign of arsenicosis followed by hyperkeratosis. At present, hairs, nails, and urine are effective biomarkers of arsenic exposure detection while blood, hematological parameters, hormones, tumour markers, and immunological parameters may act as a biomarker for arsenic toxicity in the future. Since, the increase in level of arsenic is directly correlated with an increase in different hormone levels including metabolic hormones including T3, T4, TSH, and steroidal hormones including testosterone, estrogen, and progesterone. The rise in the level of these hormones is directly correlated with the dose and duration of arsenic exposure which showed that not only female hormone estrogen and progesterone but male hormones testosterones are also increased by an increase in arsenic levels. Arsenic is associated with RBCs and it may act as an effective biomarker in finding arsenic load in an individual. Blood arsenic is a very good biomarker to detect arsenic mobilization between different tissues. Free oxygen radicals are showing overexpression due to arsenic exposure. Levels of hydrogen peroxide, superoxide radicals, hydroxyl radicals, peroxyl radicals, and glutathione peroxidase is showing high increase in people getting arsenic exposure. The expression is directly proportional to concentration and duration of exposure which indicate that it may also act as a biomarker for detecting arsenic toxicity. Many tumour markers are increasing in arsenic-induced cancer which showed a direct correlation of these tumour markers with carcinogenesis. The level of arsenic determines the expression of these tumour markers. So, it is concluded that haematological, biochemical, hormonal, and tumour markers may work as biomarkers for future detection of arsenic among people residing in the arsenic hit areas.

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## 16.1 Arsenic Contamination Scenario

Groundwater is the valuable natural resource, with an enormous increase in extraction in past few decades. Hydrogeologists have referred this massive groundwater utilization as the "silent revolution," because it has taken place in many regions of the world in completely uncontrolled and unplanned manner (Stone et al. 2019). Arsenic (As)-mediated contamination of groundwater resources at alarming levels occurs as a result of natural or anthropogenic causes, affecting millions of people from several nations (Ali et al. 2019). The principle source of As release and decrease in its quality are rock-water interactions of aquifer systems (Fendorf et al. 2010). Natural As contamination in groundwater has been observed worldwide, South Asian and South American countries represents majority of its cases (Ravenscroft et al. 2011). According to global data, 107 nations are impacted by As pollution in groundwater beyond the WHO maximum allowed limit of 10 ppb, with Asian and European regions reporting the most cases (Shaji et al. 2021). As contamination is mostly reported from deltas and river basins around the world, such as the Paraiba do Sul delta in Brazil, the Bengal Delta in India and Bangladesh, the Mekong Delta in Cambodia, the Danube River Basin in Hungary, the Hetao River Basin in Mongolia, the Duero Cenozoic Basin in Spain, and the Zenne River Basin in Belgium (Shankar and Shanker 2014). Among the countries that produce As, China is the leading producer of white As, accounting for about half of the global supply, followed by Peru, Chile, and Morocco, and all provinces of China have naturally occurring As concentrations of more than 10 μg/L (Sanjrani et al. 2019). Groundwater As pollution in the Bengal Delta Plain, which includes Bangladesh and the Indian state of West Bengal, has been deemed the world's largest and most devastating ecological disaster for more than three decades (Koley 2022). In Bangladesh, out of 64 districts, 61 had As levels higher than the WHO limit of 10 μg/L for drinkable water (Huq et al. 2020). Groundwater As pollution is currently threatening a population of over 50 million people in India (Chakraborti et al. 2018). In India, 20 states (including West Bengal, Jharkhand, Bihar, Uttar Pradesh, Assam), and four Union territories (Delhi, Puducherry, and Daman and Diu, are affected from groundwater As contamination (Shaji et al. 2021). Around 19% of the Indian population, or almost 25.46 lakh individuals, while around 65% of the Assam population, 60% of the Bihar population, and 44% of the West Bengal population are at high risk of As poisoning (Shukla et al. 2020). As in plain terrain including states like Bihar, Uttar Pradesh, West Bengal, Haryana, and Punjab is primarily derived from alluvium, which rivers deposit over millions of years. However, volcanic rocks in the plateaus including states of Chhattisgarh and Karnataka are blamed for As contamination of groundwater (Ranjan 2019). Aside from groundwater, As has been found in agricultural crops such as rice and other vegetables grown in As-contaminated areas of the Bengal Basin. As in crops

and vegetables is thought to come from As-affected soil and polluted groundwater collected from shallow bore wells for irrigation (Sarkar et al. 2022).

## 16.2 Biomarkers as a Tool for Toxicity Assessment

A biomarker is considered as "any substance, structure, or process that's able to be assessed in the body or its metabolites that regulates or indicates the occurrence of consequence or disease, as well as the impact of therapies, interventions, and sometimes even unintentional contact with chemicals or nutrients" (Strimbu and Tavel 2010). Biomonitoring (or the repeated, regulated assessment of biomarkers in secretions, tissues, or other subject-accessible substances who have been exposed or will be subjected to physical, chemical or biological risk variables at work or elsewhere in the environment) might be utilized to determine chemical doses that may endanger human health (Manno et al. 2010). Biomarkers utilized in human health investigations are often classified into three types. The first is biomarker of effect which include cellular changes, such as changing expression of metabolic enzymes, but they could also be markers for early pathogenic changes in complicated disease development. Sometimes the categorization is ambiguous; for example, DNA adducts might be employed as exposure biomarkers but could also indicate an effect, and susceptibility biomarkers indicate an individual's inherent responsiveness to specific exposures (Watson and Mutti 2004). Heavy metals have long biological half-lives and are hazardous at extremely low levels, the kidney is one of many organs impacted by metals, and its capacity to reabsorb and store divalent metals makes it an important target organ, exposure to metals including As, cadmium, and lead caused increased urine porphyrins excretion, which has been proposed as an useful biomarker for metal exposure, other include lungs, liver, blood, and nervous system (Wang and Fowler 2008). Exhaled air, urine, and tissue samples and blood can all be evaluated for biomarkers (Silins and Högberg 2011). As biomarkers study the impact of As-contaminated water on the health of population. Hair, nails, urine, and blood are among the most often utilised biological samples in epidemiology studies on As health risks (Marchiset-Ferlay et al. 2012).

## 16.3 Health Impacts of Arsenic

The degree of methylation and oxidation state of As can both be used to predict how toxic it will be. A higher methylation state indicates lower toxicity, a lower oxidation number indicates higher toxicity. Therefore, As in trivalent forms (MMAIII > DMAIII > iAsIII) are comparatively more cytotoxic than their pentavalent forms (iAsV > MMAV ≈ DMAV) (El-Ghiaty and El-Kadi 2022). In general, the affinity of trivalent species, both inorganic and organic, for biomolecules containing sulfhydryl

groups, particularly proteins and peptides, can be attributed to their toxic interactions. Covalent interactions between free cysteine (Cys) thiols and neutral trivalent arsenicals can result in structural and functional deviations in the target protein. As has been linked to the inactivation of 200 enzymes because of this (Shen et al. 2013). Hair and nail proteins contain cysteine and have an active -SH group. As accumulates in these keratin tissues, including the hair, nails, sole, and palm (Chakraborti et al. 2017). Additionally, unbound As produces intermediates of reactive oxygen species during its metabolic activation and redox cycling processes, which lead to DNA damage (Ratnaike 2003).

After entering the body, As is distributed throughout many organs, including the skin, liver, lungs, and kidney. As a result, it can be challenging to detect early arsenicosis symptoms as the same symptoms are also present in other chronic conditions (Flora 2020). Epidemiological studies repeatedly confirmed As-related diseases, including cancers, dermal effects, respiratory effects, gastrointestinal effects, neurological effects, cardiovascular effects, and endocrinological effects (diabetes mellitus) (Chakraborti et al. 2017). Symptoms of acute toxicity on the skin include erythema, flushing, facial edema, urticaria, acrodynia, alopecia, nail loss, and Mees lines apparent on nails about eight weeks after exposure and chronic skin manifestations usually involve hyperpigmentation, hypopigmentation that is characterized as "raindrops", punctate hyperkeratosis on the soles and palms, Blackfoot disease, Bowen's disease (BD), squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) (Hunt et al. 2015). Other health effects of As include the development of other types of cancers like lung, bladder, liver, and kidney cancer. Consuming As can also have hematological side effects like anaemia and leukopenia as well as general gastrointestinal complaints like diarrhoea and cramping (Rahman et al. 2009). As exposure over a long period through drinking water may have harmful effects on pregnancy outcomes including stillbirths, preterm births, and spontaneous abortions (Quansah et al. 2015). After exposure to As, adults and children with impaired cognitive and motor abilities show significant neurological impairments (Gong et al. 2011). As causes an increase in mortality rate from pulmonary tuberculosis, and bronchiectasis (Smith et al. 2011). The endocrine effects include altered hormone regulation through thyroid hormone, estrogen, and RAR (retinoic acid receptors), and an increased risk of developing diabetes, especially at higher doses and for exposure periods of more than 10 years (Naujokas et al. 2013).

## 16.4 Biomarkers Showing Association with Arsenic Toxicity

Biomarkers are required for appropriate analysis of As related health hazards and to comprehend the mechanism of As toxicity (Hall et al. 2006). Early detection of As exposure is essential for avoiding As poisoning because there is no cure for endemic arsenicosis. For early diagnosis and prevention, it is possible to measure

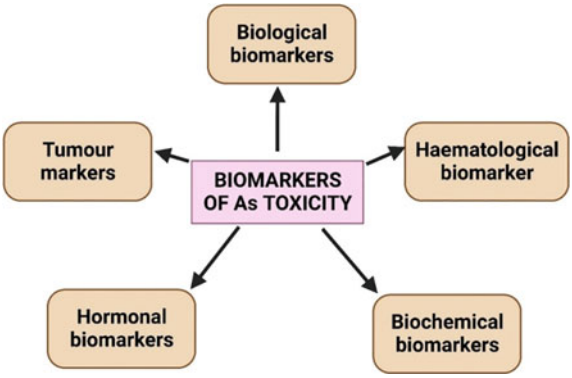


**Fig. 16.1** Common biomarkers expressed with arsenic toxicity

directly the As exposure levels and its detrimental consequences using highly sensitive biomarkers. Currently, the main screening methods for As exposure are urine, blood, hair, and nails, but in recent years, saliva samples have drawn attention from researchers and sparked a lot of interest as a quick, non-invasive detection method (Liu et al. 2017). The analytic assessment of total As (tAs) in urine serves as the most prevalent As biomarker of exposure (Wang et al. 2002). Dermatologic lesions formed after chronic consumption of iAs have been used as a biomarker of accumulative As exposure (Chen et al. 2005). Blood As levels have been suggested as a marker of chronic exposure, although As from acute exposure can be removed off from the blood fairly quickly (McClintock et al. 2012). Some of the typical biomarkers of As exposure are biological biomarkers, haematological biomarkers, biochemical biomarkers, hormonal biomarkers, and tumour markers (Fig. 16.1).

## *16.4.1 Biological Biomarkers Expressed with Arsenic Exposure*

### 16.4.1.1 Dermatological Biomarkers

Skin is assumed to be highly susceptible and to show the initial signs of arsenicosis (Rahman et al. 2009). A study conducted in Bangladesh found that those exposed to water containing 50–100 μg/L of As had a 70% higher risk of developing skin lesions than those exposed to water containing < 10 μg/L, and that this risk increased steadily over time with higher concentration, with a risk that was more than three times higher for those exposed to the highest concentration (≥ 200.1 μg/L) (Argos et al. 2011). A study conducted in China revealed a significantly higher risk of skin lesions beginning at well water concentrations of 5.1 μg/L and continuing to rise as concentration levels increased (Xia et al. 2009). Evidence from Taiwan, South Asia, Mexico, USA, and Eastern Europe supports a similar dose-related pattern in As exposure and skin cancers (Karagas et al. 2015). Abnormal skin manifestations were seen in a total of

125 patients with chronic kidney disease including hyperpigmentation in 54.4% of the palms and 39% of the soles, low keratosis in 23.2% of the palms and 17.6% of the soles, and elevated urinary As levels (Jayasumana et al. 2013). In India, West Bengal, water As concentrations above 50 μg/L also indicated an increase in the risk of dermal manifestations (Haque et al. 2003).

Corns are also visible on the bellies and thorax region. Severe Keratosis was observed in the palm and soles of people residing in West Bengal. Lamellar desquamation and acral hyperkeratosis seen along with changes in nail like Beau's line, total leukonychia, Mees line, dystrophy, periungual pigmentation, and dystrophy are common symptoms of acute exposure whereas spotted melanosis, leukomelanosis, diffuse melanosis or raindrop pattern, mucosal pigmentation, and dyschromia, are symptoms of chronic As toxicity (Figs. 16.2 and 16.3) (Rajiv et al. 2022). Diffused hyperpigmentation is most frequently found over the body areas that are sun-protected, such as palms and soles (Sarma 2015). Spotted melanosis typically manifests as spotty hyperpigmentation that resembles "rain drops on a dusty road" on the trunk back, chest, and limbs (Das et al. 2014). About one-third of patients have leukomelanosis, which is characterized by depigmented macules that appear on normal skin or a background of hyperpigmentation (Saha et al. 1999). When macules are simultaneously hyper and hypopigmented, it is referred to as dyschromia (Sarma 2015) and the mucosal pigmentation develops on the underside of the tongue, gums, or buccal mucosa as diffuse or blotchy pigmentation (Das et al. 2014). These lesions are thought to increase an individual's risk of developing cancer of skin and other types (Ghosh et al. 2007), including skin epithelial cancers, such as intraepidermal carcinomas (Bowen disease), SCC, BCC and there are other indications of negative effects of As including hyperpigmentation, keratosis, and many cutaneous malignancies. (Isokpehi et al. 2012). Bowen's disease manifests as skin-colored scaly macule, or plaque, erythematous, pigmented, can be multiple or solitary. As-induced Bowen's disease and SCC primarily affects skin protected from the sun, whereas BCC primarily affects skin exposed to the sun and frequently comes in large groups, but a greater metastatic potential is exhibited by SCC (Schwartz 1997).

#### 16.4.1.2 Urine as Biomarker

Because urine is the primary method of excretion for the majority of As species, the biomarker most frequently used is urinary As. With a half-life of about four days in humans, absorbed As is excreted via urine primarily (Gomez-Caminero et al. 2001). The body's burden from heavy and prolonged As ingestion take a bit longer to excrete after a stop of ingestion, but small amount remains after exposure has ended (Valentine et al. 1979). The recent development of As-speciation techniques has contributed to the establishment of As-speciation according to its oxidation states. Human urine has been found to contain MMA as MMAIII and DMA as DMAIII and the urinary analysis of MMAIII may be a useful tool for the assessment of health risks linked to iAs exposure due to the harmful biological effects of these metabolites (Marchiset-Ferlay et al. 2012). It is now possible to distinguish between exposure to inorganic and

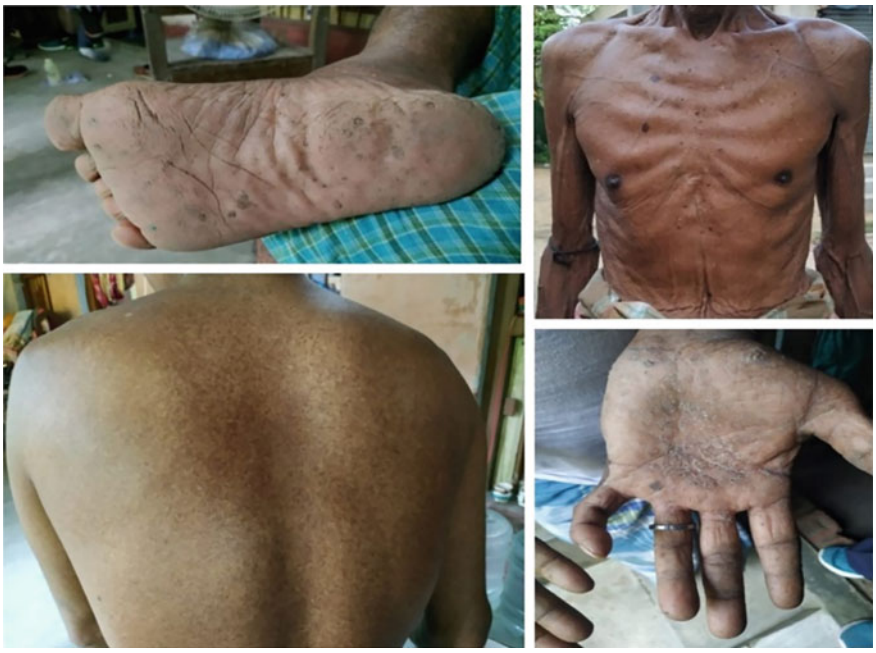

**Fig. 16.2** Severe pigmentation in the back of people residing in the As-hit area

organic As through urine As speciation (Francesconi and Kuehnelt 2004). Urinary As background concentrations range from 5 to 50 μg/L. The determinant value suggested biologic exposure level for iAs exposure in the workplace is 35 μg/L (Hughes 2006). Rasheed et al. (2019) found that males have significantly higher iAs, MMA, and tAs concentrations in urine than females. In women of childbearing age, choline is synthesized under the influence of estrogen; estrogen contributes to choline synthesis by regulating the PMET (Phosphatidylethanolamine N-methyltransferase) pathway which is responsible for this difference in concentrations in male and female.

#### 16.4.1.3 Hairs and Nails as Biomarkers

Various studies have shown that As concentrations in toenails and hair are closely related to those in drinking water and considered as biomarkers for As exposure (Schmitt et al. 2005). Although fingernails and hairs are thought to be more prone to contamination (such as from shampoos, dusts, and some cosmetic procedures), limit their use as biomarkers of long-term As exposure. Fingernails and hairs, similar to toenails having the slow growth rate, similar composition, and their ability of As accumulation (Marchiset-Ferlay et al. 2012). Positive correlations were found between groundwater and nail/hair As concentrations (Gault et al. 2008). As in hairs and nails used to calculate the time length of As exposure. As has an affinity for the

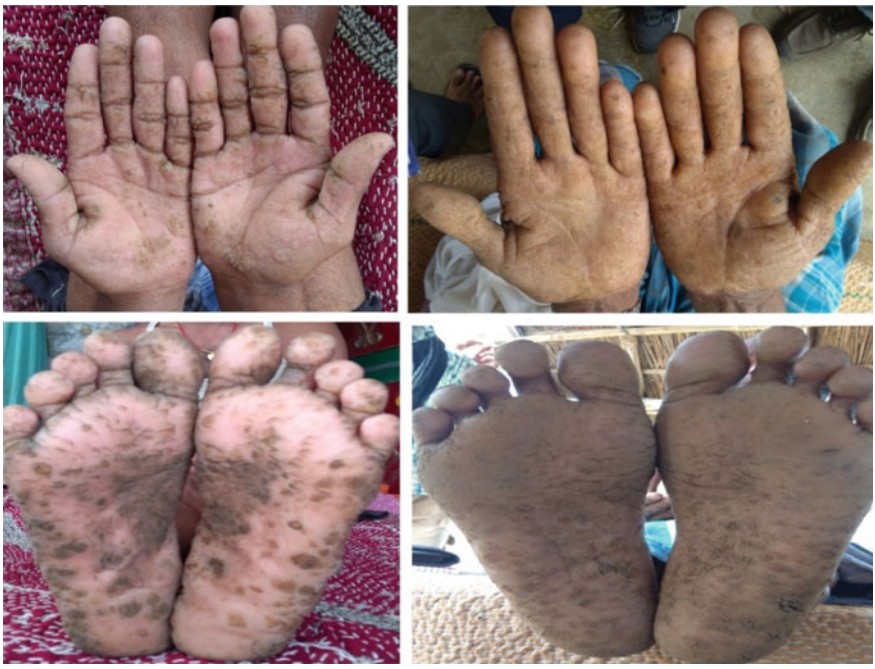

**Fig. 16.3** Severe keratosis found on the palm and sole of people of the young age group (20–25 years) residing in As-hit areas of Bihar (district Begusari)

sulfhydryl groups in cysteine in keratin and therefore, easily accumulates in nails and hairs (Hopps 1977). An increase in 1 mg/L As in drinking-water was predicted to result in 2.7 ng As/g of the toenail (Slotnick and Nriagu 2006). Because toenails are simple to collect and store and are thought to be less prone to external contamination than hair, so are advantageous for large epidemiological studies (Marchiset-Ferlay et al. 2012). Before 30 years ago, methods for determining the amount of As in hair required large samples (1 g), so results had to be the average of many hairs. As levels in individual hairs can now be measured using neutron activation techniques, but efforts to link its toxic effects to As levels in hairs have led to a lot of confusion. The Interpretation of the results are difficult from a single hair as the levels of As within and between hairs differs greatly. Additionally, the avidity with which different subjects' hair samples adsorb As creates challenges in the interpretation of the results (Hindmarsh 2002).

The Asian nations, particularly Bangladesh, China, and India, had the highest concentrations of As in toenails. Toenail As concentrations may correlate with other trace elements that can accumulate there, indicating common exposure sources. As levels in toenails have been linked to cadmium, lead, and manganese concentrations (Signes-Pastor et al. 2019). Male subjects had higher As levels in their toenails, according to Hinwood et al. (2003), whereas female subjects had higher As levels in their fingernails, according to Mandal et al. (2003). Lima (1968) discovered that hair

growth had only increased by about 3.5 mm after start ingesting Fowler's solution, discovered the hair As location 10 days later in humans.

#### 16.4.1.4 Breast Milk as Biomarkers

The reference food for an infant is breast milk because it contains the nutrients required for healthy growth and development as well as biologically active compounds that protect against infections. Breast milk, however, may contain high concentrations of materials that the mother takes from her environment, which could potentially be harmful. Due to the possibility that it serves as a pathway for maternal excretion, heavy metals are regarded as significant hazardous pollutants in human breast milk (Yurdakök 2015). In fact, breast milk regarded as a trustworthy environmental biomarker (Bernasconi et al. 2022). The exposure to As that neonates and infants receive may have negative consequences on their growth and development (Raqib et al. 2009). Fängström et al. (2008) provided the first study that made it clear that the major form of As excreted in breast milk is the arsenite, and that there exists a substantial correlation between the levels of As in milk and maternal blood. Yet, despite their significant As exposures, the rural Bangladeshi women in the study had generally lower As levels in their breast milk (approximately 1 μg/kg. The highest concentrations of As were discovered in cord blood ($Med_{(As)}$3.3 ng/g) and breast milk ($Med_{(As)}$0.8 ng/g) of Greek women (Miklavčič et al. 2013). The mean (SD) levels of As were 1.23 (0.63) μg/L, which may have been caused by metals absorbed by the mother during pregnancy (Kelishadi et al. 2016). These values were greater than those reported from the European countries (De Felip et al. 2014) but were equivalent to the levels recorded from certain Asian nations (Gürbay et al. 2012). According to a study, only 154 out of 187 samples of breast milk from nursing mothers had any measurable levels of As. The study assessed the contamination of the milk throughout the first three months of lactation. In another investigation, the mean As concentration was 0.8 ± 0.66 μg/L, with 3.73 μg/L and As intake for infants per day ranged between 0.01 and 0.17 μg/kg of body weight, which is less than the daily allowance for adults (Salmani et al. 2018). A study in Iran showed As levels (mean ± SD) in breast milk to be 10.75 ± 7.62 μg/L, having the highest levels at 30.10 μg/L in milk samples (Samiee et al. 2019).

### *16.4.2 Haematological Biomarkers Expressed with Arsenic Exposure*

As has an impact on hematological parameters, and changes to these parameters used for assessing As exposure in the environment (Lavanya et al. 2011). Only a few reports on the As speciation in plasma, blood serum, RBCs, or haemolyzed blood have been reported (Marchiset-Ferlay et al. 2012). Blood is a challenging matrix to

deal with in comparison to urine, and invasive sampling makes it more challenging to collect blood samples for epidemiological research. Blood As analysis is more appropriate for acute exposures and can also be used to demonstrate chronic As exposure (Hall et al. 2006).

#### 16.4.2.1 RBC as Biomarkers

After systemic absorption, RBCs are the first target of As compounds (Saha et al. 1999). Studies on the alterations in erythrocyte deformability brought on by As exposure in in-vitro conditions are available. This could have an impact on microcirculation and help to cause circulatory problems (Winski et al. 1997). When exposed to stress caused by As toxicity, RBCs lost their typical discoid shape and began to take on the evaginated shape known as echinocytes, which had protruding spicules. Echinocytes are the evaginated version of discocytes with protruding spicules (Biswas et al. 2008). Erythrocytes' adaptive compensatory technique aims to expand surface area (SA) of membrane relative to their cell volume, which enables the cell to store a significant amount of water (Zeni et al. 2002). The extracellular vesicles that the spicules form after they have irreversibly budded off make RBCs more or less spherical. This results in RBC's decreased SA-to-volume ratio. Membrane instability, hemoglobin release, and intravascular hemolysis are the results of these events. Cell shrinking brought on by the formation of spherocytes results in eryptosis and extracellular hemolysis. All these things affect erythrocyte survival, which finally causes anemia (Biswas et al. 2008). AsV treatment causes degradation of lipids of membrane and changes in internal microviscosity, which alters RBC rheologic properties. These effects impair fluid behavior of blood, which contributes to anemia, which is the clinical manifestations of As chronic intoxication.

#### 16.4.2.2 WBC as Biomarkers

DNA damage in lymphocytes can be employed as a biomarker of As exposure, perhaps indicating a greater sensitivity to As-induced carcinogenicity (Basu et al. 2005). After short-term and low-dose As exposure, leukocytes produced an excess of ROS, causing an imbalance in the antioxidant response. As a result, oxidative stress may be seen as an earlier indicator of cellular damage with potential biological consequences (Reyes-Becerril et al. 2019). PMNs (polymorphonuclear cells) and MNs (mononuclear cells) play a significant role in the immune system's ability to combat pathogens. PMNs phagocytose invading pathogens, which then are destroyed by oxidative and nonoxidative mechanisms. By phagocytosing invading pathogens, PMNs destroy them oxidatively and nonoxidatively (Bhatnagar et al. 2010). The formation of ROS as a defense against xenobiotics is a function of active monocytes (Bauer et al. 2011). In one study, oxidative DNA damage biomarker 8-OHdG was abundantly expressed in peripheral blood PMNs but not in MNs in all individuals studied. By assessing adverse health effects caused by chronic exposure to lower

levels of As directly through peripheral blood PMNs, oxidative stress could serve as a sensitive biomarker (Pei et al. 2013). Neutropenia and lymphocytosis have been linked to persistent exposure to high levels of As in drinking water, which may influence patients' immunological responses (Islam et al. 2004). There have been a number of studies in humans demonstrating a connection between As exposure and changes in global and gene-specific DNA methylation in leukocytes, as well as alterations in DNA methylation associated with health problems triggered by As exposure (Niedzwiecki et al. 2015). The researchers examined the link between As exposure and DNA methylation in maternal and umbilical cord leukocytes. As exposure was also linked to increased methylation of certain of the CpG sites evaluated in the p16 promoter region in the umbilical cord and maternal leukocytes (Kile et al. 2012). An association between chronic exposure to As and the length of leukocyte telomeres (LTL), as well as common polymorphisms in genes involved in As metabolism (GSTT1 and GSTM1) and DNA repair (hOGG1 and XRCC1) have been reported by Borghini et al. (2016). Telomere shortening may contribute to As-related illness. The interaction between hOGG1 and XRCC1 DNA repair polymorphisms leads to increased damage to telomeric DNA. Prenatal As exposure affects specific T-cell subsets and, to a lesser extent, B-cell subsets in cord blood, and As was found to be significantly related to leukocyte subsets, specifically CD + 4 and CD + 8 populations (Kile et al. 2014).

### *16.4.3 Common Biochemical Biomarkers Expressed with Arsenic Exposure*

Certain metals are also redox active, which means they can cause oxidative stress in addition to the biochemical response associated with metal poisoning (Correia et al. 2002).

#### 16.4.3.1 Reactive Oxygen Species (ROS)

An imbalance seen between the generation of ROS and antioxidants in the cell causing oxidative stress (Yaribeygi et al. 2020). ROS includes hydroxyl radicals ($OH^{\bullet}$), hydrogen peroxide, peroxyl radicals ($ROO^{\bullet}$), and superoxide radicals ($O_2^{\bullet -}$) (Pham-Huy et al. 2008).

As is responsible for ROS generation, which causes an imbalance between endogenous antioxidants and pro-oxidants, triggers signaling pathways, leads a cell towards apoptosis (Flora 2011), and overall reduces the defence system mechanism of the body (Manna et al. 2008). Methylated metabolites of iAs are responsible for inducing oxidative stress which is considered as the mechanisms responsible for As-induced carcinogenesis (Yamanaka et al. 1990). A study conducted by Pi et al. (2002) revealed a relation between oxidative stress and As and showed that the high As exposure

group had an elevated level of lipid peroxides (LPO) in serum and an increase in the production of ROS can be the possible reason for this. Prakash et al. (2016) assessed the preferred mechanism responsible for mitochondrial oxidative stress induced by As by increasing generation of oxidative stress within the brain. Apoptosis and the production of ROS through complexes I and III are caused by As's alteration of mitochondrial integrity and membrane potential, which also causes Cyt-c release and apoptotic protein (Bax) activation, decreased Bcl2 expression, and loss of mitochondrial organization (Mishra et al. 2008). Glutathione (GSH) and other thiols are required for the methylation of As, which alters the redox status by the depletion of GSH and other thiols, resulting in As methylation metabolites that increase oxidative stress (Dopp et al. 2010). A membrane-associated enzyme called [NAD(P)H] oxidase (Nox) is implicated in the production of ROS in response to As (Ellinsworth 2015). Other sources of ROS that have been proposed include ER stress brought on by iron released from ferritin and DMA III as a result of methylated As species (Hu et al. 2020).

#### 16.4.3.2 Liver Function Test (LFT)

LFT can assess liver functions, its disorders, and liver injury induced by drugs. Liver is the important target affected by chronic As exposure in humans, with numerous epidemiological studies demonstrating a link between As and liver diseases such as liver fibrosis, hepatomegaly, hepatoportal sclerosis, and cirrhosis of the liver (Mazumder 2005). Because of affinity of $As^{3+}$ for vicinal dithiol in hepatic cytosolic protein, the liver is regarded as the main target of inorganic As (Al-Forkan et al. 2016). Inorganic As metabolism takes place in the liver for As detoxification, and its metabolites are eliminated via urine. Chronic As exposure, on the other hand, can interfere with the liver's detoxifying function, causing As bioaccumulation in this organ (Souza et al. 2018). Chronic As exposure is also related to dysregulated liver functions characterized by severe disturbances of gastrointestinal tract and clinical increases of liver enzymes including alanine amino transferase (ALT), aspartate amino transferase (AST), and alkaline phosphatase (ALP) (Guha 2001). The total protein is a biomarker for the synthesizing capability of the liver (Thapa and Walia 2007). One study discovered that serum levels of ALT, AST, ALP, and bilirubin were considerably higher in the As-exposed population than in the unexposed group which clearly show that prolonged As exposure induces hepatocyte injury, including cholestatic injury, and reduction of the its biosynthetic capacity (Das et al. 2012). Liver enzyme activities found to be considerably greater in the As exposed group (> 50 μg/L), and enhanced enzyme activity were seen in the 10.1–50 μg/L exposure group when compared to the group exposed with 10 μg/L (Islam et al. 2011). During 90-day sodium-arsenite exposure research, there was a considerable rise in blood liver enzyme activity of As-intoxicated rats (Al-Forkan et al. 2016).

#### 16.4.3.3 Kidney Function Test (KFT)

Kidney is the primary organ of excretion of As, as well as renal damage caused by As exposure (Nordberg 2010). Hong et al. (2004) verified dose–effect association between As levels and urine indications of early kidney impairment, with albumin having the highest sensitivity. Several effective biomarkers of As-induced kidney injury include N-acetyl-beta-D-glucosaminidase (NAG), 2-microglobulin (2-MG), microalbumin (mALB), and retinol-binding protein (RBP) (Feng et al. 2013). Urinary α1-MG can serve as a potential biomarker of kidney damage caused by low levels of As exposure, while MMA and t-As may represent As exposure biomarkers (Feng et al. 2013). Urinary RBP and 1-MG were found to be significantly higher in the medium and severe As toxicity groups than in the control group, and transferrin (TRF) significantly increased in the severe toxicity group compared to the control group, indicating that renal tubular impairment became more severe with increased As poisoning (Zhang et al. 2006). Yang et al. (2000) observed that serum and urinary 2-MG levels in patients with chronic As poisoning induced by coal-burning were considerably higher than controls, implying that As exposure from coal-burning could disrupt renal tubular reabsorption performance. Chronic exposure to 100 ppb sodium arsenite in drinking water caused a rise in the acute-phase protein C-reactive protein (CRP) in the liver and kidney of mice (Druwe et al. 2012). As exposure was linked to reduced plasma GSH (glutathione) and EhGSH (reduction potential of the GSSG/2GSH pair) (GSSG glutathione disulfide), as well as an elevated risk of As-induced inflammation (Peters et al. 2015).

### *16.4.4 Hormonal Biomarkers Expressed with Arsenic Exposure*

#### 16.4.4.1 Effect on Estrogen Level

Ovaries produce estrogen hormone and inhibin that regulate the hypothalamic-pituitary axis through a feedback mechanism and regulate levels of FSH and LH (Nilsson and Gustafsson 2002). As is a potent endocrine disruptor that can mimic estrogen and thereby activate estrogen receptors, stimulating its production (Xu et al. 2014). $NaAsO_2$ (Sodium arsenite) is responsible for a decrease in levels of estradiol and disrupts the signaling pathway of estrogen either by decreasing the action of ER and estrogen-responsive genes or generating ROS which is responsible for oxidative disruption of proteins that are involved in the signaling pathway of estrogen and regulate structure as well as the function of the uterus (Chatterjee and Chatterji 2010). As binds to Cys residues of ER (Estrogen receptors) and GR, blocks ligand and receptor interaction, and suppresses functions of the target proteins (Stancato

et al. 1993). When estrogen binds to $ER_\alpha$ and $ER_\beta$ as well as to nuclear receptors, its action is activated (Gangopadhyay et al. 2019). As may act as an environmental estrogen substance by interacting with the ER receptor to generate the As-ER complex, which can increase the expression of ER and disrupt the ER signal pathway, thereby impacting the development of cancer (Che et al. 2019). $As^{+3}$ (arsenite) acts as either a competitive antagonist or agonist depending on endogenous estrogen levels and reactivates $ER_\alpha$ via $ER_\alpha$ promoter's demethylation which is inactive due to the process of hypermethylation (Du et al. 2012). A study conducted by Chatterjee and Chatterji (2010) showed that As downregulates the estrogen receptor and estrogen-responsive genes but Chen et al. (2022) discovered that exposure to As caused an increase in estradiol levels. Zhang et al. (2022) found a positive association between As exposure and estradiol. Davey et al. (2007) demonstrated the effect of As on ER using human breast cancer MCF-7 cell lines. Cell treated with the non-cytotoxic level of As (0.25–3 μM) inhibits genomic activation mediated by estradiol, whereas no stimulatory effect at a low exposure level of As. $As_2O_3$ shows interaction with the MAPK pathway and is responsible for the reduction in the level of $ER_\alpha$ (Bae-Jump et al. 2008) whereas does not affect $ER_\beta$ (Chen et al. 2002). $As_2O_3$ at low concentration (0.25–1 μM) inhibits cell proliferation induced by estradiol and at higher concentration (2 μM), apoptosis is stimulated in MCF-7 Breast cancer cell lines (Chow et al. 2004). Cells treated with 1 μM arsenite have resulted in a 60% reduction in the amount of ER-α and a 40% reduction in ER-αmRNA in a parallel way (Stoica et al. 2000).

#### 16.4.4.2 Effect on Testosterone Level

Leydig cell maintains the structure and function of seminiferous tubules and is responsible for the synthesis of testosterone which is required in post-meiotic spermatogenesis stage (Sharpe et al. 1990). As affects the production of testosterone. Mice treated with As show degeneration of Leydig cells which in turn affects testosterone production (Hazra et al. 2008). As exposure results in a reduction in morphometric parameters of the testis, and testosterone levels, thereby As exposure caused reproductive abnormalities (Souza et al. 2021). In healthy animals, As bioaccumulation in testis and epididymis tissues disturbs antioxidant enzyme activities (Souza et al. 2019). $NaAsO_2$ treatment degraded testicular structure, decreased activity levels of catalase and testicular superoxide dismutase, and increased levels of lipid peroxidation are all connected with decreased levels of testicular steroidogenic enzymes such as 3- and 17-hydroxysteroid dehydrogenases (Venkaiah et al. 2022). Chiou et al. (2008) concluded that As treatment results in impairment in the reproductive system of a male which in turn causes atrophy of seminiferous tubules, hampers the testosterone pathway, and later disrupts spermatogenesis. Upon treatment of As (3 mg/kg b.w) in mice, the level of testosterone decreases from 2.7 to 2.5 ng/ml after 2 weeks which further decreases to 1.31 ng/ml after 8 weeks which demonstrates that testosterone level gradually declines when the duration of As exposure increase (Kumar et al. 2013). An in vitro research conducted by Tian et al.

(2021) on Leydig cells demonstrated that low-dose As exposure has an endocrine-disrupting effect by promoting Leydig cell steroidogenesis and increasing urinary steroid excretion and that high-dose As exposure has an opposite relationship with the production of sex steroid hormones. In Leydig and Sertoli cells, exposure to As decreased cell viability and proliferation, increased lactate dehydrogenase, a cytotoxicity marker, and induced oxidative stress and apoptosis which also affects maintenance of spermatogenesis and testosterone production (Aydin and Orta-Yilmaz 2022).

#### 16.4.4.3 Effect on Progesterone Level

As is considered a major hazard to the reproductive health of females, constrained the functions and structure of the uterus, by changing the gonadotrophins and steroid hormone levels (Akram et al. 2010). Arsenite being a potent environmental estrogen, mimic the effects of estradiol hormone and results in an elevation in progesterone receptors and pS2 levels (Stoica et al. 2000). The various effects of progesterone are governed by Progesterone receptors (PR) and estrogen is responsible for the induction of this PR in most of the target tissues (Graham and Clarke 1997). The PR concentration increased 22 times upon treatment of MCF-7 cells with 1 nm arsenite for a period of 24 h and this increase in the concentration of PR was similar to the increase in PR upon MCF-7 CELLS treatment with 1 nm estradiol (Stoica et al. 2000). iAs concentrations of 7.7–77 ppb in drinking water cause enhancement in gene transcription mediated by progesterone (Bodwell et al. 2006). As treatment at a concentration of 10 mg/L in female rats for 7 days stimulates the production of progesterone in a caspase-3-dependent manner and also influences estrogen (Yuan et al. 2012). A study by (Guo et al. 2011) showed a drastic reduction in serum level of progesterone after chronic exposure to As.

#### 16.4.4.4 Effect on LH and FSH Level

Spermatogenesis is initiated and maintained by LH and FSH in rats (Russell et al. 1987). Mondal et al. (2022) investigated the amount of harm $NaAsO_2$ caused to the rat's female reproductive system. The lowering of serum LH, FSH, and extended diestrus index were further effects of the toxin. At larger doses, sodium arsenite-induced ROS production targets the female rats' reproductive system. FSH and LH levels were positively correlated with urinary As, and a possible link between As exposure and primary ovarian insufficiency (POI) in females was discovered by Pan et al. (2020). According to certain research, blood As levels above 5.8 μg L are associated with an increased risk of a reduced LH level and reduced sperm motility (Mahurpawar 2015). As mice were given 15 mg/L of As (III) at puberty, their levels of the hormone LH dramatically rose when compared to the control group, increasing female sexual precocity (Li et al. 2018). Adult rats when treated with $NaAsO_2$ (0.4 ppm) for 28 days showed a reduction in levels of LH and FSH

along with reduced uterine peroxidase activity (Chattopadhyay et al. 2003). Wistar rats (4 months old) when treated with $NaAsO_2$(5 and 6 mg/kg/day) intraperitoneally for 26 days showed a decrease in sperm count and plasma level of testosterone, LH, and FSH along with degeneration of stage VII germ cells (Sarkar et al. 2003). Bombino (1989) demonstrates that Glucocorticoids decrease LH receptors in the testis and are thereby responsible for the suppression of testosterone production and its secretion and resulting in a decrease in spermatogenesis and sperm count (Sarkar et al. 2003). In Male rats, when sodium arsenite is administered with or without hCG and estradiol for 4 weeks (6 days a week), a significant change was noticed in levels of corticosterone, LH, FSH, and testosterone depict that As cause degeneration of germ cells and toxicity of testis, which inhibits the production of androgens in male rats (Jana et al. 2006).

#### 16.4.4.5 Effect on Prolactin Level

There exists an inverse association between As and prolactin levels in 219 male volunteers (Meeker et al. 2009). Upon treatment with $NaAsO_2$ for 28 days, female rats show altered mammary gland morphology, reducing lactiferous duct branching and effects the concentration of prolactin and estradiol (Jahan et al. 2012). In vivo As exposure to 25 and 100 ppm causes a reduction in prolactin levels, and induces apoptosis by causing oxidative stress (Ronchetti et al. 2016). A micromolecular dose of iAs is responsible for the inhibition of secretion of the anterior pituitary via feedback mechanisms or directly affects cells of the anterior pituitary (Poliandri et al. 2006). Demonstrate that exposure to iAS at a concentration level of 25–100 ppm in vivo results in a reduction in serum levels of prolactin, where As directly inhibits the release of prolactin, generates oxidative stress and thereby apoptosis (Ronchetti et al. 2016).

### *16.4.5 Tumour Markers as Biomarkers of Arsenic Toxicity*

A tumour marker is identified in urine, blood, or tissues, elevated due to the existence of different forms of cancer (Kilpatrick and Lind 2009). CA-15-3 (Cancer antigen), CEA (Carcinoembryonic antigen) (Donepudi et al. 2014), CA-19-9, and CA-125 (Magalhaes et al. 2021) that demonstrated clinical usefulness and were authorized as potential biomarkers. CA-15-3 is the most often utilized blood marker in women having breast cancer (Duffy et al. 2010). Although increased levels of CA-15-3 are observed in the majority patients with metastatic breast cancer, high concentrations may occur in individuals with numerous distinct forms of advanced adenocarcinoma, including pancreatic, ovarian, lung, and gastriccancer (Stieber et al. 2003). CA-19-9 is expressed in small concentrations in serum as well as overexpressed in numerous benign gastrointestinal illnesses; nevertheless, its plasmatic levels rise with neoplastic disease (Scarà et al. 2015). CA-125 is a tumor-associated antigen that

has been frequently found in advanced forms of ovarian cancer. It is mostly formed from coelomic epithelium, which supports increases in benign or malignant conditions (Stieber et al. 2015). Since the International Agency for Research on Cancer (IARC) has categorized arsenic as a class-I carcinogen in humans, indicating that there is substantial evidence of carcinogenicity in humans (Martinez et al. 2011), these tumour markers can act as biomarkers for detecting As toxicity.

## References

Akram Z, Jalali S, Shami SA, Ahmad L, Batool S, Kalsoom O (2010) Adverse effects of arsenic exposure on uterine function and structure in female rat. Exp Toxicol Pathol 62:451–459

Al-Forkan M, Islam S, Akter R, Shameen Alam S, Khaleda L, Rahman Z, Salma Chowdhury DU (2016) A sub-chronic exposure study of arsenic on hematological parameters, liver enzyme activities, histological studies and accumulation pattern of arsenic in organs of Wistar albino rats. J Cytol Histol S 5

Ali W, Rasool A, Junaid M, Zhang H (2019) A comprehensive review on current status, mechanism, and possible sources of arsenic contamination in groundwater: a global perspective with prominence of Pakistan scenario. Environ Geochem Health 41:737–760

Argos M, Kalra T, Pierce BL, Chen Y, Parvez F, Islam T, Ahmed A, Hasan R, Hasan K, Sarwar G (2011) A prospective study of arsenic exposure from drinking water and incidence of skin lesions in Bangladesh. Am J Epidemiol 174:185–194

Aydin Y, Orta-Yilmaz B (2022) Synergistic effects of arsenic and fluoride on oxidative stress and apoptotic pathway in Leydig and Sertoli cells. Toxicology 475:153241

Bae-Jump VL, Zhou C, Boggess JF, Gehrig PA (2008) Arsenic trioxide ($As_2O_3$) inhibits expression of estrogen receptor—alpha through regulation of the mitogen-activated protein kinase (MAPK) pathway in endometrial cancer cells. Reprod Sci 15:1011–1017

Basu A, Som A, Ghoshal S, Mondal L, Chaubey RC, Bhilwade HN, Rahman MM, Giri AK (2005) Assessment of DNA damage in peripheral blood lymphocytes of individuals susceptible to arsenic induced toxicity in West Bengal, India. Toxicol Lett 159:100–112

Bauer M, Goldstein M, Christmann M, Becker H, Heylmann D, Kaina B (2011) Human monocytes are severely impaired in base and DNA double-strand break repair that renders them vulnerable to oxidative stress. Proc Natl Acad Sci 108:21105–21110

Bernasconi S, Street ME, Iughetti L, Predieri B (2022) Chemical contaminants in breast milk: a brief critical overview. Glob Pediatr 100017

Bhatnagar N, Hong HS, Krishnaswamy JK, Haghikia A, Behrens GM, Schmidt RE, Jacobs R (2010) Cytokine-activated NK cells inhibit PMN apoptosis and preserve their functional capacity. Blood J Am Soc Hematol 116:1308–1316

Biswas D, Banerjee M, Sen G, Das JK, Banerjee A, Sau TJ, Pandit S, Giri AK, Biswas T (2008) Mechanism of erythrocyte death in human population exposed to arsenic through drinking water. Toxicol Appl Pharmacol 230:57–66

Bodwell JE, Gosse JA, Nomikos AP, Hamilton JW (2006) Arsenic disruption of steroid receptor gene activation: complex Dose−response effects are shared by several steroid receptors. Chem Res Toxicol 19:1619–1629

Bombino TH (1989) Direct effect of glucocorticoids upon testicular luteinizing hormone receptor and steroidogenesis in vivo and in vitro. Endocrinol 125:209–216

Borghini A, Faita F, Mercuri A, Minichilli F, Bustaffa E, Bianchi F, Andreassi MG (2016) Arsenic exposure, genetic susceptibility and leukocyte telomere length in an Italian young adult population. Mutagenesis 31:539–546

Chakraborti D, Rahman MM, Das B, Chatterjee A, Das D, Nayak B, Pal A, Chowdhury UK, Ahmed S, Biswas BK (2017) Groundwater arsenic contamination and its health effects in India. Hydrogeol J 25:1165–1181

Chakraborti D, Singh SK, Rahman MM, Dutta RN, Mukherjee SC, Pati S, Kar PB (2018) Groundwater arsenic contamination in the Ganga River Basin: a future health danger. Int J Environ Res Public Health 15:180

Chatterjee A, Chatterji U (2010) Arsenic abrogates the estrogen-signaling pathway in the rat uterus. Reprod Biol Endocrinol 8:80

Chattopadhyay S, Pal S, Ghosh D, Debnath J (2003) Effect of dietary co-administration of sodium selenite on sodium arsenite-induced ovarian and uterine disorders in mature albino rats. Toxicol Sci 75:412–422

Che W, Yang M, Cheng Y, Wu M, Lan Y, Zhang H (2019) Arsenic induces gender difference of estrogen receptor in AECII cells from ICR fetal mice. Toxicol Vitr 56:133–140

Chen G-C, Guan L-S, Hu W-L, Wang Z-Y (2002) Functional repression of estrogen receptor a by arsenic trioxide in human breast cancer cells. Anticancer Res 22:633

Chen C-J, Hsu L-I, Wang C-H, Shih W-L, Hsu Y-H, Tseng M-P, Lin Y-C, Chou W-L, Chen C-Y, Lee C-Y (2005) Biomarkers of exposure, effect, and susceptibility of arsenic-induced health hazards in Taiwan. Toxicol Appl Pharmacol 206:198–206

Chen Y, Sun Y, Zhao A, Cai X, Yu A, Xu Q, Wang P, Yao J, Wang Q, Wang W (2022) Arsenic exposure diminishes ovarian follicular reserve and induces abnormal steroidogenesis by DNA methylation. Ecotoxicol Environ Saf 241:113816

Chiou T-J, Chu S-T, Tzeng W-F, Huang Y-C, Liao C-J (2008) Arsenic trioxide impairs spermatogenesis via reducing gene expression levels in testosterone synthesis pathway. Chem Res Toxicol 21:1562–1569

Chow SKY, Chan JYW, Fung KP (2004) Suppression of cell proliferation and regulation of estrogen receptor alpha signaling pathway by arsenic trioxide on human breast cancer

Correia AD, Lima G, Costa MH, Livingstone DR (2002) Studies on biomarkers of copper exposure and toxicity in the marine amphipod Gammarus locusta (Crustacea): I. induction of metallothionein and lipid peroxidation. Biomarkers 7:422–437

Das N, Paul S, Chatterjee D, Banerjee N, Majumder NS, Sarma N, Sau TJ, Basu S, Banerjee S, Majumder P (2012) Arsenic exposure through drinking water increases the risk of liver and cardiovascular diseases in the population of West Bengal, India. BMC Public Health 12:1–9

Das S, Chowdhury J, Ghoshal L (2014) An introspection into the cutaneous manifestations of chronic arsenicosis as reported in a tertiary care centre in Kolkata. J Pakistan Assoc Dermatologists 24:286–291

Davey JC, Bodwell JE, Gosse JA, Hamilton JW (2007) Arsenic as an endocrine disruptor: effects of arsenic on estrogen receptor–mediated gene expression in vivo and in cell culture. Toxicol Sci 98:75–86

De Felip E, Bianchi F, Bove C, Cori L, D'Argenzio A, D'Orsi G, Fusco M, Miniero R, Ortolani R, Palombino R (2014) Priority persistent contaminants in people dwelling in critical areas of Campania Region, Italy (SEBIOREC biomonitoring study). Sci Total Environ 487:420–435

Donepudi MS, Kondapalli K, Amos SJ, Venkanteshan P (2014) Breast cancer statistics and markers. J Cancer Res Ther 10:506–511

Dopp E, Kligerman AD, Diaz-Bone RA (2010) Organoarsenicals. Uptake, metabolism, and toxicity. Organometallics Environ Toxicol 7

Druwe IL, Sollome JJ, Sanchez-Soria P, Hardwick RN, Camenisch TD, Vaillancourt RR (2012) Arsenite activates NFκB through induction of C-reactive protein. Toxicol Appl Pharmacol 261:263–270

Du J, Zhou N, Liu H, Jiang F, Wang Y, Hu C, Qi H, Zhong C, Wang X, Li Z (2012) Arsenic induces functional re-expression of estrogen receptor α by demethylation of DNA in estrogen receptor-negative human breast cancer. PLoS ONE 7:e35957

Duffy MJ, Evoy D, McDermott EW (2010) CA 15–3: uses and limitation as a biomarker for breast cancer. Clin Chim Acta 411:1869–1874

El-Ghiaty MA, El-Kadi AOS (2022) The duality of arsenic metabolism: impact on human health. Ann Rev Pharmacol Toxicol 63
Ellinsworth DC (2015) Arsenic, reactive oxygen, and endothelial dysfunction. J Pharmacol Exp Ther 353:458–464
Fängström B, Moore S, Nermell B, Kuenstl L, Goessler W, Grandér M, Kabir I, Palm B, Arifeen SE, Vahter M (2008) Breast-feeding protects against arsenic exposure in Bangladeshi infants. Environ Health Perspect 116:963–969
Fendorf S, Michael HA, van Geen A (2010) Spatial and temporal variations of groundwater arsenic in South and Southeast Asia. Science 328:1123–1127
Feng H, Gao Y, Zhao L, Wei Y, Li Y, Wei W, Wu Y, Sun D (2013) Biomarkers of renal toxicity caused by exposure to arsenic in drinking water. Environ Toxicol Pharmacol 35:495–501
Flora SJS (2011) Free radical biology & medicine arsenic-induced oxidative stress and its reversibility. Free Radic Biol Med 51:257–281. https://doi.org/10.1016/j.freeradbiomed.2011.04.008
Flora SJS (2020) Preventive and therapeutic strategies for acute and chronic human arsenic exposure. Arsen Drink Water Food 341–370
Francesconi KA, Kuehnelt D (2004) Determination of arsenic species: a critical review of methods and applications, 2000–2003. Analyst 129:373–395
Gangopadhyay S, Sharma V, Chauhan A, Srivastava V (2019) Potential facet for prenatal arsenic exposure paradigm: linking endocrine disruption and epigenetics. Nucl 1–16
Gault AG, Rowland HAL, Charnock JM, Wogelius RA, Gomez-Morilla I, Vong S, Leng M, Samreth S, Sampson ML, Polya DA (2008) Arsenic in hair and nails of individuals exposed to arsenic-rich groundwaters in Kandal province, Cambodia. Sci Total Environ 393:168–176
Ghosh P, Banerjee M, De Chaudhuri S, Chowdhury R, Das JK, Mukherjee A, Sarkar AK, Mondal L, Baidya K, Sau TJ (2007) Comparison of health effects between individuals with and without skin lesions in the population exposed to arsenic through drinking water in West Bengal, India. J Expo Sci Environ Epidemiol 17:215–223
Gomez-Caminero A, Howe PD, Hughes M, Kenyon E, Lewis DR, Moore M, Aitio A, Becking GC, Ng J (2001) Arsenic and arsenic compounds. World Health Organization
Gong G, Hargrave KA, Hobson V, Spallholz J, Boylan M, Lefforge A, O'Bryant SE (2011) Low-level groundwater arsenic exposure impacts cognition: a project FRONTIER study. J Environ Health 74:16–23
Graham JD, Clarke CL (1997) Physiological action of progesterone in target tissues. Endocr Rev 18:502–519
Guha MD (2001) Arsenic and liver disease. J Indian Med Assoc 99:314–315
Guo H, Hao G, Xia Y, Guo W, Li C, Guo Z (2011) Effects on serum estadiol and progesterone of female mice exposed to arsenic chronically. Wei sheng yan jiu= J Hyg Res 40:120–121
Gürbay A, Charehsaz M, Eken A, Sayal A, Girgin G, Yurdakök M, Yiğit Ş, Erol DD, Şahin G, Aydın A (2012) Toxic metals in breast milk samples from Ankara, Turkey: assessment of lead, cadmium, nickel, and arsenic levels. Biol Trace Elem Res 149:117–122
Hall M, Chen Y, Ahsan H, Slavkovich V, Van Geen A, Parvez F, Graziano J (2006) Blood arsenic as a biomarker of arsenic exposure: results from a prospective study. Toxicology 225:225–233
Haque R, Mazumder DNG, Samanta S, Ghosh N, Kalman D, Smith MM, Mitra S, Santra A, Lahiri S, Das S (2003) Arsenic in drinking water and skin lesions: dose-response data from West Bengal, India. Epidemiology 174–182
Hazra J, Upadhyay SN, Singh RK, Amal ROY (2008) Arsenic induced toxicity on testicular tissue of mice. Indian J Physiol Pharmacol 52
Hindmarsh JT (2002) Caveats in hair analysis in chronic arsenic poisoning. Clin Biochem 35:1–11
Hinwood AL, Sim MR, Jolley D, de Klerk N, Bastone EB, Gerostamoulos J, Drummer OH (2003) Hair and toenail arsenic concentrations of residents living in areas with high environmental arsenic concentrations. Environ Health Perspect 111:187–193

Hong F, Jin T, Zhang A (2004) Risk assessment on renal dysfunction caused by co-exposure to arsenic and cadmium using benchmark dose calculation in a Chinese population. Biometals 17:573–580

Hopps HC (1977) The biologic bases for using hair and nail for analyses of trace elements. Sci Total Environ 7:71–89

Hu Y, Li J, Lou B, Wu R, Wang G, Lu C, Wang H, Pi J, Xu Y (2020) The role of reactive oxygen species in arsenic toxicity. Biomolecules 10:240

Hughes MF (2006) Biomarkers of exposure: a case study with inorganic arsenic. Environ Health Perspect 114:1790–1796

Hunt KM, Srivastava RK, Athar M (2015) Cutaneous toxicology of arsenic. Handb Arsen Toxicol 301–314

Huq ME, Fahad S, Shao Z, Sarven MS, Khan IA, Alam M, Saeed M, Ullah H, Adnan M, Saud S (2020) Arsenic in a groundwater environment in Bangladesh: occurrence and mobilization. J Environ Manage 262:110318

Islam LN, Nabi AHMN, Rahman MM, Khan MA, Kazi AI (2004) Association of clinical complications with nutritional status and the prevalence of leukopenia among arsenic patients in Bangladesh. Int J Environ Res Public Health 1:74–82

Islam K, Haque A, Karim R, Fajol A, Hossain E, Salam KA, Ali N, Saud ZA, Rahman M, Rahman M (2011) Dose-response relationship between arsenic exposure and the serum enzymes for liver function tests in the individuals exposed to arsenic: a cross sectional study in Bangladesh. Environ Heal 10:1–11

Isokpehi RD, Udensi UK, Anyanwu MN, Mbah AN, Johnson MO, Edusei K, Bauer MA, Hall RA, Awofolu OR (2012) Knowledge building insights on biomarkers of arsenic toxicity to keratinocytes and melanocytes. Biomark Insights 7:BMI-S7799

Jahan S, Ahmed S, Razzaq S, Amed H (2012) Adverse effects of arsenic exposure in the mammary glands of adult female rats. Pakistan J Zool 44:691–697

Jana K, Jana S, Samanta PK (2006) Effects of chronic exposure to sodium arsenite on hypothalamo-pituitary-testicular activities in adult rats: possible an estrogenic mode of action. Reprod Biol Endocrinol 4:9

Jayasumana C, Paranagama PA, Amarasinghe MD, Wijewardane K, Dahanayake KS, Fonseka SI, Rajakaruna K, Mahamithawa AMP, Samarasinghe UD, Senanayake VK (2013) Possible link of chronic arsenic toxicity with chronic kidney disease of unknown etiology in Sri Lanka

Karagas MR, Gossai A, Pierce B, Ahsan H (2015) Drinking water arsenic contamination, skin lesions, and malignancies: a systematic review of the global evidence. Curr Environ Heal Rep 2:52–68

Kelishadi R, Hasanghaliaei N, Poursafa P, Keikha M, Ghannadi A, Yazdi M, Rahimi E (2016) A randomized controlled trial on the effects of jujube fruit on the concentrations of some toxic trace elements in human milk. J Res Med Sci Off J Isfahan Univ Med Sci 21

Kile ML, Baccarelli A, Hoffman E, Tarantini L, Quamruzzaman Q, Rahman M, Mahiuddin G, Mostofa G, Hsueh Y-M, Wright RO (2012) Prenatal arsenic exposure and DNA methylation in maternal and umbilical cord blood leukocytes. Environ Health Perspect 120:1061–1066

Kile ML, Houseman EA, Baccarelli AA, Quamruzzaman Q, Rahman M, Mostofa G, Cardenas A, Wright RO, Christiani DC (2014) Effect of prenatal arsenic exposure on DNA methylation and leukocyte subpopulations in cord blood. Epigenetics 9:774–782

Kilpatrick ES, Lind MJ (2009) Appropriate requesting of serum tumour markers. BMJ 339

Koley S (2022) Future perspectives and mitigation strategies towards groundwater arsenic contamination in West Bengal, India. Environ Qual Manag 31:75–97

Kumar R, Khan SA, Dubey P, Nath A, Singh JK, Ali MD, Arun Kumar A (2013) Effect of arsenic exposure on testosterone level and spermatogonia of mice. WJPR 2:1524–1533

Lavanya S, Ramesh M, Kavitha C, Malarvizhi A (2011) Hematological, biochemical and ionoregulatory responses of Indian major carp Catla catla during chronic sublethal exposure to inorganic arsenic. Chemosphere 82:977–985

Li X, Sun Z, Manthari RK, Li M, Guo Q, Wang J (2018) Effect of gestational exposure to arsenic on puberty in offspring female mice. Chemosphere 202:119–126
Lima FW (1968) Exogenous contamination of hair by capillary action of arsenic solutions. Instituto de Energia Atomica, Sao Paulo (Brazil)
Liu T, Guo H, Xiu W, Wei C, Li X, Di Z, Song W (2017) Biomarkers of arsenic exposure in arsenic-affected areas of the Hetao Basin, Inner Mongolia. Sci Total Environ 609:524–534
Magalhaes JD, Jammal MP, Crispim PC, Murta EF, Nomelini RS (2021) Role of biomarkers CA-125, CA-15.3 and CA-19.9 in the distinction between endometriomas and ovarian neoplasms. Biomarkers 26:268–274
Mahurpawar M (2015) Effects of heavy metals on human health. Int J Res Granthaalayah 530:1–7
Mandal BK, Ogra Y, Suzuki KT (2003) Speciation of arsenic in human nail and hair from arsenic-affected area by HPLC-inductively coupled argon plasma mass spectrometry. Toxicol Appl Pharmacol 189:73–83
Manna P, Sinha M, Sil PC (2008) Protection of arsenic-induced testicular oxidative stress by arjunolic acid. Redox Rep 13:67–77
Manno M, Viau C, Cocker J, Colosio C, Lowry L, Mutti A, Nordberg M, Wang S (2010) Biomonitoring for occupational health risk assessment (BOHRA). Toxicol Lett 192:3–16
Marchiset-Ferlay N, Savanovitch C, Sauvant-Rochat M-P (2012) What is the best biomarker to assess arsenic exposure via drinking water? Environ Int 39:150–171
Martinez VD, Vucic EA, Becker-Santos DD, Gil L, Lam WL (2011) Arsenic exposure and the induction of human cancers. J Toxicol 2011
Mazumder DNG (2005) Effect of chronic intake of arsenic-contaminated water on liver. Toxicol Appl Pharmacol 206:169–175
McClintock TR, Chen Y, Bundschuh J, Oliver JT, Navoni J, Olmos V, Lepori EV, Ahsan H, Parvez F (2012) Arsenic exposure in Latin America: biomarkers, risk assessments and related health effects. Sci Total Environ 429:76–91
Meeker JD, Rossano MG, Protas B, Diamond MP, Puscheck E, Daly D, Paneth N, Wirth JJ (2009) Multiple metals predict prolactin and thyrotropin (TSH) levels in men. Environ Res 109:869–873
Miklavčič A, Casetta A, Tratnik JS, Mazej D, Krsnik M, Mariuz M, Sofianou K, Špirić Z, Barbone F, Horvat M (2013) Mercury, arsenic and selenium exposure levels in relation to fish consumption in the Mediterranean area. Environ Res 120:7–17
Mishra D, Mehta A, Flora SJS (2008) Reversal of arsenic-induced hepatic apoptosis with combined administration of DMSA and its analogues in guinea pigs: role of glutathione and linked enzymes. Chem Res Toxicol 21:400–407
Mondal R, Mukhopadhyay A, Chattopadhyay A, Bandyopadhyay A, Mukhopadhyay PK (2022) Ovarian follicular atresia and uterine toxicity after subchronic oral exposure of postpubertal rats to sodium arsenite. Comp Clin Path 1–16
Naujokas MF, Anderson B, Ahsan H, Aposhian HV, Graziano JH, Thompson C, Suk WA (2013) The broad scope of health effects from chronic arsenic exposure: update on a worldwide public health problem. Environ Health Perspect 121:295–302
Niedzwiecki MM, Liu X, Hall MN, Thomas T, Slavkovich V, Ilievski V, Levy D, Alam S, Siddique AB, Parvez F (2015) Sex-specific associations of arsenic exposure with global DNA methylation and hydroxymethylation in leukocytes: results from two studies in Bangladesh. Cancer Epidemiol Biomarkers Prev 24:1748–1757
Nilsson S, Gustafsson J-Å (2002) Biological role of estrogen and estrogen receptors. Crit Rev Biochem Mol Biol 37:1–28
Nordberg GF (2010) Biomarkers of exposure, effects and susceptibility in humans and their application in studies of interactions among metals in China. Toxicol Lett 192:45–49
Pan W, Ye X, Zhu Z, Li C, Zhou J, Liu J (2020) A case-control study of arsenic exposure with the risk of primary ovarian insufficiency in women. Environ Sci Pollut Res 27(20):25220–25229
Pei Q, Ma N, Zhang J, Xu W, Li Y, Ma Z, Li Y, Tian F, Zhang W, Mu J (2013) Oxidative DNA damage of peripheral blood polymorphonuclear leukocytes, selectively induced by chronic arsenic

exposure, is associated with extent of arsenic-related skin lesions. Toxicol Appl Pharmacol 266:143–149
Peters BA, Liu X, Hall MN, Ilievski V, Slavkovich V, Siddique AB, Alam S, Islam T, Graziano JH, Gamble MV (2015) Arsenic exposure, inflammation, and renal function in Bangladeshi adults: effect modification by plasma glutathione redox potential. Free Radic Biol Med 85:174–182
Pham-Huy LA, He H, Pham-Huy C (2008) Free radicals, antioxidants in disease and health. Int J Biomed Sci IJBS 4:89
Pi J, Yamauchi H, Kumagai Y, Sun G, Yoshida T, Aikawa H, Hopenhayn-Rich C, Shimojo N (2002) Evidence for induction of oxidative stress caused by chronic exposure of Chinese residents to arsenic contained in drinking water. Environ Health Perspect 110:331–336. https://doi.org/10.1289/ehp.02110331
Poliandri AHB, Esquifino AI, Cano P, Jiménez V, Lafuente A, Cardinali DP, Duvilanski BH (2006) In vivo protective effect of melatonin on cadmium-induced changes in redox balance and gene expression in rat hypothalamus and anterior pituitary. J Pineal Res 41:238–246
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
Quansah R, Armah FA, Essumang DK, Luginaah I, Clarke E, Marfoh K, Cobbina SJ, Nketiah-Amponsah E, Namujju PB, Obiri S (2015) Association of arsenic with adverse pregnancy outcomes/infant mortality: a systematic review and meta-analysis. Environ Health Perspect 123:412–421
Rahman MM, Ng JC, Naidu R (2009) Chronic exposure of arsenic via drinking water and its adverse health impacts on humans. Environ Geochem Health 31:189–200
Rajiv SV, George M, Nandakumar G (2022) Dermatological manifestations of arsenic exposure. J Ski Sex Transm Dis 1–8
Ranjan A (2019) Spatial analysis of arsenic contamination of groundwater around the world and India
Raqib R, Ahmed S, Sultana R, Wagatsuma Y, Mondal D, Hoque AMW, Nermell B, Yunus M, Roy S, Persson LA (2009) Effects of in utero arsenic exposure on child immunity and morbidity in rural Bangladesh. Toxicol Lett 185:197–202
Rasheed H, Kay P, Slack R, Gong YY (2019) Assessment of arsenic species in human hair, toenail and urine and their association with water and staple food. J Expo Sci Environ Epidemiol 29:624–632
Ratnaike RN (2003) Acute and chronic arsenic toxicity. Postgrad Med J 79:391–396
Ravenscroft P, Brammer H, Richards K (2011) Arsenic pollution: a global synthesis. Wiley
Reyes-Becerril M, Angulo C, Sanchez V, Cuesta A, Cruz A (2019) Methylmercury, cadmium and arsenic (III)-induced toxicity, oxidative stress and apoptosis in Pacific red snapper leukocytes. Aquat Toxicol 213:105223
Ronchetti SA, Bianchi MS, Duvilanski BH, Cabilla JP (2016) In vivo and in vitro arsenic exposition induces oxidative stress in anterior pituitary gland. Int J Toxicol 35:463–475
Russell LD, Alger LE, Nequin LG (1987) Hormonal control of pubertal spermatogenesis. Endocrinology 120:1615–1632
Saha JC, Dikshit AK, Bandyopadhyay M, Saha KC (1999) A review of arsenic poisoning and its effects on human health. Crit Rev Environ Sci Technol 29:281–313
Salmani MH, Rezaie Z, Mozaffari-Khosravi H, Ehrampoush MH (2018) Arsenic exposure to breast-fed infants: contaminated breastfeeding in the first month of birth. Environ Sci Pollut Res 25:6680–6684
Samiee F, Leili M, Faradmal J, Torkshavand Z, Asadi G (2019) Exposure to arsenic through breast milk from mothers exposed to high levels of arsenic in drinking water: Infant risk assessment. Food Control 106:106669
Sanjrani MA, Zhou B, Zhao H, Bhutto SA, Muneer AS, Xia SB (2019) Arsenic contaminated groundwater in China and its treatment options, a review. Appl Ecol Environ Res 17:1655–1683
Sarkar M, Chaudhuri GR, Chattopadhyay A, Biswas NM (2003) Effect of sodium arsenite on spermatogenesis, plasma gonadotrophins and testosterone in rats. Asian J Androl 5:27–32

Sarkar A, Paul B, Darbha GK (2022) The groundwater arsenic contamination in the Bengal Basin-a review in brief. Chemosphere 134369
Sarma N (2015) Skin manifestations of chronic arsenicosis. Arsen Expo Sources Heal Risks Mech Toxic 127–136
Scarà S, Bottoni P, Scatena R (2015) CA 19–9: biochemical and clinical aspects. Adv Cancer Biomarkers From Biochem Clin Crit Rev 247–260
Schmitt MT, Schreinemachers D, Wu K, Ning Z, Zhao B, Le XC, Mumford JL (2005) Human nails as a biomarker of arsenic exposure from well water in Inner Mongolia: comparing atomic fluorescence spectrometry and neutron activation analysis. Biomarkers 10:95–104
Schwartz RA (1997) Arsenic and the skin. Int J Dermatol 36:241–250
Shaji E, Santosh M, Sarath KV, Prakash P, Deepchand V, Divya BV (2021) Arsenic contamination of groundwater: a global synopsis with focus on the Indian Peninsula. Geosci Front 12:101079
Shankar S, Shanker U (2014) Arsenic contamination of groundwater: a review of sources, prevalence, health risks, and strategies for mitigation. Sci world J 2014
Sharpe RM, Maddocks S, Kerr JB (1990) Cell-cell interactions in the control of spermatogenesis as studied using Leydig cell destruction and testosterone replacement. Am J Anat 188:3–20
Shen S, Li X-F, Cullen WR, Weinfeld M, Le XC (2013) Arsenic binding to proteins. Chem Rev 113:7769–7792
Shukla A, Awasthi S, Chauhan R, Srivastava S (2020) The status of arsenic contamination in India. Arsen Drink Water Food 1–12
Signes-Pastor AJ, Doherty BT, Romano ME, Gleason KM, Gui J, Baker E, Karagas MR (2019) Prenatal exposure to metal mixture and sex-specific birth outcomes in the New Hampshire Birth Cohort Study. Environ Epidemiol 3
Silins I, Högberg J (2011) Combined toxic exposures and human health: biomarkers of exposure and effect. Int J Environ Res Public Health 8:629–647
Slotnick MJ, Nriagu JO (2006) Validity of human nails as a biomarker of arsenic and selenium exposure: a review. Environ Res 102:125–139
Smith AH, Marshall G, Yuan Y, Liaw J, Ferreccio C, Steinmaus C (2011) Evidence from Chile that arsenic in drinking water may increase mortality from pulmonary tuberculosis. Am J Epidemiol 173:414–420
Souza ACF, Marchesi SC, de Almeida Lima GD, Machado-Neves M (2018) Effects of arsenic compounds on microminerals content and antioxidant enzyme activities in rat liver. Biol Trace Elem Res 183:305–313
Souza ACF, Bastos DSS, Sertorio MN, Santos FC, Ervilha LOG, de Oliveira LL, Machado-Neves M (2019) Combined effects of arsenic exposure and diabetes on male reproductive functions. Andrology 7:730–740
Souza ACF, Machado-Neves M, Bastos DSS, Santos FC, Ervilha LOG, de Paiva Coimbra JL, de Sales Araújo L, de Oliveira LL, Guimarães SEF (2021) Impact of prenatal arsenic exposure on the testes and epididymides of prepubertal rats. Chem Biol Interact 333:109314
Stancato LF, Hutchison KA, Chakraborti PK, Simons SS Jr, Pratt WB (1993) Differential effects of the reversible thiol-reactive agents arsenite and methyl methanethiosulfonate on steroid binding by the glucocorticoid receptor. Biochemistry 32:3729–3736
Stieber P, Molina R, Chan DW, Fritsche HA, Beyrau R, Bonfrer JM, Filella X, Gornet TG, Hoff T, Jäger W (2003) Clinical evaluation of the Elecsys CA 15–3 test in breast cancer patients. Clin Lab 49:15–24
Stieber P, Nagel D, Blankenburg I, Heinemann V, Untch M, Bauerfeind I, Di Gioia D (2015) Diagnostic efficacy of CA 15–3 and CEA in the early detection of metastatic breast cancer—a retrospective analysis of kinetics on 743 breast cancer patients. Clin Chim Acta 448:228–231
Stoica A, Pentecost E, Martin MB (2000) Effects of arsenite on estrogen receptor-α expression and activity in MCF-7 breast cancer cells. Endocrinology 141:3595–3602
Stone A, Lanzoni M, Smedley P (2019) Groundwater resources: past, present, and future. Water Sci Policy Manag A Glob Chall 29–54
Strimbu K, Tavel JA (2010) What are biomarkers? Curr Opin HIV AIDS 5:463

Thapa BR, Walia A (2007) Liver function tests and their interpretation. Indian J Pediatr 74:663–671
Tian M, Wang Y-X, Wang X, Wang H, Liu L, Zhang J, Nan B, Shen H, Huang Q (2021) Environmental doses of arsenic exposure are associated with increased reproductive-age male urinary hormone excretion and in vitro Leydig cell steroidogenesis. J Hazard Mater 408:124904
Valentine JL, Kang HK, Spivey G (1979) Arsenic levels in human blood, urine, and hair in response to exposure via drinking water. Environ Res 20:24–32
Venkaiah K, Daveedu T, Prathima P, Pavani R, Sukeerthi S, Reddy MH, Pradeepkiran JA, Sainath SB (2022) Immobilization stress exacerbates arsenic-induced reprotoxic effects in adult rats. Toxicol Res (Camb)
Wang JP, Qi L, Zheng B, Liu F, Moore MR, Ng JC (2002) Porphyrins as early biomarkers for arsenic exposure in animals and humans. Cell Mol Biol (Noisy-le-grand) 48:835–843
Wang G, Fowler BA (2008) Roles of biomarkers in evaluating interactions among mixtures of lead, cadmium and arsenic. Toxicol Appl Pharmacol 233:92–99
Watson WP, Mutti A (2004) Role of biomarkers in monitoring exposures to chemicals: present position, future prospects. Biomarkers 9:211–242
Winski SL, Barber DS, Rael LT, Carter DE (1997) Sequence of toxic events in arsine-induced hemolysis in vitro: implications for the mechanism of toxicity in human erythrocytes. Toxicol Sci 38:123–128
Xia Y, Wade TJ, Wu K, Li Y, Ning Z, Le XC, He X, Chen B, Feng Y, Mumford JL (2009) Well water arsenic exposure, arsenic induced skin-lesions and self-reported morbidity in Inner Mongolia. Int J Environ Res Public Health 6:1010–1025
Xu Y, Tokar EJ, Waalkes MP (2014) Arsenic-induced cancer cell phenotype in human breast epithelia is estrogen receptor-independent but involves aromatase activation. Arch Toxicol 88:263–274
Yamanaka K, Hoshino M, Okamoto M, Sawamura R, Hasegawa A, Okada S (1990) Induction of DNA damage by dimethylarsine, a metabolite of inorganic arsenics, is for the major part likely due to its peroxyl radical. Biochem Biophys Res Commun 168:58–64
Yang YQ, Sun LY, Zhang BX, Zhang AH (2000) Changes of renal function in chronic arsenic poisoning patients caused by coal burning pollution. Stud Trace Elem Heal. 17:21–22
Yaribeygi H, Sathyapalan T, Atkin SL, Sahebkar A (2020) Molecular mechanisms linking oxidative stress and diabetes mellitus. Oxid Med Cell Longev 2020
Yuan X, Lu C, Yao N, An L, Yang B, Zhang C, Ma X (2012) Arsenic induced progesterone production in a caspase-3-dependent manner and changed redox status in preovulatory granulosa cells. J Cell Physiol 227:194–203
Yurdakök K (2015) Lead, mercury, and cadmium in breast milk. J Pediatr Neonatal Individ Med 4:e040223–e040223
Zeni C, Bovolenta MR, Stagni A (2002) Occurrence of echinocytosis in circulating RBC of black bullhead, Ictalurus melas (Rafinesque), following exposure to an anionic detergent at sublethal concentrations. Aquat Toxicol 57:217–224
Zhang T, Zhang BX, Ye P, Hu ZY, Jiang TX, Zhang AH, Mao Y (2006) The changes of trace protein in urine collected from 145 cases of arsenic poisoning patients caused by coal burning. J Chin Microcirc 10:134–135
Zhang Y, Xing H, Hu Z, Xu W, Tang Y, Zhang J, Niu Q (2022) Independent and combined associations of urinary arsenic exposure and serum sex steroid hormones among 6-to 19-year old children and adolescents in NHANES 2013–2016. Sci Total Environ 160883