Nitish Kumar *Editor*

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Nitish Kumar
Department of Biotechnology
Central University of South Bihar
Gaya, Bihar, India

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About the Editor

Nitish Kumar is a Senior Assistant Professor at the Department of Biotechnology, Central University of South Bihar, Gaya, Bihar, India. He received his master's degree in Agricultural Biotechnology from Himachal Pradesh Agricultural University, Palampur in 2003 and his Ph.D. in Botany from Bhavnagar University in 2009. Dr. Kumar is currently a plant biologist with a focus on Microbial Biotechnology, Plant Tissue Culture, Molecular Marker Development, and Transgenic Technology. He has published a number of research papers in peer-reviewed journals of national and international repute. In addition, he has received many awards/fellowships from various organizations, e.g. the CSIR, DBT, ICAR, and DST. He is an associate editor of the journal Gene.

Predicting the Outcome of Arsenic Toxicity on Exposed Juvenile Male-Humans: A Shift to Infertility

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Victor Eshu Okpashi and Abeng Fidelis Ebunta

Abstract

Toxicity caused by arsenic ingestion on the health of the human male reproductive axis has been researched upon. Numerous pathways linking arsenic toxicity including the endocrine system and hormonal cascade have been elucidated. In this text, several aspects of arsenic effect on human reproductive health, including how arsenic triggered DNA methylation, deregulate spermatogenesis, and decline sperm quality will be discussed. The route of arsenic ingestion, connecting occupational exposure, and polluted water resources are verily implicated in the etiology of arsenic effect on male infertility. Nevertheless, the populaces are worried about how their reproductive health is negatively impacted by arsenic ingestion and its derivatives or combinations. This text exposes several areas, pathways, and mechanisms of actions that necessarily lead to male infertility overtime if adequate intervention and awareness are not brought to bear. The endpoint is that knowledge and awareness by individuals is a key to provoking environmental health campaigns and strategic intervention plans to ameliorate arsenic effect. Diagnostics instruments may be required to avert the onset of arsenic effect before the manifestation and complication of infertility in men due to arsenic ingestion. Therefore, if the knowledge and clinical evidence present here is not appreciated, it will be predicted that over time, there will be physical appearance of two different sexes, with sexually inactive men. That will be the predictive shift to infertility by men due to the effect caused by arsenic and its combination.

V. E. Okpashi (✉)
Department of Biochemistry, Cross River University of Technology, Calabar, Nigeria

A. F. Ebunta
Department of Chemistry, Cross River University of Technology, Calabar, Nigeria

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1.1 Introduction to Arsenic

Arsenic is among the metalloid that is characteristically clustered with other metals when allowing for its progressive and procreative toxicity (Ferm 1972). Arsenic is categorized with light-in-weight metals such as lithium, chromium, fluoride, boron, and aluminum that are originally based on biological substances in minute quantities and perform natural exertion.

Arsenic subsists in three allotropies—yellow, black, and gray. The steadiest allotropes of arsenic are the silver-grey and inelastic-see-through crystal (Blank 1932). It discolors speedily in air, and at elevated heat, it scorches to form arsenic trioxide which appears as a white cloud. Arsenic is a group "Va" metal that combines easily with numerous elements. Arsenic can become inelastic, discolors upon heating, it speedily rusts to arsenic trioxide, with a garlic odor. The non-metallic arsenic is less-reactive but thaws upon heating with strong acids and alkalis.

Hardly do arsenic exists in the form of metal. A source such as incineration, sources-smelters, and coals are generally formed arsenic oxide (particulates) but enters into the soils and water as arsenite and arsenate (Jin et al. 2014). Arsenic from artificial sources such as commercials, industries is used as stable arsenate (Jin et al. 2014). Biological arsenic combination enters the surrounding through saleable application in tiny quantities and is naturally not fragmented into the artificial arsenic. Arsine is been applied in biotechnology factories that culture microorganisms to remediate and degrade polluted soil, it is swiftly dissolved to arsenate and arsenide (USPHS/ATSDR 1999). Arsenic is adhesive to the soil particles, partition in the soil strata, but can percolate into the water during the raining seasons. In a location with increased earth-arsenic deposit (naturally from sulfide raw material and volcanic soils), there is an increase in arsenic concentrations and bioaccumulation in water and plant (USPHS/ATSDR 1999).

1.1.1 Applications of Arsenic

Most arsenic derivatives are utilized in the construction of distinctive varieties of glasses, preservation of wood and, newly, in the construction of semiconductor—gallium arsenate with the capacity to translate current from electricity to laser-light. Arsine (AsH3) gas is a vital dopant in the microchip industry used to alter the properties of some substances such as conductivity. Although, strict compliance is required during utilization of arsenic compounds because of toxicity. However, during the medieval era, several arsenic mixtures were applied as medications. For example, copper acetoarsenite that was previously applied as a green-pigment had different appellations.

1.1.2 Environmental Arsenic

Arsenic can occur naturally on the earth's crust in tiny amounts. It befalls in the soil and may go to the air, water, and land via wind-blown, dust, and surface water run-off (USDHEW (1966). Atmospheric arsenic emanates from different cradles like volcanoes may discharge about 3000 tons per year and microorganisms may as well liberate about 20,000 tonnes of explosive methyl arsines per year, while human activity is perceived to give out about—80,000 tonnes of per year (Air Quality and Emission Data 1968). In spite of its infamy as a lethal toxin, arsenic is still a vital delineating element for some animals, and humans at 0.01 mg/day intake.

Arsenic is a constituent that is changed to water-soluble or explosives. The concept that arsenic is natural and objectively migratory suggests that huge quantities of arsenic may not be intense at a specific site (Angino et al. 1970). This is good because the negative impact of arsenic pollution has become an issue because of its spread spectrum. The immobility of arsenic makes it difficult to be mobilizing (Haq et al. 2012). Human activities such as mining and smelting, and immobile arsenic have been transported and are now seen in locations other than where they previously existed. Tiny un-combined arsenic can occur as microcrystals (Bibha et al. 2016). Some arsenic is seen in aggregation form with sulfur—arseno-pyrite (AsFeS), realgar (an orange-red mineral consisting of arsenic sulfide and having a resinous luster), orpiment (an uncommon orange to lemon-yellow element comprising of built-in trisulfide of arsenic), and enargite. None of these minerals are mined because they are been produced as by-products of refining copper and lead ores. The production of arsenic oxide is about 50,000 tonnes annually globally, in excess of that required by industries. The main country that exports arsenic oxide is China next is Chile and Mexico. The global production of arsenic from copper and lead raw materials had exceeded ten million tonnes.

1.1.3 The Outcome of Arsenic Concentration in the Environment

The arsenic dominance in the environment and atmospher is caused and sustained by anthropological meddling. Therefore, the termination of arsenic in the environmental media and in living organisms is predictable if arsenic pollution is control. Arsenic originates from the industries that mined copper, lead, and zinc (EPA 1986). It is difficult to destroy arsenic once it has permeate the soil strata and, additional, the concentration of arsenic may spread and cause defect on the health of humans and animals at various locations. Plants readily absorb arsenic, such that at increase concentrations may have a dominant concentration in food and crops. The level of synthetic arsenic in surface waters is sufficient to trigger a genetic alteration in fish like zebra (Janell et al. 2016). This trigger is caused by a build-up of arsenic in the frames of edible vegetables, fruits, and freshwater creatures (Sayan et al. 2012, Okpashi et al. 2019). Carnivores and herbivores who feed exclusively from organic matter (plants and animals) will always ingest high amounts of arsenic and may suffer injury or death due to arsenic poisoning.

1.1.4 How Arsenic Contaminate the Water

Naturally, arsenic can be seen in some soil strata and layers. When arsenic is mixed with groundwater it may remain in the water as a recalcitrant contaminant. Arsenic is a metal-like, which fundamentally suggests that it has the properties of a metal and that of a non-metal. As a composite, arsenic can be exceedingly toxic. That is why it is ordinarily used in the formulation of rat poison. The industrial production of arsenic from lead and copper ores and the application of insecticides on farmland are implicated as sustainable sources of generating and circulating arsenic in the environment. Furthermore, arsenic is an essential ingredient for preserving wood. The WHO recommends that a 10 ppb of arsenic ought to be the maximum concentration in groundwater. Even though arsenic may be in surface water due to run-off, groundwater is the main source of arsenic because of percolation. Inevitably, a level above 10 ppb can be ascertained unsurprisingly in groundwater. Arsenic is water-insoluble and biological arsenic (AS-V) anions or (AS-III) molecules exist in groundwater.

1.1.5 Effects of Arsenic on Human Health

Arsenic is among the noxious metals in the earth's layer. Despite the noxious outcome of arsenic, synthetic arsenic appears on the soil innately in tiny quantities. Human beings can be unprotected to arsenic through food, liquid, and airborne. The unproductiveness of individuals can befall through skin connection with the soil or water containing arsenic. The arsenic levels in food may be reasonably low since its toxicity is drastically reduced during food processing and coking. Marine organisms such as planktons, small jellyfish, comb jellies, sober-toothed—(called arrowworms or chaetognaths) may contain high level of arsenic because they usually imbibe arsenic from the surroundings. Providentially, this form of organic arsenic is fairly mild in reactions, but fish that bears substantial quantities of synthetic arsenic can be dangerous to the health of humans (Young et al. 2014). Exposure to arsenic might be greater for people working in arsenic extracting factories, people living in woods houses that are preserved with arsenic, and farmers who spray their farmlands with arsenic formulated insecticides and pesticides. Contact with synthetic arsenic can result in a number of health effects, including stomach irritation and intestines, dwindled red and white blood cells formation, change in skin complexion, and lungs exasperation (Buchet et al. 1981). The uptake of substantial measures of synthetic arsenic can build up the chances of developing cancer, particularly the probabilities of incurring different types of cancers like cancer of the skin, lung, liver, and lymphatic. Prolonged contact with synthetic arsenic can cause infertility and reproductive insufficiencies in women (Cecilia et al. 2017), and weakened the competition against infectious diseases, heart disorders, and brain damage in men and women (Cecilia et al. 2017). Synthetic arsenic can originate DNA mutilation (Victor et al. 2011). A lethal dose of arsenic oxide is about 100 mg (Barbara et al. 2004).

1.2 Absorption, Distribution, and Excretion of Arsenic

In humans, the accumulative concentration of arsenide and arsenate in the intestinal strip is about 90% (Vahter and Envall 1983). Nadir values of about 39.9% and 49.9% were reported in hamsters (Odinaka et al. 1980). Oral administration of arsenic indicated that bioavailability in humans is about 55% and 79.9% for synthetic arsenic (Buchet et al. 1981). Surface availability of arsenic in the soil and household dust polluted with radiations from smelting showed 14.9% in monkeys upon inhalation (Freeman et al. 1995). In rat's intestine, phosphate represses the absorption of arsenate (Gonzalez et al. 1995). In animals, the immersion of arsenic upon intratracheal linking is about 89.9% for soluble arsenic composites. Vahter and Envall (1983) quoted a previous investigation by Holland et al. (1959) wherein 86–89% of arsenic was set-down in cigarette smoker's lungs.

The binding of arsenic is to plasma proteins is a loss, but readily fused with red blood cells before binding to intracellular proteins (Vahter and Envall 1983). Arsenic is rapidly distributed to tissues. Arsenide is strongly bound to dithiol and vicinal thiol moiety; it is well linked to protein than arsenate (Styblo et al. 1995). The binding of arsenic to metallothionein has not been observed (Chen and Whanger 1994). Kreppel et al. (1994) proposed that treatment with zinc could serve as an inhibitor of arsenic pestilent. Primarily, the eradication of arsenic follows through the excretion of urine, with a trifling biliary contribution of arsenic which varies in species (Vahter and Envall 1983).

1.2.1 Metabolism of Arsenic

The breakdown of arsenic differs among species, but similar in components of their pathways. Methylation is the main mechanism where decontamination of arsenic can occur, granting that the latest reports on binding of zinc to intracellular protein restrained arsenic toxicity in the liver and gut. Lately, a protein that binds to arsenide was recognized in the liver of the rabbit (Bogdan et al. 1994). Arsenide binds to glutathione and gets methylated to s-adenosyl methionine. At the intracellular level, arsenate is transformed to arsenide via redox cycling to methylation as a first step mechanism. Lately, it was proposed that when glutathione binds to arsenate and biological arsenic, it becomes reduced before methylation takes place (Delnomdedieu et al. 1994). During urination, mono-, di-, and tri-methylated species are eliminated as waste. There is a breakdown of biological arsenic. Humans lack the enzymes that break down arsenic to carbon (As-C) bond in arsenobetaine, occasionally expelled unaffected (Lee and Ho 1994). The substantial volumes of arsenide and arsenate do not originate from swallowing organic arsenic (Buchet et al. 1994). Their types vary due to methylation (i.e., the quantity of nonmethylated arsenic expelled), the methylated types forms what is called mono, di, tri-methyl arsenate. The biliary excretion of arsenic and binding to tissues before and later methylation can be predicted (Vahter et al. 1995). There is a broader spectrum of arsenic methylation in some mammals such as rats, mice, and dogs, than in hamsters, rabbits, and

humans. Remarkably, two studies showed that non-human primate types—marmoset monkeys and chimpanzees were not enable to methylate arsenic (Vahter et al. 1995), and it is applicable to guinea pigs (Healy et al. 1996). The central place for methylation is the live, with a wide-ranging medication. However, some cells have arsenic methylation capacity (Fischer et al. 1985). The rabbits, hamsters, and rats have exhibited key biliary secretion while less biliary excretion is observed in mice and humans. Humans can expel a substantial quantity of monomethyl arsenate. Diverse methyl transferases are implicated in the mono and dimethylation pathways. Efforts are ongoing to ascertain arsenic binding proteins that ought to help in the clarification of relative metabolism.

Some researches explain the differences in methylation among animal species built on acute, single-dose administration. Though there are metabolites enlisted to be linked to habitually unprotected persons Foa et al. (1984); Valentine et al. (1979 suggest that prolonged treating may not modify the pathway that breakdowns arsenic. Severe doses in mice can decelerate methylation and result in the accumulation of intermediary products (Hughes and Menache 1994). Conversely, no index that measures methylation—the threshold to ascertain arsenic toxicity in humans to establish the disparity in the rising of arsenic has been identified (Hopenhayn-Rich et al. 1993). At the physiological level, and pharmacokinetic (PBPK) representations, there is a hope that across species, dosing will correlate the concentration of arsenic in the tissue of different species and show similar lethal reactions. PBPK has been formulated for the testing of hamsters and rabbits models, the classes of animals with close resemblance to humans in terms of methylation patterns (Mann et al. 1996); still, fetal barrier and procreative structures were not incorporated in the designed model.

1.2.2 The Role of Arsenic in Male Reproductive Functions

Arsenic has a great influence on male reproductive health. Even though men suffer privation in terms of the ability to be gauged reproductive cycle, success has been achieved in appraising trials that will ascertain chemical hazards and assess reproductive health risks. The need for reactive chemicals with the capacity to covalently interact with biological systems should be appraised, and demarcated as mutagens and/or carcinogens. This will rate them as potential actuators of aneuploidy, chromosomal anomalies, usually distress the motility of sperm and affect hormonal actions.

The male reproductive system can be impacted negatively by a straight attack of arsenic on the testis. Eventually, that will modify the sperm making process, by diminishing the auxiliary secretion of the sex gland, and neuroendocrine system, which causes the disparity in hormone (Chandra et al. 2012). Adverse effects of arsenic on the fertility of men comprise the transformed sperm, which modifies the spermatogenetic pathway, causes loss of gestation, and heritable disease in offspring. Shared endpoints for evaluating the male procreative task embrace the size of the testis, quality of semen, secretory role of the prostate and seminal vesicles,

procreative endocrine task, the ineffectiveness of sperm, and sterility (Nordberga et al. 2005). Existing proof implicated the environment as culpable reasons why there is a fall in sperm quality.

Additionally, contact with pesticides containing arsenide has been linked to the modifications in the spermatogenetic pathway. When measuring the arsenic effect on the reproductive health of men, it is important to create a space for possible influences of exposure to some other contaminants. Their combination usually acts via accumulation, potentiation, synergistic, or antagonizing. Some toxic metals like lead, copper, and cadmium are predominant in the soil and amass in the soil and edible crops over a lifetime (Okpashi et al. 2019). The indicators for lead and cadmium toxicity usually correlate with the toxicity of arsenic (Lin et al. 2010).

Recent evidence point out that male reproductive capability has depreciated. The advent of industrialization has caused many couples to search for in vitro insemination (IVI) due to deprived semen quality (Nordberga et al. 2005). Data collated over the last three decades have revealed alarming drifts in male reproductive health. Erstwhile reports discovered that men birth later than 1970 years had about 25% sperm count lower than men birth earlier than the year 1959, an average of 2.1% decline (Brown and Caseldine 1999). The lowness of sperm count was linked to deprived semen quality (Waissmann 2002). The wide variance in the mean semen level between countries, and diverse localities within a country, has been detected. The men have comparatively minute fertility chances, likened to other animals. For instance, the quantity of sperm for each ejaculation by a human is about twofold–fivefold greater than the quantity of semen from an abridged fertility, while the quantity of sperm from mouse, rabbit, and bull for each ejaculation is several times (up and about 1400-fold) greater than the quantity that yields fertility. Male-humans require a noticeably reduced size of the testis and a low rate of sperm making daily for each gram of testis, by a factor greater than 3, compared to mouse, rat, or monkey. The ratios of motile spermatozoa to healthy spermatozoa in men's semen are lesser relative to other mammals.

The human male may be susceptible to arsenic toxicity than rat for the reason of shoddier efficiency of the antioxidant, resistance to the coordination and superior susceptibility to oxidative injury, spermatozoa DNA and attack by sulfhydryl (–SH) moiety, which is needed to repair sperm maturation and motility. Since the variances between arsenic effect in procreative endpoints and the pathway of arsenic toxicity can be monitored, the duration of contact to arsenic and data from experimental animals may be beneficial for approximating permissible human contact limit. Granting that studies on animal models have shown the adverse outcome of arsenic on the reproductive pathway, increase amounts of various metals may be suitable to elicit shielding effects against other heavy metals (lead, copper-zinc, selenium, and magnesium). The dosages of the metals were not sedate and very few types of research have appraised the special effects of long-term vocal administration or induction of arsenic to an animal. For most metals other than arsenic, data pertinent to individuals are short and incomplete by insufficient regulation and modifications that will affect confusing variables (Nordberga et al. 2005). The male reproductive tract that is attacked by an endocrine disruptor can upset some marked cells or

receptors such as testes that are paired for the making of sperm and androgens. There are regulations at the para- and autocrine compartments of the testes under influences of pituitary and hypothalamus. According to a report by Zubair et al. (2016), oxidative stress (OS) occasioned by reactive oxygen species (ROS) is a possible negative outcome of contact to arsenic. Thus, a high level of arsenic can subdue gonadotroph sensitivity to GnRH and gonadotropin secretion by raising the plasma level of glucocorticoids. These can eventually widen the toxicity of the gonad in men thereby causing a shortfall in sperm quantity, sperm capability, and motility. A substantial relapse of germ cells and modifications of luteinizing hormone, follicle-stimulating hormone, and testosterone are feasible. ROS-hydrogen peroxide (H2O2), superoxide anion, singlet oxygen, and hydroxyl radical can impair cellular DNA and protein. Hydroxyl radical is considered a dire species that rightly attack DNA. In order for hydroxyl radicals to cause arsenic carcinogenesis, iron which is a free transition metal is necessary for the Haber–Weiss sequences to cause DNA mutilation. Comparing the different compounds of arsenic, iron releasers from ferritin methylated arsenic were extra energetic than arsenate or arsenide. The trivalent arsenic was extra active compared to pentavalent arsenic while the DMA (III) was a more active iron releaser from ferritin (Ahmad et al. 2000 cited in Flora et al. 2007). A collective exposure of in vitro ascorbic acid and DMA (III) gives rise to a great synergistic rise in iron released from ferritin and a significant synergistic rise in DNA impairment (Ahmad et al. 2000). The induction of rats with arsenite causes the liver cell and kidney cells heme-oxygenase isoform 1 (Kitchin et al. 1999).

The induction of heme-oxygenase initiate the making of CO, biliverdin, and iron. Also, 8-Hydroxy-2′-deoxyguanosine (8-OhdG) is among the main ROS that causes DNA impairment. It is used as an indicator of OS to DNA (Yamanaka et al. 2001). In enduring carcinogenesis research, liver cells 8-OhdG levels amplified in DMA cured patients signify that DMA raises the percentage of a free radical bout on DNA (Wanibuchi et al. 1997). Barchowsky et al. (1999) verified the making of free radicals in mice, after severe contact to synthetic arsenic. In human lymphocytes that were cultured and exposed to arsenite, a rise in sister chromatid give-and-take regularity was alienated via the inclusion of superoxide dismutase and catalase (Nordenson and Beckman 1991). Initiation of micronuclei in 20 ml of arsenide (CHO-K1 cells) was alienated by nitric oxide synthase inhibitors—superoxide dismutase and uric acid (Gurr et al. 1998). This outcome proposes that specific clastogenic effect of arsenic is facilitated by free radicals—peroxynitrite, superoxide, H2O2, and free iron. Toxicity of trivalent arsenic is done by attacking—SH groups, and by generating ROS (Chen et al. 1998). The toxicity of synthetic arsenic (iAsv) gives the impression that it is facilitated by its tendency to replace phosphate moiety, by upsetting the enzymes that rely on the moiety, by interfering with the ATP and DNA synthesis. However, the mechanism for making reactive intermediate is not entirely implicit, even though Yamanaka et al. (2001) wished-for the realization of intercessory arsenic types.

Further likelihoods for arsenic to generate ROS are based on the oxidation of iAsIII to iAsV in functional circumstance, which will yield H_2O_2:

$H3AsO_3 + 2H_2O + O_2\ H_3AsO_4 + H_2O_2$. Hydroxyl radicals are the originators of lipid peroxidation (LPO), where iron-catalyzed Fenton in membranes (Halliwell and Gutteridge 1986). Erythrocytes are at risk of oxidative injury due to haem-iron, polyunsaturated fatty acid (PUFA), and oxygen, that kick start the reactions that cause oxidative injuries in red blood cells. The antioxidants enzyme in the erythrocyte often neutralizes OS. For illustration purposes, superoxide dismutase (SOD) catalyzes the conversion of superoxide radical (O_2-) to H2O2 while catalase (CAT) and glutathione peroxidase (GSH-Px) convert H2O2 to H2O. These antioxidant enzymes help to lessen the lethal effects of ROS. The cell has several ways of alleviating OS, repairing the damage, and weakening the incidence of oxidative damage (OD) via enzyme and non-enzyme antioxidants activities. The enzyme and non-enzyme antioxidants help to sift free radicals and ROS. A non-enzyme antioxidant—vitamin E and vitamin C helps to overwhelm the OS (Lee and Ho 1994). The oxidants impaired the macromolecules in the cells and function as secondary messengers, which lead to changes in the expression of gene and improvement of successive cells multiplication (Farber 1994).

1.2.3 Impairment of the Male Reproductive System by Arsenic

In men, arsenic can weaken the quality of semen. In research that evaluated the semen based on its motility, capability, membrane veracity, and DNA, these parameters were considered as key in men's procreative role (Zubair et al. 2016). In one experiment, 177 males adults age less than or equal to 50 years ingested about 50 ppb of arsenic in potable water. The report showed an increase in the risk of erectile dysfunction due to reduced testosterone in circulation (Hsieh et al. 2008). Previous reports directed that men exposure to arsenic can deregulate semen quality and be of assistance to determine the urinary biomarkers. In another report, about 159 fresh semen were collected from the sterile men and 65 controls collected from Chines were separated on the premise of Ureaplasma and urealyticum (Uu). An increased level of arsenic was observed in patients with Uu syndrome bearing a high level of spermatozoa quality more than patients without Uu syndrome (Wang et al. 2005). In the same report, it was observed that 75 semen samples that were collected from sterile men and 75 semen samples collected from productive men within the age 38 years were screened for the concentration of arsenic (Inhorn et al. 2008). The arsenic level in the semen was lower in men that were sorted from infertile-environment-occupation and compared with men found at fertile-environment and infertile-environment. Oligospermia (low sperm count), azoospermia (absence of spermatozoa from the seminal fluid), and asthenospermia (immotile spermatozoa in the ejaculate) had lower arsenic in the semen than usual spermatozoa counts. Oligoasthenospermia (a combination of Oligospermia and asthenospermia) had a marginally greater arsenic level in the spermatozoa, though it was not suggestively greater than the average spermatozoa counts (Inhorn et al. 2008). Environmental exposure of 96 men aged 32 and 36 years to arsenic reduces the semen quality by

lessening the sperm count. This was clearly linked to arsenic level in the blood and semen (Xu et al. 2012).

The toxic outcome of arsenic ingestion on the reproductive structure of male adult mice has been investigated. The mice were ingested with 40 mg/L of sodium metaarsenite into potable water for 30, 45, and 60 days, respectively. Observation revealed that the interruption of spermatogenesis and post-meiotic stages together with the disruption of spermatocyte formation from spermatogonium of mouse response depends on the dosage of ingested arsenic. See Fig. 1.1 for illustration on how arsenic toxicity affects the steroidogenic pathway and consequently causes infertility in exposed male adults. This occurs by reducing the diameter of seminiferous tubules, gametogenic—the inactive spermatocyte, pachytene, step 1 to 7 spermatid declines excluding spermatogonia (undifferentiated germ cells in male) and atrophy in Leydig cells (Sanghamitra et al. 2008). A cross-sectional research in Chinese by Weipan et al. (2012) reported that environmental exposure to arsenic may reduce human semen quality. They further stated that an in vitro and in vivo study recommended arsenic as an endocrine disruptor (compounds that mimic and interfere with hormone). The exposure of male rats to As shows steroidogenic impairment which leads to sterility. The different species of arsenic (As) can be obtained through several metabolic pathways such as methylation, the major pathway that creates synthetic (Asi) in men. It was reported that the pathway that breakdowns Asi utilizes the following reaction mechanism: AsiV+2e– →Asi III + CH_3 + →MMAV (CH_3) AsO (OH)2) + 2e– →MMA III + CH_3 + →DMAV (CH3) 2AsOOH) + 2e– →DMA III + CH_3 + →TMAO (trimethylarsine oxide) (Madhyastha et al. 2018). Still, these mechanisms of reaction do not completely breakdown As, and their derivatives—Asi, MMA III, and MMAV, may remain in the body to cause methylation of DNA (Argos et al. 2012; Kim and Kim 2015). To establish the loci for As outcome on the men procreative organ, Kaviyarasi et al. (2018) stated that specific proteins involved in spermatogenesis were deregulated after treatment with arsenic. Calcium-binding protein and spermatid-specific protein 1 (CABS1) were vastly expressed in extended spermatids. It is particularly involved in the readjustment of a composite structure which arises from haploid germ cells during spermatogenesis (Tamba et al. 2009). Exposure of male mice to 1, 5, and 25 mg/L of sodium arsenite for 6 months raised CABS1 sideways with a deficiency in reorganizing a compound structure that transpires in a haploid germ cell, and hinders spermatogenesis in male rats (Huang et al. 2016). Exposure to sodium arsenide and sodium arsenate at 0.01 mg/L and 10 mg/L/for 56 days in potable water reduces the procreative properties of male rats. The administration of 10 mg/L of the arsenide moiety caused a decreased sperm in production due to the overproduction of H2O2 and damage to germ cells. It revealed that reduction of sperm count in epididymis can decrease the percentage of sperm as well as the intact membrane. A quantity of 10 mg/L of arsenate which was given to such a group of rats facilitated the OS in the epididymis, which damages the sperm membrane with no effect on fertility.

Arsenic (As) is considered a major environmental health hazard all over the world. Prolonged ingestion is connected with amplified health risk like cancer,

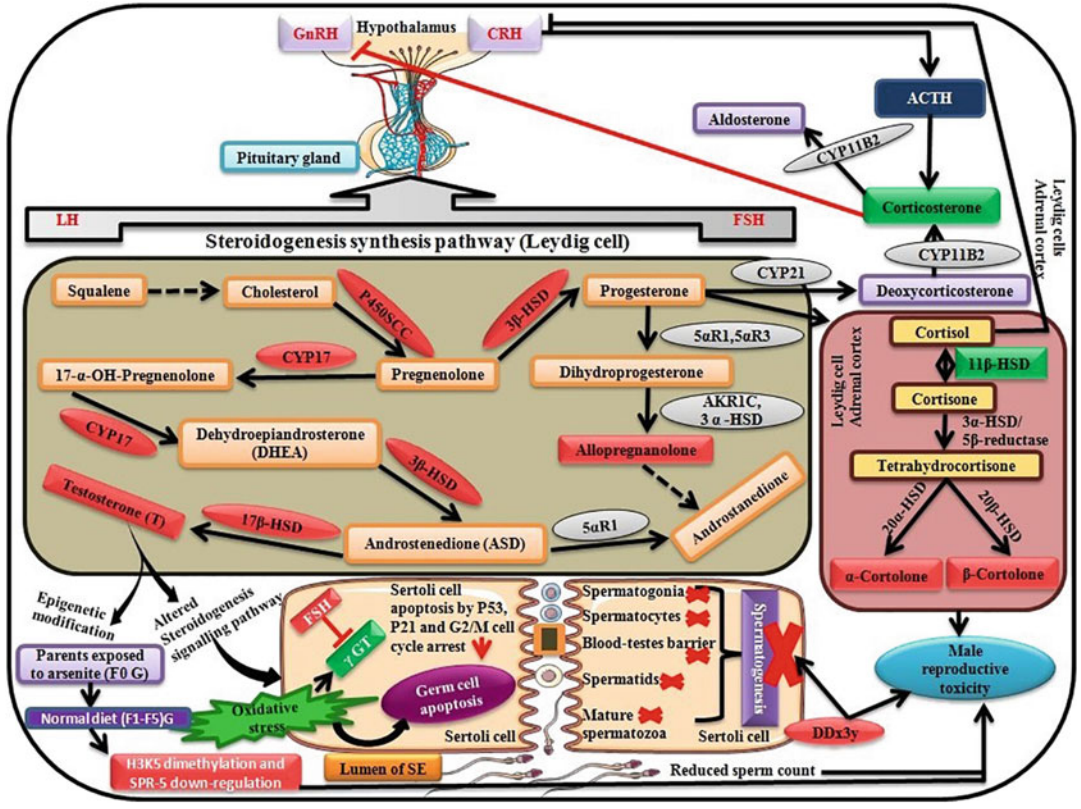

Fig. 1.1 Induction of male reproductive system with arsenic. This explain how arsenic affects the function of endocrine—GnRH, CRH, LH, and FSH, deregulate testosterone synthesis (from cholesterol to testosterone by reducing the level of enzymes—P450SCC, 3β-HSD, CYP17, and 17β-HSD; metabolite allopregnanolone and testosterone) and cortisol pathways (cortisol to cortolone by increasing 11β-HSD enzyme and corticosterone which inhibits GnRH, decreased metabolites—Cortolone) in Leydig cells, decreased testosterone synthesis defects the process of steroidogenesis signaling pathways in Sertoli cells (inhibition of spermatogenesis, germ cell apoptosis, Sertoli cell apoptosis, increased OS mediates the Sertoli marker γ-GT, downregulation of Ddx3y gene), epigenetic modification through down regulation of SPR-5 upon H3k5 dimethylation. Red color indicates decreased enzymes/metabolites after arsenic treatment. Green color indicates increased enzymes/metabolites after arsenic treatment. Adapted from Kaviyarasi et al. (2018)

diabetes mellitus, and cardiovascular disease, submits that trace levels of about 5–10 ppb can exacerbate the health risks. Jack et al. (2004) agreed that a 0.05–1 íM (6–120 ppb) of arsenic can exert energetic outcome on the glucocorticoid receptor (GR)-mediated gene activation in rat's EDR3 hepatoma cells having endogenous tyrosine aminotransferase (TAT) gene and reporter genes having TAT glucocorticoid response elements. At a trace concentration of about 1–3 M As may become inhibitory. Accordingly, on a small concentration, the As effects may change after stimulation of a twofold to fourfold or greater than two-fold inhibition of inactivity. The suppression outcome of GR on AP1- and NF-B-mediated gene activation was not affected by As. The cellular level of hormone-activated GR is dependent on the degree of stimulating and inhibiting the GR. Deletion mutation indicates that the DNA binding domain (DBD) of GR is the area for As to elicit effect and without using free sulfhydryls moiety. Point mutations located within the DBD usually changed the GR responses to As binding significantly.

Arsenic trioxide (As_2O_3) has gain thoughtfulness for the reason that it can cause an ample decrease in serious promyelocytic leukemia (APL) (Tzeon-Jye et al. 2008). Despite the result of arsenic trioxide (As_2O_3), the U.S. Food and Drug Administration had ratified the application of As_2O_3 in the cure for degenerated acute promyelocytic leukemia (APL). The beneficial prospective and antitumor action of As2O3 has blowout to non-APL leukemia, myelodysplastic disorders, and various myeloma, including solid growths and cancer cell lines, together with neuroblastoma, renal, prostate, colorectal, and hepatocellular tumors (Lin et al. 2006). Antitumor activity arises through inducing cell apoptosis (Oketani et al. 2002; Zhang and Wang 2006). Arsenic exerts its toxicity by producing ROS during redox cycling and activation of metabolic routes that causes tissue injuries. The sensitivity of cells to As_2O_3 is contrariwise correlated to their intracellular glutathione level and the action of antioxidant enzymes (Nakagawa et al. 2002). Arsenite fixes thiol (S-H) moiety in tissue proteins and abates the protein function. Despite the in-depth studies, there is no clearer report on the results of As_2O_3 on the men procreative structure.

The report on the venous injection of radioactive arsenate (As-V), or arsenide (As-III) to mice and hamsters by Danielsson et al. (1984) submitted that arsenic accumulates in the duct and lumen of epididymal. This proposes that there was continuous ingestion of arsenic to the rat's sperms in the lumen in vivo. Sarkar et al. (2003) also informed about the inhibitory action of sodium arsenide on spermatogenesis, gonadotrophin, and testosterone in rats. There are several possible mechanisms meant for the antigonadal actions against toxic chemicals. They wield an inhibitory action on the testis and affect the hypothalamic–pituitary axis by triggering changes in plasma concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). It has been established that by reducing plasma LH, Leydig cells are greatly damaged thereby causing a decrease in testosterone production. Testosterone is an essential hormone for normal spermatogenesis, whereas FSH is needed for normal testicular role and spermatogenesis (Jana et al. 2006).

1.2.4 How Arsenic Impact the Male Reproductive System

Arsenic could upset the men procreative system when a precise procreative organ is targeted or when they act on the endocrine system. The former can be termed direct target while the latter is called an indirect target. The distress could be prolonged irreversibly especially when the Sertoli cells are interrupted at the time of developing the fetus. The amount of Sertoli cells defines the number of spermatozoa that can be manufactured by an adult-human since every Sertoli cell can be cared for in a limited quantity of germ cells that will mature into sperm. Agreeing with Apostoli et al. (2007), Sertoli cells multiply at the time of fetal, neonatal, and pre-pubertal development, while each of these phases is liken to suffer from arsenic effect. The interruption of spermatogenesis at any phase of differentiating cells in men can shrink the total spermatozoa count, surge the irregular spermatozoa count, weaken the strength of spermatozoa chromatin, or injure the DNA of spermatozoa (Mangelsdorf et al. 2003). When arsenic accumulates in the epididymis, prostate, vesicular seminalis, or seminal fluid might weaken the continuous sperm motility (Hess 1998). Thus, arsenic can reason imbalance in several hormones through the endocrine system, by unsettling androgen discharge in the Leydig cells or inhibit B cells in the Sertoli cells (Jensen et al. 2006). There are mounting indications that OS is connected with the pathogenesis of men sterility (Pizent et al. 2012). See Fig. 1.1 for illustration.

It has been established that spermatozoa from human are susceptible to OS. The peroxidation of polyunsaturated fatty acids inside the plasma membrane is caused by a disproportionate generation of ROS in the spermatozoa (Koppers et al. 2008). Several arsenic combinations, including iron, copper, and lead, usually increase the generation of ROS, deregulate glutathione and other antioxidant levels, improve lipid peroxidation of the cell membrane, reason for apoptosis, and add to the generation of OD on the DNA (Jones et al. 1979). Damage of the sperm membrane decreases the motility of sperm and its affinity to oocyte while the mutilation of spermatozoa DNA can damage the parental genomic of the embryo (Tremellen 2008) and raises the sterility chances, abortion, or serious teratogenicity of the progeny (Aitken et al. 1993). Some teratogenicity of the men procreative parameter, such as cryptorchidism (undescended testicle), hypospadias (a reproductive abnormality in men where the urethral meatus opens from the ventral side of the phallus and not on the tip of the penis), thus cancer of the prostate and testicular may arise upon contact to endocrine-disrupting metals such as arsenic (Chedrese et al. 2006). Suggestions are commonly restricted to animal data or to in vitro studies (Iavicoli et al. 2009). The medical and epidemiological consequences are rare and contentious, and usually challenging to infer due to numerous exposures to diverse causes and latency of effects.

1.2.5 How Arsenic Weakens Spermatogenesis in Male Rat Testis

Spermatogenesis is a cellular progression that takes place in seminiferous tubules and generates mature sex cells within 74 days (Mangelsdorf et al. 2003); it begins at puberty and often continues till death. It is a compound development that produces mature spermatozoa that is crucial for reproduction in men. According to Qingyu et al. (2016) who reported that five upward-regulating and five downward-regulating proteins, and one decreased metabolite were observed in spermatogenesis as reactive to the treatment of arsenic in rat testis. Glutathione peroxidase 4 (GPx4) is the leading selenoenzyme in testis and is crucial for spermatogenesis (Schneider et al. 2009). Overexpression of glutathione peroxidase 4 in rat testis triggered a spermatogenetic defect, together with haploid cell loss, seminiferous epithelium disorganization, and apoptosis of spermatocyte (Puglisi et al. 2007). Similarly, endocrine-disrupting chemicals (EDC) pose a harmful effect on spermatogenesis by an abnormal heightening of GPX4 expression in rat testis (Baek et al. 2007). Corticosteroid 11β-dehydrogenase isozyme 1 (11β–hydroxysteroid dehydrogenase, HSD11B1) catalyzes the conversion of inactive cortisone to active cortisol, it is situated completely in the Leydig cells. HSD11B1 was proposed to play a significant function in sustaining steroidogenesis via making cortisol which is implicated in the formation of testosterone (Sharp et al. 2007). A greater level of HSD11B1 activity has been connected with lesser spermatozoa count and upper level of abnormal spermatozoa (Nacharaju et al. 1997). Nuclear autoantigenic sperm protein (NASP)—a histone chaperone binds to H1 linker histones is responsible for transportation of arsenic into the nucleus of dividing cells. Testicular NASP (tNASP) is intricate in cell advancement in spermatogenetic cells, possibly through the interface with the Cdc2/cyclin B and Hsp70-2 complex (Alekseev et al. 2005). Overexpression of tNASP during androgen receptor obstruction would possibly inhibit spermatocyte meiosis (Stanton et al. 2012). Calcium-binding and spermatid-specific protein 1 (CABS1) is a calcium-binding protein that precisely showed the elongated spermatids. It is included in the compound structure and reorganizations in the haploid germ cells during spermatogenesis (Kawashima et al. 2009). Heat shock 70 kDa protein 4-like (HSPA4L) is an HSP110 heat shock protein family is expressed all in the testis. It has been reported that the ratio of matured sperm to sperm motility may reduce hugely in HSPA4L-deficient male mouse occasioned by increased levels of apoptosis in the germ cells (Held et al. 2006). When the expression of GPX4, HSD11B1, NASP, and CABS1 is raised, spermatogenesis will be decreased and low sperm quality would be inevitably formed, this buttressed the fact that the number of spermatozoa and spermatozoa motility can decline in arsenic ingested rats, see Fig. 1.2. Though, the upward-regulation of HSPA4L may show opposition to arsenic-induced germ cell apoptosis. Scaffold attachment factor B1 (SAFB1) bears a transcriptional repression domain and can bind to some receptors and repress their activity. Male SAFB1 mouse can be sterile due to apoptosis amplification germ cells, Leydig cell hyperplasia, and small testosterone deregulation, which is caused by the decrease in circulating insulin-like

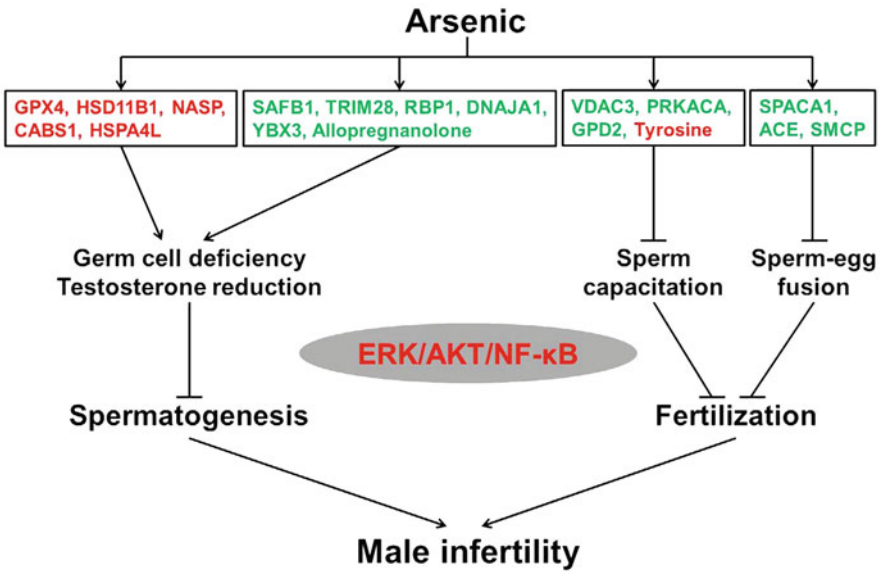

Fig. 1.2 Representation of pathways affect by arsenic induces male reproductive toxicity in rat testis. Molecules in red denote upward-regulation, while the green signify downward-regulation. Adapted from Qingyu et al. (2016)

growth factor 1 (IGF1) and loss of SAFB1-mediated repression of hormone receptors (Ivanova et al. 2005).

Transcriptional intermediary factor 1 (TIF1) β (also called KAP-1 or TRIM28) is a co-repressor that plays a role in spermatogenesis and initial embryonic development. During spermatogenesis, TIF1β is biasing to heterochromatin structures of Sertoli cells and round spermatids, meiotic chromosomes (Weber et al. 2002). Herzog et al. (2011) observed that the lack of TIF1β may lead to a defect in spermatogenesis occasioned by the poor release of spermatid and degenerating testis. Retinols are necessary for the upkeep of spermatogenesis in testis, and sustained shortage of retinol may give rise to spermatogenic arrest at the preleptotene spermatocytes trailed with widespread loss of germinal epithelium in rats. Retinol is conveyed into the seminiferous tubules by retinol-binding protein 1 (RBP1), found in Sertoli cells (specific plasma transport protein). The roles of RBP1 include the transfer of retinol to the developing germ cells (Rajan et al. 1990). DNAJ1 homolog subfamily of A member 1 (DNAJA1) works with a co-chaperone of Hsp70s in protein folding and mitochondrial protein import. It has been observed that the loss of DNAJA1 in mice led to a failing of Sertoli cells in preserving spermatogenesis, increasing androgenetic receptor (AR), and interruption of Sertoli-germ cell, which shows a dire role of DNAJA1 in spermatogenesis via AR-mediated signaling in Sertoli cells (Terada et al. 2005).

The protein family with a Y-box has been recognized to be among the utmost preserved families of nucleic acid-binding protein. A notable reduction in protamine

2 transcription will occur when the PAF-RE and Y-box binding protein 3 (YBX3, YB2) is erased, and proposes that YBX3 is required for the activation of protamine 2 transcription in post-meiotic germ cells (Kota et al. 2010). Allopregnanolone is a metabolite of progesterone produced by the reaction of 5α-reductase and 3α-HSD (Santoru et al. 2014). Since progesterone is the main intermediary in testosterone biosynthetic, it is correct that arsenic ingestion declines allopregnanolone levels since it facilitates the reduction of progesterone and impaired testosterone production. This mechanism is connected to the decrease in testosterone and sperm quality. Therefore, the weakening of SAFB1, TRIM28, RBP1, DNAJA1, YBX3, and allopregnanolone could damage the irregular spermatogenetic process due to paucity of germ cells and lesser testosterone level in arsenic-exposed male organisms.

1.2.6 How Arsenic Obstructs Insemination of Rat Sperm

In female mammals, insemination is the combination of a spermatozoon with an ovum, which first forms a zygote and progresses to the embryo. Qingyu et al. (2016) reported that 6 downward-regulated proteins and 1 improved metabolite are linked with impregnation of mouse exposed to arsenic. Voltage-dependent anion channel protein 3 (VDAC3) is an isoform of VDACs, inherent in the mitochondrial proteins of eukaryotes (Craigen and Graham 2008). VDAC3 is contained in the acrosomal region and midpiece. The blocking of VDAC3 decreases the acrosome action, phosphorylation of tyrosine, and later impregnation, which signifies the crucial function of VDAC3 in male fertility (Kwon et al. 2013). A cAMP-dependent protein kinase catalytic subunit alpha (PRKACA) is a serine/threonine kinase activated by cAMP, which progresses downstream with phosphorylation of tyrosine. The restrictions of PRKACA have abolished the phosphorylation of tyrosine signaling and eventually impede spermatozoa capacitation (McPartlin et al. 2011).

Glycerol-3-phosphate dehydrogenase 2 (GPD2) is among the proteins that enable the phosphorylation of tyrosine during the capacitation of spermatozoa. The activity of GPD2 relates with hyperactivation and acrosome reaction, which advanced the function of GPD2 in spermatozoa capacitation. GPD2 activity is needed for the making of ROS in mouse spermatozoa during capacitation. Thus, without the GPD2 activity, capacitation is impaired (Kota et al. 2010). Tyrosine phosphorylation of proteins is the commonest mechanisms where numerous signal transduction pathways are adjusted in spermatozoa. It regulates various aspects of sperm roles, like motility, hyperactivation, capacitation, acrosome reaction, and insemination (Katoh et al. 2014). Therefore, it is obvious that arsenic can induce the suppression of VDAC3, PRKACA, and GPD2 and the abnormal rise of L-tyrosine could interrupt the degree of protein tyrosine phosphorylation necessary for sperm capacitation; caused failure in insemination and male sterility.

Sperm acrosome membrane-associated protein 1 (SPACA1) is found in the equatorial fragment of spermatozoa and plays a role in the fusion of sperm-egg in mammals. Interruption of SPACA1 will lead to unusual shaping of the semen head (globozoospermia), which caused male mice sterility (Yoshitaka et al. 2012).

Additionally, antibodies against recombinant SPACA1 can deregulate the sperm affinity to the ovum; impede the binding and fusion of sperm to zona-free eggs (Haq et al. 2012). Angiotensin-converting enzyme (ACE) is a permeating membrane ectoprotein in mammal's tissues, and germinal cells ACE (gACE, is also named testicular ACE), is located entirely inside the germinal cells after meiosis in male. A germinal ACE knockout in mice could cause a deficiency in semen binding to the zona pellucida of the oocyte (Kwon et al. 2014). Li et al. (2014) revealed that the lack of gACE expression is accountable for the failure in fertilization of semen mitochondrial-associated cysteine-rich protein (SMCP), a component of keratinous capsule that surrounds spermatozoa mitochondria and improves sperm motility. The erasure of SMCP diminishes sperm motility, which prevents sperm from migrating into the female reproductive tract and penetrates the egg membranes during conception (Nayernia et al. 2002). Given the decrease in the expressions of SPACA1, ACE, and SMCP in testis of rat, it is suggested that arsenic affects impregnation by impeding the binding (affinity) and fusion (adhesion) of spermatozoa to the ovum.

1.3 Mechanism of Arsenic Toxicity on the ERK/AKT/NF-κB-Pathway: A Molecular Perspective

Mitogenic-activation protein kinases (MAPKs) are major controlling proteins in cell signaling and partake in various roles activated by the reaction of many exterior stimuli. Earlier investigations have exposed that the male procreative roles, comprising spermatozoa, and Sertoli cell tasks are moderated by MAPK signaling pathways (e.g., extracellular signal-regulated kinases, ERKs) (Li et al. 2009). Wang et al. (2012); Xia et al. (2012) stated that the activation of the ERK1/2 (MAPK3/1) signaling pathway will damage the roles played by Sertoli cells and proliferate the apoptosis of germ cell in mouse testes. Protein kinase B (AKTB) is a central controller of cell development and growth, persistence, spread, inflammatory, and immune reaction in reaction to OS. Exposure to PM 2.5 of OS by phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway reduced procreative organ of male mouse (Cao et al. 2015). MAPK and AKT pathways perform rightly by phosphorylating the nuclear factor kappa B (NF-κ B) subunits and upset the ability of NF-κ B to bind to DNA and rise the transactivation of NF-κ B-dependent genes (Rui et al. 2016). NF-κ B deals with spermatogenesis by controlling cellular apoptosis and function of Sertoli cell in the testis, and the activation of NF-κ B encompassing defective sperm in mice and humans (Chen et al. 2012; Yu et al. 2015). Besides contact with arsenic, investigation has showed that arsenic triggers the ERK, PI3K/AKT, and NF-κ B signaling pathways in diverse cells (Huang et al. 2015; Tsai et al. 2016). The differential proteins and metabolites allied to male reproduction are included in ERK/AKT/NF-κ B pathway (Fig. 1.3). The upward-regulation of ERK1/2, PI3K, AKT, IKKγ, and NFKB expression improved the phosphorylation level of ERK/AKT in rat testis. The implication of arsenic in the men procreative noxiousness by the activation of the ERK/AKT/NF-κ B pathway is well established.

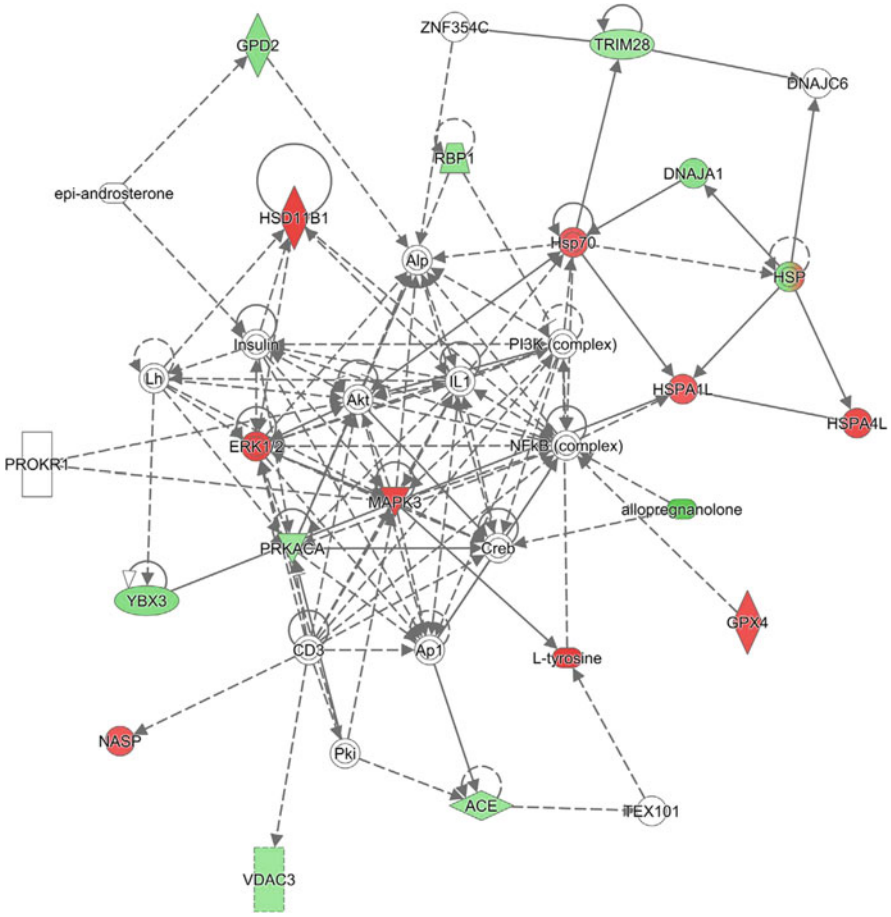

Fig. 1.3 Analyses of the different proteins and metabolites involved in arsenic toxicity. A network that describes molecules involved in the development and function of reproductive system, organ morphology, as well as organismal injury and abnormalities. Molecules are in nodes. Nodes in red represent upward-regulated molecules, while nodes in green symbolize downward regulated. Molecules exemplified with white nodes are noticed observed. Solid lines indicate direct interactions or regulation, while dashed lines indicate indirect effects mediated by additional molecules. Source: Qingyu et al. (2016)

Summarily, considering the collective proteomic and metabolomic investigation, research has shown that exposure to arsenic affects the expression of proteomic and reproductive pathways in rat testis. A sequence of different proteins and metabolites related to the male sex parameters has been recognized. Therefore, the deregulation of about 17 proteins and 3 metabolites by challenging the cells with arsenic would damage sperm and hinder insemination processes by activating ERK/AKT/NF-κB-dependent pathway.

1.4 Conclusion

Arsenide (As-3) is a type of synthetic arsenic, exposures to As-3 occurs through arsine gas which causes diverse toxicological sketch created by the binding of arsenic to hemoglobin and red blood cell lysis. Arsenate, arsenide, and alkylated arsenic are used for commercial purposes. Synthetic arsenic is predominant in environmental media. Organic arsenic—methyl (cacodylate), dimethyl, and trimethyl accumulate in mammals tissues. Arsenobetaine can be found in fish and seafood, while arsenocholine, arsenosugars, and arsenolipids are in plants. A mixture of gene, environment, and social lifestyle are contributing factors that unfriendly affects arsenic-exposed men. Investigations had submitted that different compounds of arsenic exert adverse effects on the male reproductive function. Conversely, evidence about the reproductive effects of human exposure to arsenic is scarce and/or inconsistent. This text abridges the information from numerous clinical and scientific studies on the consequential exposure of men to reproductive function. Intervention is given to studies that consider the effects of different arsenic compounds. For instance, information on the dose-dependent effect at modest- to low-level contact to arsenic on the prostate gland and serum level of testosterone is reviewed. The adverse effects of arsenic on the quality of semen and the change in serum hormones were elucidated. Just a few investigations have examined the procreative effects of simultaneous contact with some metals that work in synergy with arsenic and are controlled for prospective complement. Future studies should consider the contribution of combined exposure to various metals and other factors that may influence individual vulnerability to reproductive health impairment in men.

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Arsenic and Oxidative Stress: An Overview

2

Felor Zargari

Abstract

There are many people in the world that they are exposed to arsenic and in risk of related diseases such as diabetes, arteriosclerosis, neuropathy, infertility, and many types of cancer. Arsenic (As) is the most important toxic metalloid in the earth. Some causes of arsenic toxicity and the development of these disorders include: oxidative stress (OS), increased ROS (reactive oxygen species) production, alteration of some signaling pathway and gene expression, damages to structure and function of some proteins, especially SH-proteins, impairment of mitochondria, alteration of antioxidant defense system, changes in the secretion of some hormones such as FSH, LH, and testosterone (dysfunction of men and women reproductive system), disturbance in the structure of cellular components such as lipids, proteins, carbohydrates, and DNA. This section focused on the association of As with some diseases, e.g. diabetes, atherosclerosis, male and female infertility, and neurodegenerative disorders and sources of ROS production in these disease.

Keywords

Arsenic · Disease · Oxidative damage · Free radicals · Toxicity

F. Zargari (✉)
Department of Medical Sciences, Marand Branch, Islamic Azad University, Marand, Iran
e-mail: felorzargari@marandiau.ac.ir

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2.1 Generation of ROS in Oxidative Stress

Oxidative stress (OS) damages cell by disturbance of the balance between production of highly reactive molecules such as $^{\cdot}OH$, $O_2^{\cdot -}$ (reactive oxygen species) and $^{\cdot}NO$ or nitric oxide (reactive nitrogen species) and antioxidant defense system (Nordberg and Arnér 2001; Reuter et al. 2010; Valko et al. 2006; Ďuračková 2010). Free radicals are energetic molecules that have unpaired electrons in atomic orbits. The most important radicals in living system are ROS (Miller et al. 1990; Halliwell and Gutteridge 1999). ROS have a major role in stimulation of cell signaling pathway. However, overgeneration of ROS is deleterious (Thannickal and Fanburg 2000).

The overproduction of RNS (nitrosative stress) and ROS induces oxidative damage and damage to components of the cell such as DNA, lipid, protein, cell structure, and cell membranes (Valko et al. 2006; Noori 2012). ROS interact at the site of formation or far from their production site) Kohen and Nyska 2002). The toxic effects of arsenic are attributed to the generation of ROS and OS and the change of antioxidant enzymes activity (Heidari Shayesteh and Ranjbar 2013; Zargari et al. 2014). One of the mechanisms of arsenic toxicity is oxidative stress (Ercal et al. 2001).

The sources of ROS and RNS are exogenous and endogenous [*enzymatic* (produced under the physiological conditions, such as monoamine oxidase, NADPH oxidase, xanthine oxidase, cyclooxygenase, myeloperoxidase) and *non-enzymatic* (produced by Fenton's and Haber's reaction, such as H_2O_2, $^{\cdot}OH$, HOCL, ONOO)] (Noori 2012).

2.2 Arsenic and Oxidative Stress

Arsenic is the 33rd element of the periodic table and toxic metalloid in the form of inorganic (iAs) or organic compounds in the environment (Jomova et al. 2011). The most important forms in water are arsenite (As III: the most toxic and carcinogen form, reacting with enzymes and transcription factors) and arsenate (As 5^+). Arsenic levels of drinking water in some countries such as Mexico) García-Vargas et al. 1991), Tiwan (Yen et al. 2007), and Indo-Bangladesh are more than the amount recommended by WHO (10 μg/l) (Kinniburgh and Smedley 2001). Arsenic changes mitochondrial integrity and its membrane potential. Mitochondria is the most important organelle for the generation of ROS (by complex I and complex II of the electron transport chain). Arsenic acts directly or by the production and accumulation of ROS on the matrix of mitochondria (Pulido and Parrish 2003). The formation of superoxide anion radical and the decrease in cellular oxidant defense result in production of peroxyl radicals ($ROO^{\cdot}$), anionic form of O2 ($O_2^{\cdot -}$), singlet oxygen or dioxygen ($^1O_2$), hydroxyl radical ($^{\cdot}OH$), dihydrogen dioxide (H_2O_2), and dimethylarsine radical [$(CH_3)_2As^{\cdot}$] (Flora et al. 2007). H_2O_2 is produced by the oxidation of arsenite to arsenate ($H_3AsO_3 + 2H_2O + O_2 \rightarrow H_3AsO_4 + H_2O_2$) (Valko et al. 2005). H_2O_2 with iron generates highly reactive hydroxyl radical (Fenton reaction) with

mutagenic effect (Hei et al. 1998). In addition, arsenic generates RNS during metabolism (Shi et al. 2004) (Fig. 2.1).

2.3 Arsenic Detoxification Mechanisms (Methylation of Arsenic)

The biotransformation of As or its detoxification and production of metabolites induces oxidative stress (Flora 2011). Arsenic detoxification mechanisms are as follows:

- Conversion of As^{+5} to As^{+3} by PNPase (purine nucleoside phosphorylase) in plasma (Radabaugh et al. 2002) [Tripeptide glutathione (GSH) and other thiol compounds are required for this conversion] (Scott et al. 1993; Flora et al. 2007).
- The methylation of As^{+3} via As^{+3} methyltransferase (As_3MT) (Hayakawa et al. 2005; Lin et al. 2002) in liver (Marafante et al. 1985) and the production of arsenic acid monomethyl (MMAA), and finally arsenic acid dimethyl (DMAA) [s_ adenosyl_methionine (SAM) is involved in arsenic methylation) (Rossman 2003; Németi and Gregus 2002). Like other toxic metals, it is converted to the less toxic form by methylation and other reductant factors, such as TR (thioredoxin reductase), TRX (thioredoxin), dihydrolipoic acid] (Waters et al. 2004). Arsenic can conjugate with GSH and produce arsenite trigluthatione and then MMA $(SG)_2$(monomethylarsenic diglutathione and DMA (SG) (dimethylarsinic glutathione) (Kenyon et al. 2008).
- The reduction of methylation capacity increases the toxic effects of arsenic, e.g., hypo methylation of DNA leads to impaired gene expression, such as oncogenes or tumor—the suppressor genes (Roy and Saha 2002). In vitro studies indicated that MMAA inhibits glutathione reductase. MMAA is very toxic to human liver cells. The degree of cytotoxicity is: $MMAA^{+3}$ > arsenite > arsenate > $MMAA^{+5}$ = $DMAA^{+5}$ (Petrick et al. 2000).

2.4 Arsenic and Signaling Pathways

Arsenic altered some signaling pathways, such as:

- Tyrosine phosphorylation pathway including receptor tyrosine kinase (RTKs), such as growth factor receptors and nonreceptor tyrosine kinase (NTKs), such as Src family (Blume-Jensen and Hunter 2001). Arsenic induces the phosphorylation of epidermal growth factor receptor (EGFR) in the cell. It interacts with the SH-group of EGFR (Wu et al. 1999)
- The mitogen-activated protein (MAP) kinase (Kumagai and Sumi 2007)
- Alteration of the major transcription factors, such as NF-Kappa B and activated protein-1 (AP-1) (stress-induced transcription factors), regulating proinflammatory genes in defense of cell (Chen and Shi 2002)

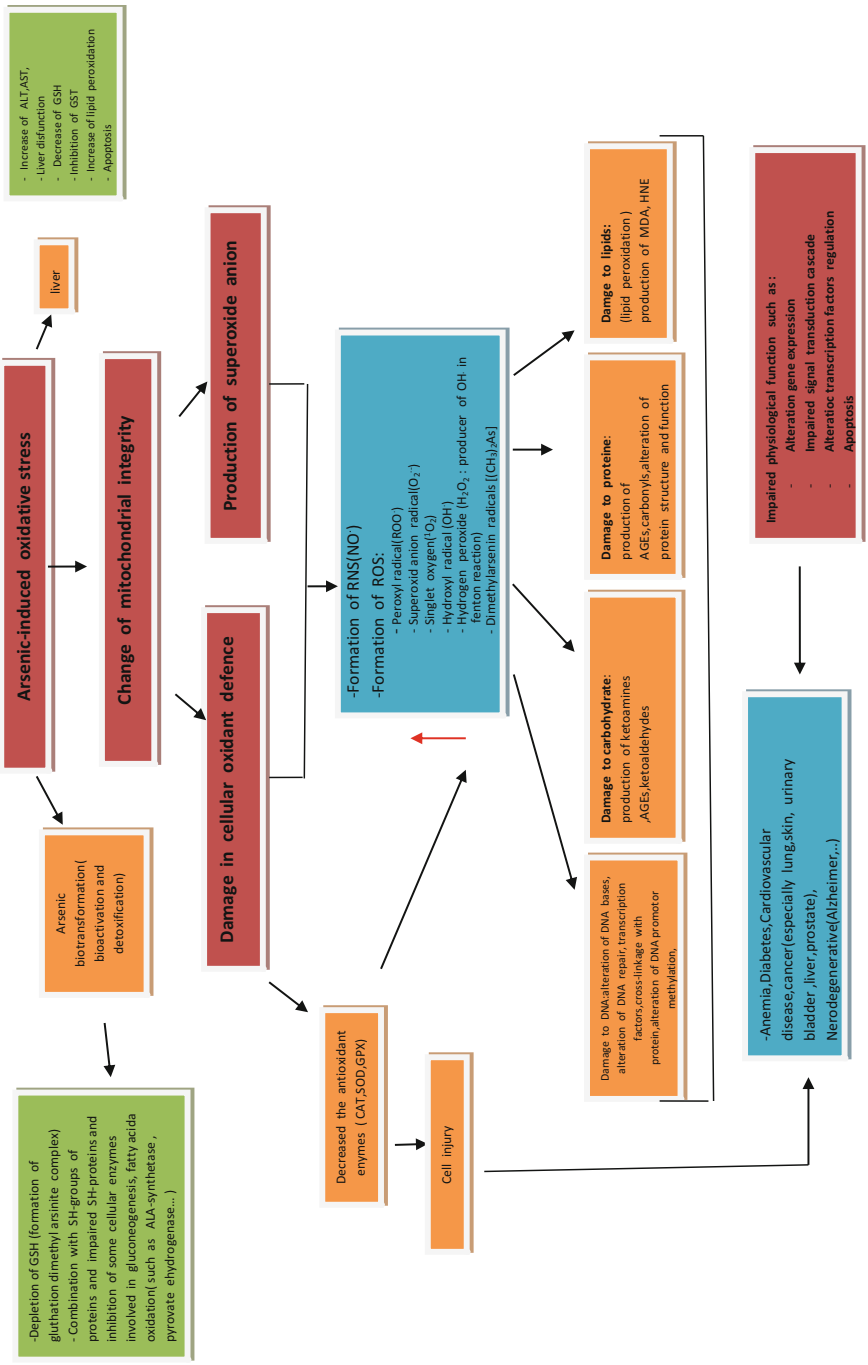

Fig. 2.1 Mechanism of arsenic-induced oxidative stress

– The activation of p53 and the induction of apoptosis (Filippova and Duerksen-Hughes 2003). Arsenic-induced apoptosis, due to the increase in cytochrome c, imbalance of Ca^{++}, increased Bax expression, and the downregulation of Bcl-2 (Das et al. 2009)

2.5 Arsenic and Antioxidant Enzymes Activity

The activity of antioxidant enzymes (SOD, CAT, GPx, GST, GR) increases with short term and low levels of arsenic exposure. The chronic exposure of arsenic decreases their activity (Shi et al. 2004; Zargari et al. 2015).

2.6 The Effect of Arsenic-Induced Oxidative Stress on Proteins

Some ROS such as $^{\cdot}OH$ and $O_2^{\cdot -}$ damage proteins (Stadtman 2004; Samuel et al. 2005; Valko et al. 2006; Kaneto et al. 2005). Arsenic has different effects on proteins that some of them are as follows:

– The production of aldehydes, keto compounds, and carbonyls [3_ nitrotyrosine as protein oxidative marker] (Kaur et al. 2011; Stadtman and Oliver 1991; Blokhina et al. 2003)
– Damage to the specific amino acid residues [in particular oxidation of cysteine and methionine residue, which may cause the formation of disulfides between (-SH) group of proteins or the formation of glutamyl semialdehyde and impaired SH-proteins] (Dalle-Donne et al. 2003)
– A change in protein structure, degradation, unfolding, fragmentation, inactivation of enzymes (Kaneto et al. 2005; Kelly and Mudway 2003; Dean et al. 1985)
– Altered cellular function (e.g., changing the energy production, due to the inhibition of pyruvate dehydrogenase by especially MMAIII) (Reichl et al. 1988; Hughes 2002)
– The change in the type and level of cellular proteins (the reduction of antioxidant enzymes) (Flora 1999)
– Production of AGEs or advanced glycated proteins. They are produced by the reaction between carbohydrates and the free amino group of proteins, e.g. pentosidine and carboxymethyl lysine (CML) as the most important of AGEs (Dalle-Donne et al. 2005)
– Increased proteolysis due to production of reactive carbonyl groups (RCGs) (Mahata et al. 2007; Kelly and Mudway 2003)

2.7 Arsenic-Induced Oxidative Stress and DNA

DNA is sensitive to the free radicals, due to the unsaturated bounds in purine and pyrimidine rings. Arsenic damages DNA by ROS production and alteration of the enzymes that are needed to repair DNA (Bartsch and Nair 2004; De Vizcaya-Ruiz et al. 2009). The important damages of arsenic on DNA are as follows:

- The alteration of DNA bases: 8-hydroxydeoxyguanosine: 8-OHdG as the marker of oxidative damage to DNA or 8-oxoadenine [detected in urine of animal exposed arsenic] thymine glycols, 5-hydreoxymethyl-uracyl are produced in oxidation of DNA (Bartsch and Nair 2004; De Vizcaya-Ruiz et al. 2009; Cooke et al. 2003). Binding of altered bases to transcription factors alters the expression of some dependent genes (Ghosh and Mitchell 1999)
- DNA strand break (single and double) (Ying et al. 2009; Mourón et al. 2006; Dong and Luo 1993)
- The loss of purines (the formation of apurinic sites) (Yamanaka et al. 1995)
- The cross-linkage of DNA–protein (Huang et al. 2004)
- Altered gene expression as a result of damage to the transcription factors (Huang et al. 2004; Lantz and Hays 2006; Díaz-Villaseñor et al. 2007). However, based on an in vitro study, As does not effect on the transcriptional regulator of DNA (Lantz and Hays 2006)

2.8 The Effect of Arsenic-Induced Oxidative Stress on Lipid

Many clinical studies indicated that arsenic causes lipid peroxidation (Wirtitsch et al. 2009; De Vizcaya-Ruiz et al. 2009). Some important damages of arsenic on lipids include:

- Production of cyclic endoperoxide, isoprotans, and hydrocarbons
- Peroxidation of cell membrane lipids. The high concentration of unsaturated fatty acids in the cell membrane leads to oxidative damage and inactivation of membrane-bound receptors.
- The formation of fatty acid radical ($ROO^{\cdot}$).
- The formation of lipid hydroperoxide, leading to a chain reaction and the oxidation of fatty acids in the membrane of the cells (Halliwell and Gutteridge 2015)
- Peroxidation of membrane lipids and generation of two important markers of lipid peroxidation called malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE) (Wirtitsch et al. 2009)

2.9 The Effect of Arsenic-Induced Oxidative Stress on Carbohydrates

– Producing ketoamines and ketoaldehydes and changing carbohydrate metabolism (the inhibition of pyruvate dehydrogenase complex, hyperglycemia, and glucose intolerance) (Ghafghazi et al. 1980)
– Producing AGEs.

2.10 Arsenic-Induced Oxidative Stress and Some Disorders

Some disorders linked to arsenic-induced oxidative stress are diabetes, cardiovascular disease, neurodegenerative disease, and infertility, which are discussed in the following.

2.10.1 Oxidative Stress and Diabetes

Some studies have demonstrated the relationship between the oxidative stress, diabetes and its complications, as micro- and macro-vascular dysfunction such as retinopathy, neuropathy, stroke, heart disease, and atherosclerosis (Phillips et al. 2004; Asfandiyarova et al. 2006). Diabetes mellitus (DM) refers to the metabolic disorder, which is characterized by the elevated levels of blood glucose caused by the lack or insufficient insulin secretion or defects in insulin action (Maritim et al. 2003). Insulin is a hormone secreted by β-cells of pancreatic islets, which has an important role in glucose, lipids, and proteins metabolism. Some mechanisms of oxidative stress-induced diabetes are as follows:

– The auto-oxidation of glucose and hyperglycemia increases the OS (Rains and Jain 2011; Maritim et al. 2003) [NADPH oxidase, an important producer of ROS in various cells, has a major role in hyperglycemia-induced oxidative stress] (Jain 1989; Wolff and Dean 1987; Jiang et al. 1990). Reactive compounds such as ketoaldehydes, superoxide anion radicals, peroxynitrite, and toxic hydroxyl radicals are produced in the presence of oxidized glucose, transition metals, and nitric oxide (Hogg et al. 1993; Halliwell and Gutteridge 1990)
– A change in the redox balance status [reduced glutathione (GSH), vit E, impaired antioxidant defense]. Glutathione is a tripeptide consisting of three amino acids cysteine, glycine, glutamate and has an important role in antioxidant defense, transferation of amino acids, redox balances, scavenging of free radicals, and enzymatic reaction (Tsai et al. 2012; Gregus et al. 1996). Some studies showed that the level of GSH reduces in diabetes. The decreased GSH results in β-cells dysfunction and other complications in diabetes, such as hyperlipidemia, inflammation, and DNA damage. Keeping the GSH redox state may be useful for diabetic patients (Dinçer et al. 2002; Das et al. 2012; Livingstone and Davis 2007; Tan et al. 2012).

- The damage to β-cells and the reduction of insulin secretion as a result of the low levels of antioxidant enzymes (Ceriello and Motz 2004; Lipinski 2001) and the production of mitochondrial superoxide activating UCP-2 [uncoupling protein-2, a mitochondrial inner membrane protein], reduction of ATP/ADP and increase of the superoxide formation (Brownlee 2003).
- The increased protein cyclin-dependent kinase inhibitor 1 and decreased insulin mRNA (Maechler et al. 1999).
- The disturbances of lipid profile, such as the production of ox LDL, and lipid oxidation (the formation of highly reactive compounds such as MDA and HNE). A change in the cellular structure and its function, especially alteration of membrane-bound receptors and membrane proteins with thiol groups. Ox LDL is associated with the risk for atherosclerosis (Tsai et al. 1994; Kawamura et al. 1994; Rabini et al. 1994; Guo et al. 2012; Cai and Harrison 2000; Goldstein et al. 1979).
- The disturbance of insulin signaling cascade that leads to the insulin resistance (Rains and Jain 2011; Ogihara et al. 2004).
- The increased stress signaling pathway, such as NF-kappaB and apoptosis of B cells by glycated proteins, reduction of insulin expression due to alteration of JNK pathway (Rhodes 2005; Kaneto et al. 2005; Mohamed et al. 1999).
- The damage to the proteins [the production of modified, nonfunctional, denatured, and glycated proteins (AGEs) such as glycated hemoglobin, glycation of lens proteins, and cataract formation (Ramalho et al. 1996; Yano et al. 1989). The protein oxidation is in side chain of cysteine, methionine, and tyrosine. The products of protein oxidation in oxidative stress are carbonyls [the marker of protein oxidation], advanced oxidation protein products [AOPPs], known as proinflammatory and prooxidant compounds (Suzuki and Miyata 1999; Pandey and Rizvi 2010; Witko-Sarsat et al. 1996).
- The damage to the mitochondria function, which increases the free radicals production, due to impaired electron transfer chain (Turrens et al. 1985; Liu et al. 2002).
- Alteration of antioxidant enzymes activity such as CAT, SOD, GPx (Goth and Eaton 2000; Giugliano et al. 1995; Shukla et al. 2012; Maritim et al. 2003). CAT is present in all living organisms and regulator of hydrogen peroxide metabolism. Catalase plays a major role in oxidative stress. The deficiency of CAT leads to the damage of β-cells, containing a large amount of mitochondria and H_2O_2 producer (increasing ROS and fibronectin expression) (Hwang et al. 2012). Patel et al. (2013) showed that high blood glucose leads to increased H_2O_2 production and downregulation of expression of CAT gene. Some studies indicated the decreased SOD level in diabetic blood and tissues (He et al. 2011; Shukla et al. 2012; Giugliano et al. 1995). SOD is an enzyme found in mammalian tissues and converts superoxide anion to molecular oxygen and hydrogen peroxide. Three forms of SOD include: cytosolic Cu-Zn superoxide dismutase (SOD1), mitochondrial Mn-SOD (SOD2), and extracellular SOD(SOD3 or EC-SOD). SOD1 and SOD2 have an important role in diabetic nephropathy and SOD3 or EC-SOD

involves in scavenging of superoxide radicals in extracellular (Oury et al. 1996; Zelko et al. 2002) (Fig. 2.2).

2.10.1.1 Arsenic Toxicity and Diabetes Mellitus (DM)

In Taiwan Lai et al. (1994) reported for the first time that there is a relationship between the prevalence of diabetes and chronic exposure to the arsenic. Other researches in Bangladesh, Swedish, and Mexico confirmed the high prevalence in the postmenopausal women (>50 years) (Rahman and Axelson 1995; Rahman et al. 1998; Coronado-González et al. 2007). Other studies indicated the relationship between diabetes and iAs (inorganic arsenic) (Tsai et al. 1999; Navas-Acien et al. 2006). Some mechanisms of diabetes are induced by inorganic arsenic (Fig. 2.3) and its methylated metabolites, especially trivalent arsenicals and they are as follows:

- The phosphorus substitution, increasing ROS and altering some genes expression, such as increasing renal hexokinase II: HK-II expression in mice, which causes pathological changes in kidney (Tseng 2004; Pysher et al. 2007).
- The insulin resistance and alteration of glucose homeostasis [by inhibiting the AKT signaling pathway and inhibiting glucose transporter 4 transposition to plasma membrane (Rudich et al. 1998; Paul et al. 2007; Hamann et al. 2014).
- The reduction of the expression of many genes, such as GLUT4, AKT (Walton et al. 2004; Paul et al. 2007; Hamann et al. 2014).
- The upregulation of Nr-f2 signaling pathway in mice increased the expression of antioxidant enzymes and the inhibition of glucose uptake (Xue et al. 2011; Duan et al. 2015).
- The inhibition of adipogenesis and decreased lipid storage capacity by inhibiting the adipocyte differentiation [the alteration of the expression of PPAR-γ and CEBP-α]. PPAR-γ is a nuclear receptor that regulates the storage of fatty acids and glucose metabolism. CEBP-α is a transcription factor and the inducer of adipogenesis (Hou et al. 2013; Hamann et al. 2014; Wauson et al. 2002).
- The damage to β-cells. One of the most important causes of β-cells dysfunction is oxidative stress. β-cells damage occurs due to low antioxidant defense, mitochondrial damage, and generation of superoxide (Kaneto et al. 2007; Tiedge et al. 1997). Arsenic is involved in the development of diabetes through damage to function of β-cells, secretion and synthesis of insulin (Zhu et al. 2014; Lu et al. 2011).
- The programmed cell death or apoptosis of β-cells, due to the production of arsenic-induced ROS and production of the activated caspase 3 and increased NF-kappaB activity (Rhodes 2005).
- The upregulation of some essential transcription factors such as Nr-f2. It is the regulator of expression of the cellular antioxidant proteins. Inhibition of TXNRD1 protein (thioredoxin reductase 1), imbalance of intracellular redox status, and inhibition of insulin secretion (Xue et al. 2011).

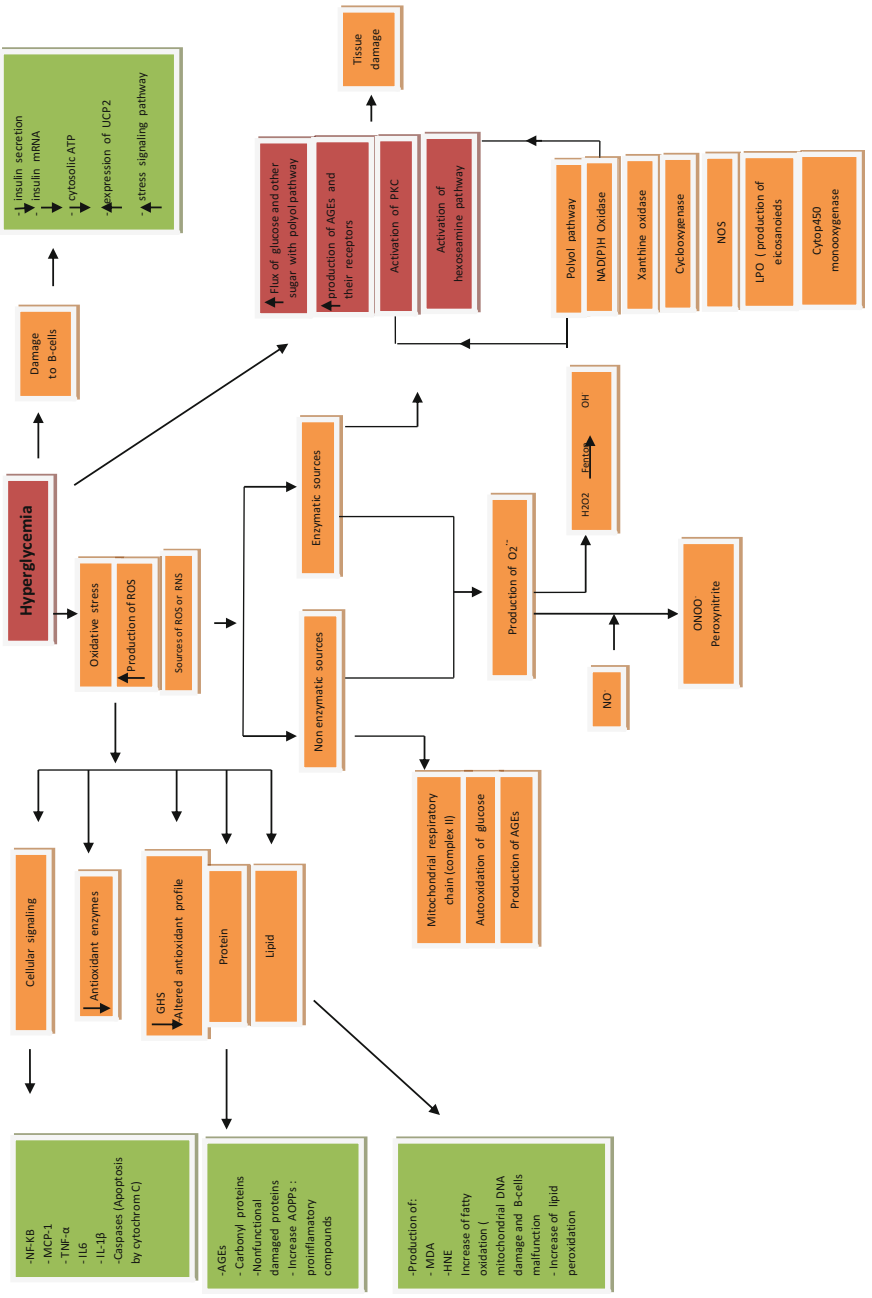

Fig. 2.2 Hyperglycemia induced oxidative stress

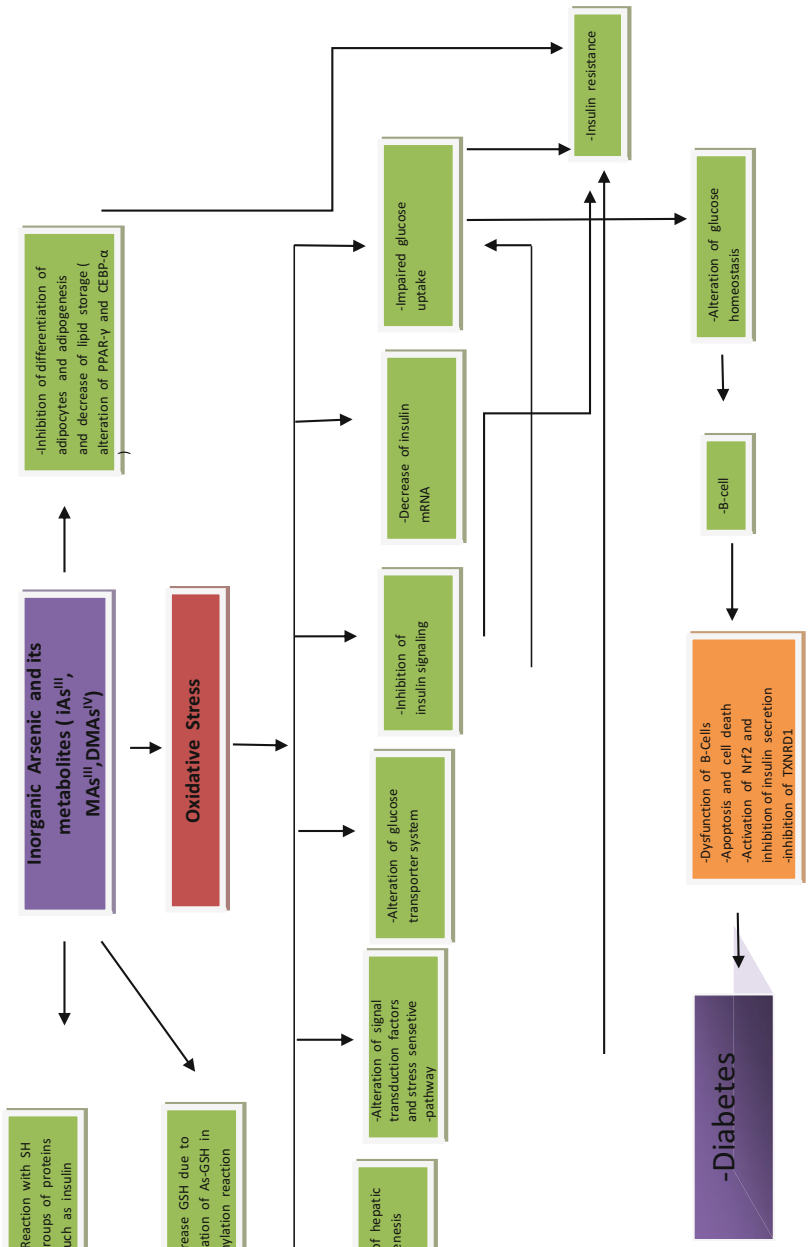

Fig. 2.3 Mechanism of arsenic-induced diabetes

– Decreased production of insulin-related mRNA due to overproduction of ROS (Díaz-Villaseñor et al. 2006).
– The stimulation of hepatic gluconeogenesis. The induction of expression of PEPC [an enzyme in the metabolic pathway of gluconeogenesis] results in fasting hyperglycemia (Díaz-Villaseñor et al. 2007).

2.10.2 Oxidative Stress and Arteriosclerosis

Arteriosclerosis is a disease characterized by hardening and thickening of the arterial wall due to the accumulation of serum lipoprotein LDL (low density lipoprotein) and endothelial damage. The oxLDL (oxidized form of LDL) plays an important role in the formation of foam cells and atherosclerosis plaque in the arterial wall (Lusis 2000). The oxLDL increases the expression of intracellular adhesion molecule-1 (ICAM-1), platelet, and selectins that facilitate the leukocytes binding and plaque formation. Plaques contain a central lipid core with crystals of cholesterol plaques, resulting in the myocardial infraction or stroke (Hennig et al. 2001; Inoue and Node 2006; Stocker and Keaney 2004; Madamanchi et al. 2005; Devasagayam et al. 2004; Lum and Roebuck 2001).

Some studies demonstrated that OS has an effective role in the development of disease and various cardiovascular disorders (Dhalla et al. 2000; Kukreja and Hess 1992).

The main and important ROS sources in atherosclerosis include:

- Smooth muscle cells (SMCs) and immune cells (macrophages) in blood vessel arteries (Antoniades et al. 2007).
- Hypercholestrolemia. It stimulates the production of superoxide anion ($O2^{-\cdot}$) from the smooth muscle cells (Vepa et al. 1999).
- Mitochondria. One of the major sources of superoxide anion ($O2^{-\cdot}$) production is electron transport chain in mitochondria. Mitochondrial dysfunction is associated with the atherosclerosis (Singh and Jialal 2006; Madamanchi et al. 2005).
- Enzymatic sources:
  – Nicotinamide adenine dinucleotide phosphate oxidase (NAD(P) H oxidase), in the vascular cells, leads to production of ROS. Some stimulators such as Ang II (angiotensin II), PDGF (platelet derived growth factor), TNF-α (tumor necrosis factor α) regulate its production (Griendling et al. 2000; Harrison et al. 2003; Droge 2002).
  – XO (xanthine oxidase) is a flavoprotein found in serum and endothelial cells. It is not present in smooth muscle cells. Two forms of XO exist, including xanthine dehydrogenase (XD) and XO and XD is transformed into oxidase. During the conversion of hypoxanthine and xanthine to uric acid by the XO superoxide anion is produced. The enzyme level is increased in the coronary

patients and in asymptomatic young individuals with familial hypercholesterolemia (Spiekermann et al. 2003; Droge 2002; Harrison et al. 2003).
  - Myeloperoxidase (MPO) produces hypochlorous acid, as more potent oxidant, from H_2O_2 and expressed in neutrophil granulocytes. Increased MPO level is shown in patients with coronary disease, due to the oxidation or modification of lipo-proteins, such as LDL by MPO and the production of modified apolipoproteins. Serum level of MPO can be utilized to prediction of cardiovascular disease (Daugherty et al. 1994; Heinecke 2003; Zouaoui Boudjeltia et al. 2004; Baldus et al. 2003; Brennan et al. 2003; Bergt et al. 2004; Pennathur et al. 2004).
- NOS (nitric oxide synthase) produces potent vasodilator nitric oxide (NO) from L-arginine under normal condition. NO production is required for the endothelial function. Endothelia NOS (eNOS) produces $O2^{-\cdot}$, H_2O_2, and peroxynitrite in absence of L-arginine and increases OS. eNOS plays an essential role in protecting the wall of blood cells from atherosclerosis. Some experimental studies indicate that the activity of eNOS in atherosclerosis is decreased (Schächinger and Zeiher 2002; Singh and Jialal 2006; Cai and Harrison 2000)
- LPO, lipoxygenase(s), catalyze the dioxygenation of polyunsaturated fatty acids (arachidonic acid) and produce biologically active lipids such as prostanoids (prostaglandins, thromboxanes, and prostacyclin), lipoxin, and leukotrienes. They are involved in inflammatory reaction and increased vascular permeability and atherogenesis (Stocker and Keaney 2004). Some experimental studies indicated some lipoxygenases oxidized LDL) Folcik et al. 1995)

2.10.2.1 ROS-Induced Damage to Vascular Function

- The damage to the cell membrane, nuclei, especially hydroxyl radicals, and dysfunction of endothelial (Suwaidi et al. 2000; Antoniades et al. 2003; Schächinger et al. 2000)
- The interaction with the vasoactive mediators in cells of endothelium (Antoniades et al. 2003).
- The formation of oxLDL. oxLDL activates monocytes and inhibits migration of macrophage and releases proinflammatory cytokines (Antoniades et al. 2007; Hennig et al. 2001).
- The production of NF-kappaB and activator protein-1 (AP-1) in oxidative stress. They increase the expression of vascular cell adhesion molecule-1 (VCAM-1), ICAM-1, E-selectin, and other cytokines. Accumulation of these molecules on the endothelial wall causes change in vascular permeability and endothelial wall dysfunction (Hennig et al. 2001; Bourcier et al. 1997; Tousoulis et al. 2007).

2.10.2.2 Arsenic Toxicity and Atherosclerosis

The association between cardiovascular disease (CVD) and arsenic exposure has not been established and evidences are limited and mechanisms are unclear (Navas-Acien et al. 2005; Wang et al. 2007a, b). Lemaire et al. (2011) demonstrated that arsenic may have proatherogenic effects on mice. Some epidemiological studies in Taiwan and Bangladesh indicated a positive association between the arsenic and

heart disease and high pulse pressure, which may be related to the arsenic detoxification and the increase of homocysteine and cardiovascular disease (Hsueh et al. 1998; Chen et al. 2007; Gamble et al. 2005; Zakharyan and Aposhian 1999; Araki et al. 1989; Lim and Cassano 2002). Based on the results of some studies, there is a relationship between arsenic and some genes expression, such as NOS3 (Balakumar and Kaur 2009; Desjardins and Balligand 2006), SOD2, monocyte chemoattractant protein-1 (MCP-1), interleukin 6 (IL-6) and ET-1 (endothelin-1) mRNA in mice (Sun et al. 2009; Lee et al. 2005; Soucy et al. 2005). They are involved in endogenous defenses against ROS and other risk factors for vascular dysfunction and maintaining vascular tone. Overproduction of ROS leads to loss of mitochondrial function, oxidative stress, alterations in the mitochondrial structure and cellular damage, endothelial cells death (Wang et al. 2002; Andreyev et al. 2005; Packer 1961). Endothelial vascular damage occurs as a result of reduced synthesis of NO and inactivation of eNOS and overgeneration of ROS. Dysfunction of vascular endothelial is a risk marker of atherosclerosis (Kumagai and Pi 2004; Lee et al. 2003; Cai and Harrison 2000; Balakumar and Kaur 2009; Davignon and Ganz 2004).

Based on the animal experimental studies, MDA and HNE accumulate in advanced lesions. They play an important role in the constitution of atherosclerotic lesion. Due to the production of proinflammatory factors such as MCP-1, IL-6, and TNF-alpha in exposure to arsenic it is an important risk factor for atherosclerosis (Tsou et al. 2005).

As induces hypertension. Many studies are needed due to increased sensitivity to calcium in blood vessels, phosphorylation of myosin and disruption of the antioxidant defense (Yang et al. 2007) (Fig. 2.4).

2.10.3 Oxidative Stress and Neurodegenerative Disease

Oxidative stress leads to neurotoxicity, mitochondrial dysfunction, severe disorders of neuronal cells and cell death (Caito and Aschner 2015; Cicero et al. 2017; Hsieh and Yang 2013).

Free radicals damage brain and neuronal cells (Chance et al. 1979; Floyd and Carney 1992; Marklund et al. 1982; Zaleska et al. 1989; Pamplona 2008; Halliwell et al. 1992). Brain and neuronal cells are prone to oxidative damage due to their high concentration of polyunsaturated fatty acids, high oxygen and glucose consumption, presence of some metals, such as Cu, Fe, vitamin C, and low levels of antioxidant enzymes.

Oxidative damage to neuronal cells leads to neurodegenerative diseases such as Alzheimer's and Parkinson's disease (Perry et al. 2002). In Alzheimer's disease (AD) there is an accumulation of misfolded protein called beta-amyloid (Aβ) plaque in the brain (Opazo et al. 2002). Parkinson's disease (PD) is associated with the accumulation of abnormal α-synuclein protein, degradation of dopaminergic neurons, in the brain due to oxidative stress (Segura-Aguilar et al. 2014; Gasser 2001; Dalfó et al. 2005). These misfolded proteins inhibit mitochondrial function

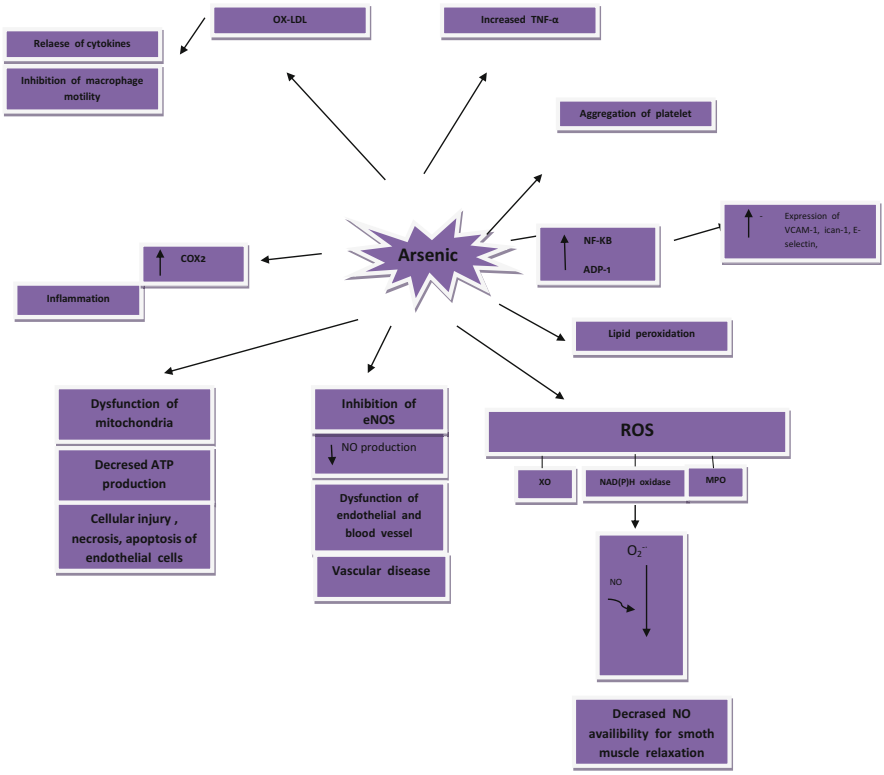

Fig. 2.4 Mechanism of arsenic-induced atherosclerosis

and induce more OS (Abramov et al. 2017; Caspersen et al. 2005). The dysfunction of mitochondria is important in both AD and PD process (Angelova and Abramov 2017; Schapira 2008; Andersen 2004). The etiology and mechanisms of damage to the neuron cells in neurodegenerative disease are unclear but the important sources of oxidative stress are related to AD and PD, which are discussed in the following.

2.10.3.1 Oxidative Damage in Alzheimer's Disease

- Decreasing the complex IV activity in the mitochondria and generation of ROS (Sheehan et al. 1997; Du et al. 2010).
- Increasing the H_2O_2 production, due to Aβ peptide accumulation and cytochrome C release (Lloret et al. 2008).
- Increasing the protein carbonyl (Bogdanovic et al. 2001; Sultana et al. 2010).
- Increasing the AGEs production and their receptors (Takeuchi et al. 2007).
- Increasing the mitochondrial VDAC1 (voltage-dependent anion channel 1) as a regulator of important metabolic function of the cell, such as homeostasis of calcium, OS, and apoptosis (Shoshan-Barmatz et al. 2018).

– Increasing the intracellular free ca^{++} that results in the reduction of GSH and accumulation of ROS (Ferreiro et al. 2008).

2.10.3.2 Parkinson's Disease and Oxidative Stress

– Dopamine (DA) metabolism. Dopamine quinone [6-hydroxydopamine as a neurotoxin (Graham 1978; Tse et al. 1976)] is produced from oxidation of dopamine. That leads to production of misfolded proteins, such as α-synuclein, Parkin protein, DJ-1, and inactivation of DA transporter, tyrosine hydroxylase, damage to mitochondria and decreased complex I in mitochondria (Betarbet et al. 2002; Schapira et al. 1989; Parker et al. 2008; Kuhn et al. 1999; Sulzer and Zecca 2000; Gluck and Zeevalk 2004; Jana et al. 2007; Van Laar et al. 2009; Whitehead et al. 2001; Andersen 2004; Betarbet et al. 2002; Parker et al. 1989).
– Mitochondrial dysfunction
  The peroxidation of cardiolipin leads to apoptosis due to release of cytochrome C (Betarbet et al. 2002; Parker et al. 1989).
  The damage to the complex I transporter chain and decreased ATP production (Mizuno et al. 1987).
  The dysfunction of some proteins, such as DJ-1, as a recognizer of OS, redox-chaperone protein, and related genes to PD, leads to more damage of mitochondria (Van Laar et al. 2009; Conway et al. 2001; LaVoie et al. 2005).
  The alteration of related genes in the regulation of mitochondrial homeostasis in PD (PINK 1- PARK-2) that inhibits the complex I activity (Valente et al. 2004; Gilks et al. 2005).
– The inflammation of neurons.
  The production of ROS and inflammatory cytokines, due to the production of neuromelanin from DA oxidation, which can interact with iron and leads to overgeneration of ROS (Garrido-Gil et al. 2013)

2.10.3.3 Arsenic Toxicity and Neurodegenerative Disease

Less investigation has been done on the association between exposure to As and neurodegenerative disease. Arsenic is one of the most important environmental risk factors for these disorders (Chin-Chan et al. 2015; Engström et al. 2010; Butterfield et al. 2002; Loh et al. 2006; Cheung et al. 2007). Recent studies indicated that As damages the mitochondria and function of neurological cells. The highest accumulation of As and its methylated components are in the hypophysis (Sanchez-Pena et al. 2010). Positive association between soil arsenic and mortality from Alzheimer's disease was reported by Li et al. in Mainland Chine (2020).

Some mechanisms of arsenic toxicity in the brain (Fig. 2.5) are as follows:

– The alteration of some signaling pathway, e.g., glucocorticoid signaling (interaction with glucocorticoid receptors and the inhibition of some transcription factors and alteration of nuclear function), cholinergic and monoaminergic signaling (Kaltreider et al. 2001; Kobayashi et al. 1987; Chandravanshi et al. 2019).
– Decreased activity of choline acetyltransferase (CHAT) and acetylcholinesterase (ACHE) (Baldissarelli et al. 2012; Nagaraja and Desiraju 1994).

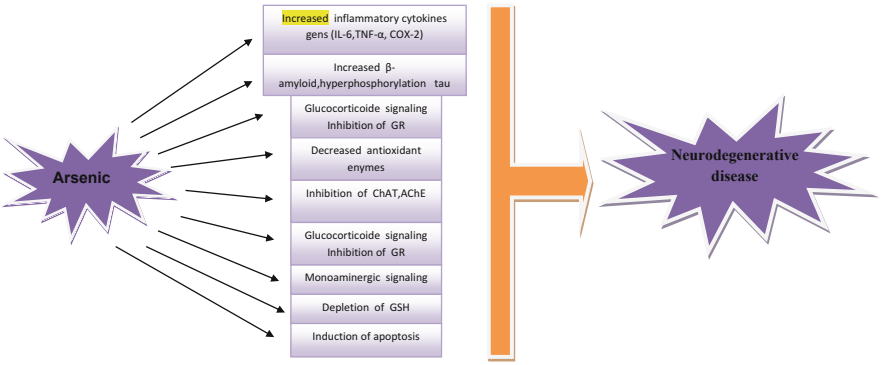

Fig. 2.5 Mechanism of arsenic-induced neurodegenerative disease

- Increased the β-amyloid protein, tau protein hyperphosphorylation, endothelial cell dysfunction, and inflammation in cell culture studies (Vahidnia et al. 2007; Giasson et al. 2002; Fry et al. 2007; Hardy and Higgins 1992; Zarazúa et al. 2011).
- The depletion of GSH and the induction of OS (Chang et al. 1991; Huang et al. 1993; Bermejo et al. 2008; Jomova and Valko 2011).
- The alteration of some transporter systems, such as brain monoamines especially dopamine, serotonin (5-HT), and noradrenaline (NA) (Martinez et al. 2008).
- Change of gene expression of some antioxidant (SOD, Trx-1) (Rodríguez et al. 2010; Lau et al. 2008; Zhang 2006).
- Activation of p38, MAPK and JNK3 signaling pathway and induction of apoptosis, oxidative damage which leads to Alzheimer's disease (Chandravanshi et al. 2018; Namgung and Xia 2001; Lu et al. 2011; Yen et al. 2012).
- The adjustment of the expression of inflammatory cytokine genes (Sun et al. 2017; Praticò and Trojanowski 2000; McGeer et al. 2006).
- The enhancement of Bcl2/Bax ratio and change in the potential of the mitochondrial membrane in brain, stimulation of apoptotic signaling, especially caspases-3, decrease in the level of Nr-f2 and Tex (Lu et al. 2014; Pradelli et al. 2010; Friedlander 2003; Shacka and Roth 2005; Srivastava et al. 2014).
- The storage of α-synuclein protein (SYN) and the oligomerization of SYN and synucleinopathies (Cholanians et al. 2016)
- Arsenic has a synergistic effect on the toxicity of dopaminergic cells in PD, as As and DA can increase toxicity in the neuronal cells, leading to the development of PD, probably with the production of DA quinone as a highly toxic free radical (Shavali and Sens 2008; Sulzer and Zecca 2000).

2.10.4 Infertility and Oxidative Stress

Infertility is considered as a serious health problem over the last decades. Recently, studies demonstrated that the oxidative stress and the overproduction of ROS (such as, OH, H_2O_2, $O_2^{\cdot -}$) damage the normal function of sperm and cause male or female infertility. One of these ROS is the H_2O_2 with the beneficial and damaging effect on sperm. The low level of H_2O_2 increases sperm–oocyte fusion (phosphorylation of tyrosine leads to the binding of sperm membrane to zona pellucida ZP3 protein) (de Lamirande and Gagnon 1995; Sharma and Agarwal 1996; Agarwal and Saleh 2002; Saleh and HCLD 2002; Twigg et al. 1998; Aitken and Clarkson 1987; Aitken et al. 1995, 1998).

There is no sufficient information about the ROS or OS and function of reproductive system. Some mechanisms of the effect of OS on the reproduction (Cicinelli et al. 1996; Halliwell and Gutteridge 1984; Penniston 1983) are as follows:

- Lipid damage, the production of lipid hydroperoxides, as cytotoxic, leads to the inactivation of enzymes, damage to DNA, cell leakage, membrane disruption (permeability to electrolytes).
- The modification of some transcriptional factors and gene expression (Paszkowski and Clarke 1996)
- The depletion of ATP, produced in the mitochondria during oxidative phosphorylation, for example, gametes use the produced ATP for mobility (Liu and Keefe 2000; Liu et al. 2000; Valko et al. 2007).

In the normal condition, low levels of ROS are essential for spermatocytes function, motility, hyperactivation, acrosome reaction, the interaction of sperm with oocyte, due to peroxidation of plasma membrane lipids and adhesion of sperm-oocyte (Agarwal et al. 2004; Griveau and Lannou 1997; Kodama et al. 1996) However, an unbalance between the production of ROS and their removing causes the development of oxidative stress in the seminal (Sikka et al. 1995; Sikka 2001; Sharma and Agarwal 1996). Spermatozoa (immature sperms) and white blood cells (leukocytes) in human semen are the most important sources of ROS. ROS are produced in spermatozoa by the NADPH oxidase in the membrane of plasma and NAD(P)H-dependent oxidoreductase in the mitochondria. High pressure of oxygen leads to the loss of sperm motility, flexibility, less or lack of interaction with oocyte for fertilization (Aitken et al. 1992, 1994; Gavella and Lipovac 1992; Aitken and Baker 1995; MacLeod 1943; Whittington et al. 1999; Kao et al. 2008).

Oxidative stress impairs to spermatocytes (Alvarez and Storey 1995; Jones et al. 1979; Aitken and Fisher 1994; De Lamirande and Gagnon 1995; Sharma and Agarwal 1996; Penniston 1983; Holland and Storey 1981; Holland et al. 1982) for:

- Low levels of scavenging enzymes [lack of integral catalase or glutathione]
- High levels of PUFA in their plasma membrane [rich in unsaturated lipids]
- High levels of mitochondria [for supply of energy]

The overproduction of ROS and defects of oxidative phosphorylation are the most important molecular mechanisms in men infertility (Cummins et al. 1994).

Excessive production of ROS damages mitochondrial function and stimulates high ROS production. Disturbance of mitochondrial membrane induces apoptosis and DNA fragmentation (by activating of caspase cascade). The different forms of damage to DNA include: DNA cross-links, the modification or deletion of bases, chromosomal rearrangement (Duru et al. 2000; Plante et al. 1994; Appasamy et al. 2007; Vermes et al. 1995; Wang et al. 2003). Some reports indicated excessive production of ROS (high levels of ROS) in the semen of infertile men. The mitochondrial system has the major role in production of ROS in infertile men [impaired and immature sperms in the semen are considered] (De Lamirande and Gagnon 1995; Padron et al. 1997; Plante et al. 1994; Huszar et al. 1997; Aitken 1999). OS has an important role in the function of ovary. Endothelial cells, phagocytic macrophages, and parenchymal steroidogenic cells are the most main sources of ROS in the ovaries. Under normal condition, ROS are involved in the maturation of follicle, ovulation, and folliculogenesis (Halliwell and Gutteridge 1988; Tamate et al. 1995; Sugino et al. 1996; Jozwik et al. 1999; Sabatini et al. 1999). The activity of some antioxidative enzymes, such as Cu-Zn SOD, Mn-SOD, GPx in human ovary is needed for normal reproduction (Suzuki et al. 1999; El Mouatassim et al. 1999; Paszkowski et al. 1995). The low expression of GPx in follicular fluid is associated with infertility. Increased nitric oxide (NO) is shown in the infertility (NO may lead to the apoptosis and fragmentation of embryo) (Bedaiwy et al. 2004). Peroxidation of lipids (increased MDA) and decreased antioxidant enzymes have reported in the infertile women (Polak et al. 2001; Shanti et al. 1999; Murphy et al. 1998).

2.10.4.1 Arsenic Toxicity and Infertility

Some human (occupational) and animal researches reported the effects of small amounts of some toxic metals, such as arsenic (As) on male reproduction. As directly affects the testicular tissue. Exposure to As in animal models leads to the reduction of testicular weight, production of sperm, number of spermatids, and decreased sperm mobility (Pant et al. 2004; Sarkar et al. 2003; Centeno et al. 2002; ATSDR 2007, 2012, 2019). As activates some signaling pathway such as ERK/AKT/NF-KB and leads to spermatogenesis disorders and reproductive toxicity (Huang et al. 2016). As exposure damages to the sperm DNA and leads to male infertility. Arsenic influences the steroid receptors activity, such as glucocorticoid and mineralocorticoid receptors. It may cause infertility by the inhibition of activity of androgen receptor (AR) (Kaltreider et al. 2001; Bodwell et al. 2006; Rosenblatt and Burnstein 2009). Some environmental pollutants such as heavy metals (lead, arsenic, cadmium), may lead to the reproductive disease by altering hormone levels. Arsenic increases ovarian tumors. Studies showed that serum As was high in infertile women (Lei et al. 2015; Mendola et al. 2008; Bloom et al. 2011; Gallagher et al. 2010; Guo et al. 2011; Tokar et al. 2011). Arsenic exposure leads to the inhibition of ovarian steroidogenesis, secretion of gonadotropins, and reduction of plasma testosterone (Chattopadhyay et al. 1999; Vreeburg et al. 1988; Hardy et al. 2005; Jana et al.

2006). The several possible mechanisms of As toxicity (Uckun et al. 2002; Jana et al. 2006; Sarkar et al. 2008) are as follows:

The direct action on testis: ROS affect the testicular function. Based on the results of the researches, exposure to the arsenic causes OS and reduction of some semen parameters, such as the reduction of number of sperm, motility of sperm, plasma levels of testosterone, FSH, LH hormones in the testis of rabbits (Manna et al. 2008; Zubair et al. 2014). The experimental studies indicated that As has toxic effects on the testis and damages the structure of testes and reduces the sex hormones (LH, FSH, testosterone) (Soleymani and Hemadi 2007; Pires Das Neves et al. 2004; Jana et al. 2006). Many researches reported the accumulation of arsenic in the testes, prostate glands. As toxicity alters the activity of mitochondrial enzymes, mitochondrial membrane potential, impairs DNA sperm and reduces testosterone. Inhibition and reduction of enzymes 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-HSD, and wasting of Leydig cells, and reduction of testosterone occur in the presence of arsenic. Arsenic influences the hypothalamic-pituitary axis, impairs Leydig cells function, and binds directly to sperm. The thiol containing proteins have main role in the motility of sperm. High levels of SH-proteins are in sperm (sperm chromatin and flagellum contain plenty of sulfhydryl) and As has high affinity to binding to these proteins. Arsenic induces cell death or apoptosis and ROS production [the peroxidation of PUFA of spermatozoa] (Das et al. 2009; Danielsson et al. 1984; Pant et al. 2001; De Vizcaya-Ruiz et al. 2009; Morakinyo et al. 2010; Sudha 2012; Kumar et al. 2002; Jana et al. 2006; Sarkar et al. 2003).

Shortly, *arsenic in male reproductive system* causes a reduction in the number of sperm, high productions of ROS in testes, abnormal secretion of hormone, a decrease in the testicular weight, abnormality of enzymes, such as LDH, sorbitol dehydrogenase, acid phosphatase, γ-glutamyl transpeptidase, a decrease in FSH, LH, resulting in low sperm count and male infertility, a decrease in the sperm mobility and viability, depletion of GSH, increases of MDA, and protein carbonyl in testes and effects on 3β-HSD and 17β-HSD, which are important for biosynthesis of testosterone.

Arsenic in female reproductive system results in the suppression in the ovarian steroidogenesis, the degeneration of ovarian cells, follicular cells and uterine cells, alteration of neurotransmitter secretion like norepinephrine, dopamine, and serotonin, leading to reduction of gonadotropin secretion, FSH, LH, and estradiol, and alteration of Δ^5-3beta-HSD and 17beta-HSD, as the regulator enzymes of steroidogenesis.

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Arsenic in Seafood: Current Status, Analysis, and Toxicity

3

B. K. K. K. Jinadasa, Scott W. Fowler, and Pawel Pohl

Abstract

Fish and seafood are popularly consumed all over the world for their rich nutritional qualities and numerous health benefits. In this chapter, we present overview of the major arsenic (As) species found in the seafood, its accumulation pathway, toxicity, and health effects, regulation analytical techniques, and risk assessment. Further, the bioavailability, bioaccessibility, and cooking effect for As species were discussed. The amount of As level, specially inorganic As and total As concentration of the seafood are highly varied. The toxicity and formation pathways of most As species and new metabolites are still not clear. This review tries to present limitation and the available data on As levels in various types of seafood and products.

Keywords

Fish · Arsenic species · Bioavailability · Arsenic toxicity

B. K. K. K. Jinadasa (✉)
Analytical Chemistry Laboratory (ACL), National Aquatic Resources Research & Development Agency (NARA), Colombo, Sri Lanka

S. W. Fowler
School of Marine and Atmospheric Sciences, Stony Brook University, Stony Brook, NY, USA

Institute Bobby, Cap d'Ail, France

P. Pohl
Department of Analytical Chemistry and Chemical Metallurgy, Faculty of Chemistry, Wroclaw University of Science and Technology, Wrocław, Poland

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3.1 Introduction

The term 'seafood' generally covers a heterogeneous group of aquatic organisms, mainly from the marine environment but also from brackish water and freshwater, including mollusks, crustaceans, all types of finfish, edible seaweeds, and aquatic plants. The benefit of high consumption of seafood has been associated with a reduced risk of developing coronary heart disease (CHD), high blood pressure, stroke, some cancers, rheumatoid arthritis, and other inflammatory diseases (Lund 2013). According to a 2018 report of the Food and Agriculture Organization (FAO), worldwide fisheries and aquaculture production peaked at about 171 million tonnes in 2016 (excluding aquatic mammals, crocodiles, alligators and caimans, seaweeds, and other aquatic plants), with aquaculture representing 47% of the total and 53% if non-food uses are excluded. Moreover, fish provided about 3.2 billion people with almost 20% of their average per capita intake of animal protein (FAO 2018). As a source of livelihood, capture fisheries and aquaculture employed 43.5 million people in 2006, and 520 million people relied on income from seafood production. Seafood is rich in proteins (including taurine), vitamins (e.g. vitamin D), very long-chain polyunsaturated fatty acids (VLC-PUFA), eicosapentaenoic acid (EPA, C20:5), docosahexaenoic acid (DHA, C22:6) and provides important micronutrients, e.g. selenium among others.

Although seafood is the most highly traded food all over the world, it is an often overlooked component of global food safety and security (Smith et al. 2010; Lund 2013). The outbreaks and recalls of seafood are caused by microbial pathogens, chemical contaminants, toxins from harmful algal blooms and xenobiotics which lead to significant public health and economic burdens. From the above-mentioned contaminants, chemical contaminants of emerging concern in seafood are toxic elemental species such as arsenic, mercury, cadmium, and lead (Marques et al. 2019). In this chapter, we discuss the arsenic (As) presence in seafood, its levels, extraction and analytical techniques, international regulations, and health risk assessments associated with seafood species consumption and their As concentrations. In the final section, the drawbacks and challenges related to As contamination of seafood are discussed.

3.2 The Accumulation of Arsenic in Seafood

The natural concentration of As in the Earth's crust is about 2 mg kg^{-1}, however, its concentration in some sedimentary rocks, such as sandstone, can be as high as 900 mg kg^{-1}, while in coal it ranges from about 2.5–17 mg kg^{-1} (Cullen and Reimer 2016). The sources of As in the environment originate from a number of anthropogenic activities and natural processes. Combustion of fossil fuels redistributes As in the environment and the crude oil contains 0.002–1.6 mg kg^{-1} of As. Another anthropogenic redistribution pathway that occurs is the gold mining and recovery processes, which result in several As contaminated by-products, usually with a very high As content. Arsenic compounds are used as a principal

ingredient of insecticides, pesticides, and herbicides, all of which also end up in the environment. Moreover, As is commonly used in the electronics industry (as gallium arsenide and arsine gas), algaecides, desiccants for mechanical cotton harvesting, glass manufacturing, nonferrous alloys, and in the feed industry as a feed additive. Finally, natural phenomena such as volcanic activity and the weathering of minerals through wind and water erosion are the main pathways in which As is distributed into the soil, water, and air. Once there, As can become transformed through a variety of chemical or biological (biogeochemical) processes that occur in the environment (Cullen and Reimer 2016; Jinadasa and Fowler 2019).

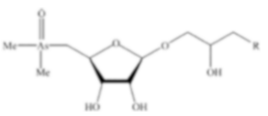
Common concentrations of As in surface soil worldwide generally lie in a range between 5 and 10 mg kg^{-1}, with an average of around 7 mg kg^{-1}. However, the As concentration in seawater is very constant worldwide (1–2 μg L^{-1}), except in estuarine areas. In freshwater, the concentration range spans four orders of magnitude, ranging from less than 0.5 μg L^{-1} to more than 5000 μg L^{-1} such as in groundwater in Bangladesh (Cullen and Reimer 2016). Aquatic organisms accumulate, retain, and transform As species inside their bodies when exposed to it through their food and other available routes and sources such as water, sediment, and suspended particles (Azizur Rahman et al. 2012). Despite the low levels of As in seawater, much higher concentrations of As are found in marine food webs compared with those in freshwater food webs. This noticeable difference may be explained by the transformation of inorganic As species (iAs) to organic As (oAs) compounds at the base of the marine food web, and the greater accumulation and retention of these organic compounds in marine organisms (Jinadasa and Fowler 2019). Seaweeds have one of the highest total As (tAs) concentrations in the marine food web, with shellfish containing higher tAs levels than those in finfish, and demersal fish often containing more tAs than pelagic fish (Taylor et al. 2017).

3.3 Arsenic Speciation in Seafood

Arsenic in marine samples was first reported over 100 years ago and shortly thereafter it was shown that common seafood types such as fish, crustaceans, and mollusks contained As at exceedingly high concentrations (Francesconi 2010). Fish and seafood contain both iAs and oAs species. iAs is identified to be present in two oxidation states, i.e. arsenite (As-III) and arsenate (As-V), however, these forms are found at lower levels in seafood compared to oAs compounds. There are more than 50 oAs species found in seafood, including the most common forms arsenobetaine (AB), monomethylarsonic acid (MMA), dimethylarsinic acid (DMA), arsenocholine (AC), arsenosugars (AS), and arsenolipids (AL) (Begerow et al. 2002; Jinadasa and Fowler 2019) (Table 3.1).

Arsenous acid/arsenite (As-III), $[As(OH)_3]$ is the most toxic iAs species among all arsenicals, more toxic than arsenic acid/arsenate $[AsH_3O_4]$ and other oAs species which are found in fish and other seafood (Jinadasa and Fowler 2019). When chemically quantified, As (V) and As (III) are normally described together and referred to as the sum of iAs. Cullen and Reimer (2016) have summarized the

Table 3.1 The most common and widely determined As speciation forms measured in seafood (Jinadasa and Fowler 2019)

Name	Acronym	Chemical structure
Arsenite	As (III)	$As(OH)_3$
Arsenate	As (V)	AsH_3O_4
Monomethylarsonous acid	MMAA (III)	$CH_3As(OH)_2$
Dimethylarsinous acid	DMAA (III)	$(CH_3)_2AsOH$
Monomethylarsonic acid	MMAA (V)	$AsO(OH)_2CH_3$
Dimethylarsinic acid	DMAA (V)	$AsO(OH)(CH_3)_2$
Trimethylarsine acid	TMAA	CH_3As_3
Arsenocholine	AC	$(CH_3)_3As(CH_2)_2OH$
Arsenobetaine	AB	$(CH_3)_3AsCH_2COOH$
Arsenosugar	AS	
Sulphate arsenoribose	_	R = SO3H
Sulfonate arsenoribose	_	R = OSO3H
Phosphate arsenoribose	_	R = $OP(O)(OH)OCH_2CH(OH)CH_2OH$
Trimethylarsoniopropionate	TMAP	$(CH_3)_3As(CH_2)_2COOH$
Tetramethylarsonium ion	TETRA	$(CH_3)_4As$
Trimethylarsine oxide	TMAO	$(CH_3)_3AsO$
Thiodimethylarsinate	Thio-DMA	$(CH_3)_2AsS$
Arsenolipids	AL	$(CH_3)_2AsO(R)COOH$
Roxarsone	ROX	$AsO(OH)_2(C_6H_6)OHNO_2$
Phenylarsonic acid	PhA	$AsO(OH)_2(C_6H_6)$
Triphenylarsine	TPA	$As(C_6H_6)_3$
Triethylarsine	TEA	$(CH_3)_3(CH_2)_3As$
2-Chlorovinylarsonous acid	CVAA	$(CH_2)_2AsCH_2CHCl$
2-Chlorovinylarsonous oxide	CVAO	$OAs(CH)_2Cl$
2-Chlorovinyldichloroarsine	Lewisite	$Cl_2As(CH)_2Cl$

range of iAs for fish (<0.1–600 μg kg^{-1}), seafood (<0.29–1700 μg kg^{-1}), and seaweed/algae (<14–2200 μg kg^{-1}). Ferrante et al. (2019) reviewed studies of As in fresh fish and mollusks harvested in the Mediterranean sea and the European coasts of the Atlantic ocean within the period 2004–2017. Although 25 research articles were cited, only 7 applied to iAs analysis. According to the summary, tAs (mg kg^{-1}, ww) differed in the three analysed group of species, i.e. demersal fish, 4.96 ± 5.28; pelagic fish, 5.90 ± 6.87; and molluscs, 3.56 ± 3.33. The same variability was noted for iAs (mg kg^{-1}, ww), e.g. demersal, 0.001 ± 0.03; pelagic, 0.01 ± 0.02; molluscs, 0.08 ± 0.15. On the basis of the speciation results, it was assessed that the iAs fraction (in relation to tAs) for each seafood group was low, i.e. demersal = 0.14%; pelagic = 0.41%; mollusks = 2.37% and for that reason the speciation analysis was not conducted. According to Molin et al. (2015) fish and seafood contained the

highest tAs concentrations, but these food groups are generally low in iAs (usually <0.2 mg As kg^{-1}, dw). However some marine algae species such as hijiki (*Hizikia fusiforme*) [>60 mg kg^{-1}] and some bivalve species such as blue mussels (*Mytilus edulis*) [up to 5.8 mg kg^{-1}, ww] contain very high iAs concentrations (Molin et al. 2015; Sloth and Julshamn 2008). As (III) and As (V) are categorized under the group 1 carcinogens with acute toxicity of LD_{50} of 15–42 mg kg^{-1} of body mass (Luvonga et al. 2020).

The main source of the oAs for general populations worldwide is seafood (Navas-Acien et al. 2011). Arsenobetaine (AB), mainly 2-trimethylarsoniumylacetate and 2-trimethylarsaniumyl acetate, is a non-toxic arsenical ($LD_{50} \geq$ 10,000 mg kg^{-1}, body weight) that is excreted in humans unchanged via the kidneys. It is the major oAs species found in most shellfish, finfish, seaweed and even zooplankton. It accounts for between 50% and nearly 100% of tAs in finfish, but its proportion is similar to that for the arsenosugars (AS) in shellfish, and this balance even shifts almost entirely to the AS in algae and seaweed (Taylor et al. 2017; Cullen and Reimer 2016; Navas-Acien et al. 2011; Luvonga et al. 2020). Although AB is the most studied As species, details on its source in the food web and the synthesis pathway for it are still unclear (Chen et al. 2020). Nevertheless, there are a number of theories and models about the biosynthetic pathway of the AB formation that have been described, e.g., by Caumette et al. (2012), Hoffmann et al. (2018), and Thomas and Bradham (2016).

There are also methylated As compounds in marine seafood, mainly resulting from enzymatic methylation of iAs by arsenite S-adenosylmethionine methyl transferases which contain 1–4 methyl groups. These compounds are monomethyl arsenic acid (MMA^V), monomethyl arsonous acid (MMA^{III}), dimethyl arsenic acid (DMA^V), dimethyl arsenous acid (DMA^{III}), tetramethyl arsine oxide (TMAO), tetramethyl arsine sulphide (TMAS), tetramethyl arsonium ion (TETRA), and arsenocholine (AC) (Taylor et al. 2017) (Table 3.1). MMA and DMA are generally either present in trace amounts or not present in seafood at all. Some detectable levels of DMA and MMA are present in fatty fish such as mackerel and herrings, and in prawns. DMA is also detected in kelp-like seaweeds and in molluscs. TMAO is reported to be present in higher concentrations in some fish species, while TETRA is found in clams and gastropods (Luvonga et al. 2020; Taylor et al. 2017). In terms of cytotoxicity, genotoxicity, and enzyme inhibition, recent data show that MMA^{III} and DMA^{III} are more active than iAs (Cui et al. 2020). MMA and DMA are classified under group 2B (possible human carcinogen) by the International Agency for Research on Cancer (IARC) (Luvonga et al. 2020).

The arsenosugars (AS) are ribose derivatives and the structure was first identified in 1981 in water-soluble components of brown kelp (*Ecklonia radiata*), and subsequently over 20 AS with different side chains in the skeletal structures have been identified, among which four types (Fig. 3.1) (AS-Gly, AS-PO_4, AS-SO_3, and AS-SO_4) are the most frequently detected (Cao et al. 2019). AS are mainly present in high concentrations (20–100 mg kg^{-1}, dw) in marine algae and also in mollusks and crustaceans. Even in seaweeds, the AS content varies among different taxa (Taylor et al. 2017). Almela et al. (2005) studied the bioaccessibility of raw and

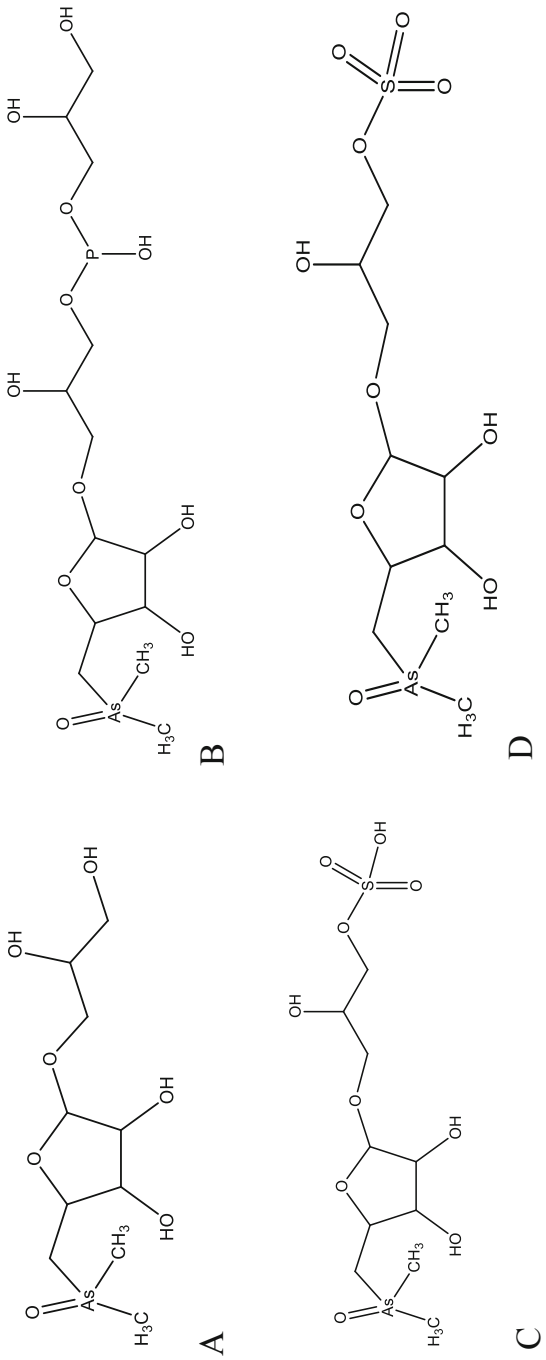


Fig. 3.1 Chemical structure of common organic arsenic species, (**a**) Arsenosugar-Gly, (**b**) Arsenosugar-PO_4, (**c**) Arsenosugar-SO_3, (**d**) Arsenosugar-SO_4

cooked seaweeds and observed a high bioaccessibility rate of >80% that did not vary with cooking. Even no degradation of As was observed as a result of the in vitro digestion. No biological functions are associated with AS, however, their important role in the transformation and cycling of As in the marine environment has been studied. AS are not considered to be acutely toxic, but they can result in slight chronic toxicity following the high consumption of seaweeds (Yu et al. 2020b).

Arsenolipids (AL) are in general organic As compounds that exhibit lipophilic properties. There are mainly five types of AL identified in seafood, namely arsenic-containing hydrocarbons (AsHCs), fatty acids (AsFAs), phospholipids (AsPLs), phosphatidylcholines (AsPCs), and fatty alcohols (AsFAl) (Cao et al. 2019; Chen et al. 2020). Following the first identification of ALs in 2017, i.e. dipalmitoylglycerophospho-2-hydroxypropyl-5-deoxy-5-(dimethylarsinoyl)-beta-ribofuranoside extracted from brown algae, more than 50 AL have been identified since then (Chen et al. 2020). There is not much information on AL in seafood, but they have been identified in some oily fish and seaweeds. Al Amin et al. (2020) assessed the AL content in 18 seafood samples, i.e. fish, shellfish, and crustaceans in Japan, and determined AsHCs in all samples (83 ± 73 ng g^{-1}, ww) and AsFAs in some of them. In 2014, the same research group studied the in vitro toxicity of AL and found that AsHCs were cytotoxic to the human liver and bladder cells in a similar way as the As (III) species (Meyer et al. 2014).

3.4 Extraction and Detection Techniques of As in Seafood

Acid digestion is a commonly used method for tAs determination in seafood samples. Different acid combinations were used by different researchers, and each method has some advantages and disadvantages. As one example, Storelli and Marcotrigiano (2000) applied the reflux extraction method for tAs determination in fish (3 g) with 10 mL of a $HNO_3/HClO_4/H_2SO_4$ mixture. The main drawback of this method was that it is time-consuming (6 h). To avoid long digestion times, microwave-assisted digestion with different reagents has been proposed, e.g. HNO_3 (Jinadasa et al. 2015), a HNO_3, and H_2O_2 mixture (Cui et al. 2020), and HNO_3, HCl, H_2O_2, and HF mixtures (Shakeri et al. 2020). Some other examples and alternatives (hot plate, water bath, etc.) are summarized in Table 3.2.

The sample extraction method is very important in the As speciation analysis of seafood due to the complexities of the matrices. Several analytical methods and extraction solvents have been used for that purpose (Table 3.2). Distillation was proposed for the extraction of As species from fish samples by Storelli and Marcotrigiano (2000). In the first step, 5 g samples of wet tissues were treated with 1 mL of HBr and 25 mL of 6 M HCl, and refluxed for 15 min. After collecting 20 mL of distillates, 20 mL of 6 M HCl were added to samples and the resulting mixtures were refluxed again. The disadvantage of the above method is that it is slow and consumes a high amount of concentrated reagents. Kalantzi et al. (2017) proposed a vortex and ultrasonic-assisted method for the extraction of iAs [As(III) and As(V)] and oAs species (AB, MMA, DMA) from fish. Freeze-dried fish powder

Table 3.2 Selected publication of As content in commonly consumed seafood

Matrix	Sampling area	Analyte	Extraction technique	Detection technique	tAs concentration (mg kg^{-1}, ww) unless otherwise mentioned	Ref.
Fish[b]	Greek	tAs, AB, As (III), As (V), DMA, MMA	MWA, UAE	HPLC-ICP MS	11.8–62.6[a]	Kalantzi et al. (2017)
Fish[b]	Brazil	tAs	_	GTAAS	0.0004–1.1451	Gusso-Choueri et al. (2018)
Fish[b]	Bulgaria	tAs	MWA	GTAAS	0.73 ± 0.05–1.1 ± 0.1	Peycheva et al. (2016)
Fish[b]	South Korea	tAs, As (III), As (V), AB, DMA, MMA, AC	WB, UAE	HPLC-ICP MS	0.02–9.65	Choi et al. (2015)
Fish[b]	China	tAs, As (III), As (V), AB, DMA, MMA, AC	MWA	ICP MS	22.02–65.66[a]	Li et al. (2017)
Fish[b]	Brazil	tAs	MWA	ICP MS	0.03 ± 0.008	Oliveira et al. (2017)
Fish[b]	UK	tAs, As (III), As (V), AB, DMA, MMA	EE	HPLC-ICP MS	3.73–98.39 ± 2.37	Sadee et al. (2016)
Fish[b]	China	tAs, As (III), As (V), DMA, MMA, AC	MWA	HPLC-ICP MS	0.748 ± 0.651	Jia et al. (2018a)
Fish[b]	Vietnam	tAs	MWA	ICP-SF MS	5.6 ± 1.2–26.1 ± 0.2[a]	Tran et al. (2018)
Fish[b]	Spain	tAs	MWA	ICP MS	0.249–7.849	Núñez et al. (2018)
Fish[b]	Turkey	tAs	MWA	ICP MS	0.31–0.67	Yabanli et al. (2016)
Fish[b]	Norway	tAs	MWA	ICP MS	2.2 ± 0.6	Frantzen et al. (2015)
Fish[b]	Serbia	tAs	MWA	ICP MS	0.001 ± 0.000–0.003 ± 0.006	Miloškovic and Simić (2015)

Fish[b]	Bangladesh	tAs	MWA	ICP MS	0.01–1.8	Ahmed et al. (2016)
Fish[b]	Bulgaria	tAs	MWA	GTAAS	0.38 ± 0.02–1.1 ± 0.1	Makedonski et al. (2017)
Fish[b]	Indonesia	tAs	_	ICP MS	0.27–8.99	Bentley and Soebandrio (2017)
Fish[b]	Mexico	tAs	MWA	HGAAS	0.524 ± 0.476–2.105 ± 1.189[a]	Spanopoulos-Zarco et al. (2015)
Fish[b]	Argentina	tAs	Furnace	HGAAS	0.152–0.439	Sigrist et al. (2016)
Fish[b]	Colombian Caribbean	tAs	Hot plate	MIP OES	<0.023–0.133	Gallego Ríos et al. (2018)
Fish[b]	Trinidad and Tobago	tAs	_	HGAAS	0.138–6.155	Mohammed and Mohammed (2017)
Fish[b]	SWAE	tAs	_	NAA	0.41–23.50	Avigliano et al. (2019)
Bigeye tuna	AO, IO	tAs	_	GTAAS	0.002–0.578	Chen et al. (2018)
Fish (canned)	Iran	tAs	MWA	HGAAS	0.25–1.42	Andayesh et al. (2015)
Fish (canned)	Brazil	tAs	MWA	ICP OES	120.06 ± 0.83–266.78 ± 2.65	Silva et al. (2017)
Fish (canned)	Serbia	tAs	MWA	ICP MS	0.17–3.73	Novakov et al. (2017)
Fish (canned)	Czech and Austria	tAs, As (V), AB, DMA, MMA	MWA	ICP MS	1.52 ± 0.21–5.56 ± 0.1[a]	Kaňa et al. (2018)

(continued)

Table 3.2 (continued)

Matrix	Sampling area	Analyte	Extraction technique	Detection technique	tAs concentration (mg kg^{-1}, ww) unless otherwise mentioned	Ref.
Fish (liver)	Norway	tAs, AL	MWA	HPLC-ICP MS	2.1–240	Sele et al. (2015)
Fish egg	Iran	tAs	MWA	ICP OES	0.01 ± 0.002	Sobhanardakani et al. (2018)
Fish, shellfish	North Sea, Brazil	tAs, As (III), As (V), DMA, MMA	MWA	ICP OES, ICP MS	0.73–50	Gao et al. (2018)
Fish, shellfish	Western Arabian Gulf	tAs, iAs, AB, TMAO, AC, TETRA, As-Gly	MWA, shaker	HPLC-ICP MS	16–118[a]	Krishnakumar et al. (2016)
Fish, shellfish	Ghana	tAs	_	AAS	0.2–2.8	Gbogbo et al. (2017)
Fish, shellfish	Italy	tAs	MWA	ICP MS	2.507 ± 0.748–9.477 ± 1.451	Copat et al. (2018)
Fish, shellfish	Italy	tAs	MWA	GTAAS	1.8–2.6[a]	Berti et al. (2015)
Fish, shellfish	Sweden	tAs, iAs	_	HPLC-ICP MS	0.859–2.01	Kollander et al. (2019)
Shellfish	China	tAs, As (III), As (V), AB, DMA, MMA, DDAR	MWA	IC-ICP MS	0.34 ± 0.01–1.90 ± 0.06	Qiu et al. (2018)
Shellfish	China	tAs, AB, As (III), As (V), DMA, MMA, AC	MWA	HPLC-ICP MS	10.506–35.110	Jia et al. (2018b)
Fish, mussels	Norway	tAs, iAs, AB, DMA, MMA, TMAO, DMAE, AC, TETRA, TMAP	MWA	HPLC-ICP MS	1.2–4.7	Molin et al. (2017)
Fish, shrimp	USA	tAs, As (III), As (V), AB, DMA, MMA	MWA, HB	HPLC-ICP MS	0.378–3.8	Schmidt et al. (2017)
Fish, shrimp	Saudi Arabia	tAs	WB	HG-AAS	0.11–0.62	Ashraf and Mian (2019)

Fish, shrimp, lobster	Persian Gulf	tAs	Hot plate, furnace	HGAAS	Fish: 62–148, shrimp: 211–265, lobster: 118–318	Rahimi and Gheysari (2016)
Fish, mussels	Italy	tAs	Hot plate, furnace	HGAAS	Fish: 4.89–105.33, mussels: 15.09–389.62	Fasano et al. (2018)
YFT, marlin, mussels	Indonesia	tAs	MWA	ICP MS	YFT: 3.47 ± 0.21[a], marlin: 2.71 ± 0.18[a], mussels: 6.77 ± 0.32[a]	Koesmawati and Arifin (2015)
YFT, marlin, mussels	(Bosnia and Herzegovina	tAs	MWA	GTAAS	0.118–0.822	Omeragic et al. (2020)
Mussels and clams	Italy	tAs	MWA	ICP MS	Mussels: 5.04 ± 2.34, clams: 4.86 ± 2.33	Chiesa et al. (2018)
Fish, seafood	Italy	tAS	MWA	ICP MS	1.35	Filippini et al. (2018)
Fish, seafood	Brazil, Spain	tAs, iAs, AB	MWA	HR-CS-GTAAS, HPLC-ICP MS	2.3–35	Zmozinski et al. (2015)
Fish, seafood	Kuwait	tAs, As (III), As (V), AB, DMA, MMA, TETRA, TMAO, AC	HB	HPLC-ICP MS	0.078–20.2	Husain et al. (2017)
Seafood (products)	Norway	tAs	MWA	ICP MS	0.28–7.50	Næss et al. (2020)
Seafood	Chile	tAs, iAs	Furnace	HGAAS	1.845	Muñoz et al. (2017)
Seafood	Turkey	tAs	_	ICP MS	0.002–0.96	Özden and Erkan (2016)
Seafood	Japan	AsHCs, AsFAs	Rotavapour	HPLC-ICP MS/ESI-MS	AsHCs: 0.083 ± 0.073, AsFAs: 0.013 ± 0.015	Al Amin et al. (2020)
Seafood	EU	tAs, iAs	MWA, WB	ICP MS	1.4–43[a]	Maulvault et al. (2015)

(continued)

Table 3.2 (continued)

Matrix	Sampling area	Analyte	Extraction technique	Detection technique	tAs concentration (mg kg^{-1}, ww) unless otherwise mentioned	Ref.
Seafood	USA	tAs, As (III), As (V), AB, DMA, MMA	MWA, HB	HPLC-ICP MS	0.74 ± 0.01–14.5 ± 0.5[a]	Schmidt et al. (2018)
Seafood	China	tAs, As (III), As (V), AB, DMA, MMA	_	HPLC-ICP MS	1.22 ± 0.12–35.1 ± 5.38	Zhang et al. (2018)
Seafood	Bangladesh	tAs	MWA	HGAAS	<0.008–0.283	Baki et al. (2018)
Seafood	Russia	tAs, oAs, iAs	WB, shaker	HGAAS	0.04 ± 0.01–28.8 ± 10.1	Kruglyakova et al. (2018)
Seafood	Canada	tAs, As (III), As (V), AB, DMA, MMA	Shaker	HPLC-NAA	2.5 ± 0.4–23 ± 2	Shi and Chatt (2018)
Seafood, seaweed, fish	Poland	tAs, iAs	Hot plate, shaker	HG-AAS	Fish: 0.46, seafood: 0.87, Hijiki: 188.6	Mania et al. (2015)
Seafood, seaweed	South Korea	tAs, As (III), As (V), AB, DMA, MMA	UAE, hotplate	IC-ICP OES	31.8 ± 0.6–168 ± 3[a]	Nam et al. (2016)
Seaweed	Ireland	tAs, iAs	MWA	HPLC-ICP MS	tAs: 59–114[a]	Ronan et al. (2017)
Seaweed	South Korea	tAs, As (III), As (V), AB, DMA, MMA, AC	UAE	HPLC-ICP MS	111.0 ± 15.7–259.1 ± 9.6	Ronan et al. (2017)
Squid	New Zealand	tAs	MWA	ICP MS	5.9–32.50[a]	Lischka et al. (2020)

AAS atomic absorption spectrometry, *AO* Atlantic ocean, *DDAR* 5-deoxy-5-dimethylarsinoyl-β-ribofuranos, *EE* enzymatic extraction, *GTAAS* graphite tube atomic absorption spectrometry, *HB* heating block, *HGAAS* hydride generation atomic absorption spectrometry, *HPLC-ICP MS/ESI-MS* high performance liquid chromatography inductively coupled plasma mass spectrometry/electrospray ionization tandem mass spectrometry, *HR-CS-GTAAS* high resolution continuum source graphite tube atomic absorption spectrometry, *iAs* inorganic arsenic, *IC-ICP MS* ion chromatography inductively coupled plasma mass spectrometry, *ICP MS* inductively coupled plasma mass spectrometry, *ICP-SF-MS* inductively coupled plasma sector field mass spectrometry, *ICP OES* inductively coupled plasma-optical emission spectrometry, *IO* Indian ocean, *MIP OES* microwave-induced plasma-optical emission spectrometry, *MWA* microwave-assisted extraction, *NAA* neutron activation analysis, *SWAE* south-western Atlantic estuaries, *UAE* ultrasound-assisted extraction, *WB* water bath

[a]dw

[b]Fish muscle or fillet

samples (0.03 g) were mixed with 1.2 mL of $(NH_4)_2HPO_4$ (10 mM, pH 7.9) and vortexed for 1 min prior to ultrasonic-assisted extraction (3 min, 40 °C). These two steps were repeated 10 times. In another study, an ultrasonic bath was used with 10 mL of a (1:1) methanol:water mixture with 30 min extraction time as an alternative enabling rapid extraction of As species (Jinadasa et al. 2020b). 5 mL of methyl tert-butyl ether (MTBE) and methanol (1.5 mL) were used for the AL extraction from seafood samples with the assistance of a rotary evaporator (1 h, room temperature) (Amin et al. 2018; Al Amin et al. 2020). Almela et al. (2005) used 20 mL of a (1:1) methanol:water mixture for extraction of AS from seaweed. The mixture was agitated for 15 min in a mechanical shaker and centrifuged at 2000 rpm for 10 min. Finally, the supernatants were collected for further analysis. Other examples of seafood sample preparation for the extraction of As species are given in Table 3.2.

Traditional instrumental methods, overwhelmingly spectrometric ones, for the tAs determination in seafood samples include thin-layer chromatography (TLC), atomic absorption spectrometry (AAS), atomic fluorescence spectrometry (AFS), spectrophotometry, inductively coupled plasma mass spectrometry (ICP MS), inductively coupled plasma-optical emission spectrometry (ICP OES), neutron activation analysis (NAA), direct current plasma-optical emission spectrometry (DCP OES), X-ray absorption spectroscopy (XAS), and X-ray fluorescence (XRF) (Mounicou et al. 2009; Hu et al. 2020). A combination of chromatographic separation with spectrometric detection is the most commonly used and well accepted approach for As speciation analysis of seafood samples. The following coupled techniques are used for that purpose, i.e. high performance liquid chromatography hyphenated with inductively coupled plasma mass spectrometry (HPLC-ICP MS), gas chromatography hyphenated with inductively coupled plasma mass spectrometry (GC-ICP MS), ion chromatography hyphenated with inductively coupled plasma mass spectrometry (IC-ICP MS), or capillary electrophoresis coupled with inductively coupled plasma mass spectrometry (CE-ICP MS), or HPLC coupled with electron spray ionization mass spectrometry (HPLC-ESI-MS) (Yu et al. 2020a; Gutiérrez Sama et al. 2018). Almost all of these techniques have a potential of rapid elemental speciation with low detection limits for the As species. Most of them require very costly and highly sophisticated analytical equipment, and that becomes a major disadvantage. Moreover, these methods are prone to spectroscopic interferences and matrix effects, and include the use of toxic solvents at the stage of sample preparation. Hence, it is necessary to develop cost-effective but highly efficient methods with new selective green alternatives to sample preparation of food matrices in order to overcome the above-mentioned problems (Olesik et al. 1998; Escudero et al. 2016).

3.5 Microextraction Techniques

The determination of some As speciation, particularly iAs in seafood, is of great importance for human health. However, it is still a challenge due to the complexity of food matrices and the relatively low concentrations of these As species in samples.

Therefore, liquid-liquid extraction (LLE) and solid phase extraction (SPE) are widely used to pre-concentrate the iAs species. Both extraction techniques evolved into microextraction techniques (MET), i.e. solid sorbent-based or solid phase microextraction (SPME), and liquid-based or liquid-phase microextraction (LPME). METs have been proven to provide similar or even better results in terms of sensitivity and reproducibility than conventional SPE and LLE. In addition, METs meet the green analytical chemistry requirements, regarding the reduction of the reagent and solvent consumption, in addition to the miniaturization and the automation of the analytical techniques. Moreover, recent METs applications, used as combined microextraction techniques (CMETs) in which ultrasonication, vortex, or microwave treatments are employed open new perspectives in sample preparation for speciation analysis of As (Werner et al. 2018; Jinadasa et al. 2020a). In particular, CMETs were proposed to combat some limitations in the enrichment factors, detection limits, and accuracy of METs. SPME was first introduced by Arthur and Pawliszyn (1990) and after that, several types of SPME such as stir bar sorptive extraction (SBSE), microextraction in packed sorbent (MEPS), magnetic micro-solid phase extraction (MμSPE), and dispersive micro-solid phase extraction (DμSPE) were developed (Jinadasa et al. 2020a). Wu et al. (2000) developed the polypyrrole (PPY) coated capillary in-tube SPME coupled with liquid chromatography electrospray ionization mass spectrometry (LC-ESI-MS) detection for the As speciation (MMA, DMA, AB, AC) analyses in aqueous samples and certified dogfish reference materials (DORM-2). Several commercial gas chromatography (GC) capillary columns were evaluated, but the best extraction performance was obtained using a lab-made PPY coated capillary which exhibited better extraction efficiency. Magnetic ferrite particles SPEME combined with an electrothermal atomic absorption spectrometry method was developed to measure iAs and MMA in DORM-4 (fish protein) and NIST 1566a (oyster tissue). The detection limit of As was 0.02 μg L^{-1} for a 10 mL sample volume (López-García et al. 2018).

LPME techniques were developed to overcome the drawbacks occurring in convention LLE, such as the use of large quantities of potentially toxic and expensive solvents, long analysis times, and the multi-stage character of the extraction of the As species. According to the current trends in sample pre-treatment, the following LPME approaches are now used to extract As species: single-drop microextraction (SDME), hollow-fibre liquid-phase microextraction (HF-LPME), and dispersive liquid-liquid microextraction (DLLME) (Werner et al. 2018; Jinadasa et al. 2020a). Shirani et al. (2015) developed a procedure for the pre-concentration and determination of tAs in fish liver based on the use of ultrasound-assisted, ionic liquid-linked, dual-magnetic multiwall carbon nanotube microextraction (USA-IL-LDMME), combined with electrothermal atomic absorption spectrometry (ET AAS). A solution of sodium diethyldithiocarbamate (NaDDTC) was used as the chelating agent for As species. The proposed method demonstrated a very high enrichment factor (398), a good linear range (10–100 ng L^{-1}), the low detection limit for As (5 ng L^{-1}), and a satisfactory precision (3.2%) (Shirani et al. 2015). There are a number of SPME and LPME applications available for the As extraction

from environmental and biological samples, but to date very few applications have been reported for complex matrices such as seafood.

3.6 As Content in Commonly Consumed Seafood

Some recent publications (2015–2020) on As concentrations in fish and seafood samples from all regions in the world are summarized in Table 3.2. A low As concentration was observed in freshwater fish species as compared to concentrations in marine species. Many authors have confirmed this difference for the freshwater environment (Kumari et al. 2017; Oliveira et al. 2017; Jia et al. 2018a; Miloškovic and Simić 2015). However, according to some references in Table 3.2, it is not always true. Accordingly, Ahmed et al. (2016) analysed three freshwater fish species, namely Rui (*Labeo rohita*), Pangas (*Pangasius pangasius*), and Tilapia (*Oreochromis mossambicus*) from Bangladesh with Tilapia showing a high As concentration (average, 1.5 ± 0.4 mg kg^{-1}, ww and range 0.98–1.8 mg kg^{-1}, ww). Moreover, Gbogbo et al. (2017) analysed a number of fish, shellfish, and gastropod species from Ghana, and found they contained a high As concentration ranging from 0.86 to 2.01 mg kg^{-1}. This was likely related due to the surrounding environmental conditions, because the river water of Ghana also showed the high As concentration, i.e. 0.2–2.2 mg L^{-1}, which was higher than the World Health Organization (WHO) recommended value for drinking water (10 μg L^{-1}). The tAs level of the seafood is also dependent on the body tissues of the analysed species. Sele et al. (2015) determined the As level in liver samples from Northeast Arctic cod (*Gadus morhua*) and observed its very high value ranging from 2.1 to 240 mg kg^{-1} ww. This kind of variation was also observed in different parts of seaweeds such as *Laminaria digitata* although the recorded tAs level was very high (59–114 mg kg^{-1} dw) despite the fact that samples came from a clean seashore area (Ronan et al. 2017).

3.7 International Regulation of As in Seafood

Many international, national, and regional level organizations, for reasons of human health, have set standards to control the amount of metals and metalloids in seafood. Such standards usually refer to maximum permissible contaminant levels (MPCL) (Jinadasa et al. 2020c). MPCL values vary in accordance with the food type and the regulation body. The MPCL values for iAs are given in different guidelines by countries, and are 2 mg kg^{-1} ww in crustaceans and fish, and 1 mg kg^{-1}, ww in mollusks and edible seaweeds [Australia New Zealand (ANZFA)]; 3.5 mg kg^{-1}, ww for fish protein, Canadian Food Inspection Agency (CFIA); 0.1 mg kg^{-1}, ww in fish, fish products and fish seasonings, Ministry of Health of the People's Republic of China (MHPRC); and 3 mg kg^{-1} for algal condiments, Centre d'Etude et de Valorisation des Algues, France (CEVA). The European Food Safety Authority (EFSA) and the Food and Drug Administration of the United States (USFDA)

have also reported MPCL values for certain foodstuffs (e.g. rice, rice-based products and infant cereals) but not for seafood (Liu et al. 2010; Llorente-Mirandes et al. 2017; Jinadasa et al. 2020c).

The 'tolerable intake' is commonly used to describe the 'safe' levels of intake. The joint FAO-WHO expert committee on food additives (JECFA) has established a provisional tolerable weekly intake (PTWI) value for As of 15 μg kg^{-1} of body weight (equivalent to 2.1 μg kg^{-1} of body weight per day). The EFSA established a tolerable weekly intake (TWI) value for As and evaluated the safe dietary exposure to iAs. The PTWI parameter is no longer appropriate and was withdrawn in 2010. The Panel on Contaminants in the Food Chain (CONTAM) and EFSA, therefore, suggested a range of values of the benchmark dose lower confidence limit (BMDL) for As, including 0.3–8 μg of As/kg of body weight per day in case of cancers of lung, skin, and bladder as well as for skin lesions. BMDL values seem to be more suitable than a single reference value in the risk evaluation related to the iAs intake. Also because of limited available data, EFSA has considered an iAs level of 0.03 mg kg^{-1} in fish and 0.01 mg kg^{-1} in seafood to be realistic for calculating human dietary exposure (Llorente-Mirandes et al. 2017; EFSA 2009).

3.8 Bioavailability and Bioaccessibility of As

The bioavailability describes the proportion of a nutrient or trace element in food that can be absorbed and participate in the functioning of the normal body (Moreda-Piñeiro et al. 2012a, b). During the gastrointestinal digestion process, food components are released and only their portions are available for the body function and storage. Hence, it is important to know the difference between bioavailability and bioaccessibility. The bioaccessibility denotes the fraction of a given compound that is released from the food matrix after ingestion and solubilization in the intestinal lumen. Thus, bioavailability defines the fraction of the solubilized compound that is absorbed in the intestinal tract and reaches the circulatory system (Barciela-Alonso and Bermejo-Barrera 2016). However, some authors used bioavailability and bioaccessibility as one term whereas it is affected by the food type, its composition, a given cooking procedure, and gastrointestinal conditions (Moreda-Piñeiro et al. 2012a, b).

There are two methods that are used to evaluate the bioavailability of different food components, namely in vivo and in vitro. In the in vivo method living organisms are used, thus it is expensive, difficult to reproduce, and ethically controversial (Barciela-Alonso and Bermejo-Barrera 2016). For that reason, the in vitro methods are mostly used to assess the bioavailability of these components, and the methods usually contain mainly two steps, i.e. gastric digestion stage and intestinal digestion stage. In some in vitro methods, semi-permeable membranes with specified pore sizes are applied during the intestinal digestion step to simulate the nutrient absorption mechanism (Moreda-Piñeiro et al. 2012a, b). Since the toxicity of elements strongly depends on their physico-chemical forms, and they are differentially bioavailable, it is necessary to assess the bioavailability of each As species.

The bioavailability (Moreda-Piñeiro et al. 2012a, b; Garcia-Sartal et al. 2012) and bioaccessibility (Contreras-Acuña et al. 2014; Cano-Sancho et al. 2015; Lyu et al. 2020; Alves et al. 2018; García-Sartal et al. 2011; Koch et al. 2007; Laird and Chan 2013; Maulvault et al. 2011; Torres-Escribano et al. 2011) studies on tAs and the As species in the seafood are summarized in Table 3.3. Moreda-Piñeiro et al. (2012a) evaluated the bioavailability of tAs and As speciation in seafood (fish and mollusks) based on the in vitro approach and using dialysis membranes. High dialyzability percentages for tAs and As species were found, i.e. ranging from 84.6 ± 1.7% to 106 ± 2.6%. These authors concluded that the fat content in the sample mainly affected the bioavailability of tAs, AB, and AC. The higher bioavailabilities of As were observed in less fat containing seafood samples. However, the authors also observed that there was no correlation between the As bioavailability and the protein content of seafood. The same bioavailability method has been used in the case of seaweed species (e.g. Kombu, Wakame, Nori, and Sea Lettuce) (García-Sartal et al. 2011, 2012). The results revealed that approximately 11–16% of tAs, of which 93–120% were AS, were recovered from dialysates. In general, As showed a higher bioavailability percentage than mercury (Hg) or cadmium (Cd) in seafood. As an example, the bioavailability of As, up to 100% of tAs, was observed in fish and crab (Maulvault et al. 2011), as much as 95% of tAs in anemones (Contreras-Acuña et al. 2014), 72–89% of tAs in different fish species (Cano-Sancho et al. 2015), and nearly 100% of tAs and As (III) in gastropods (Lyu et al. 2020). However, Contreras-Acuña et al. (2014) reported that 85% of tAs ingested by humans was eliminated from the body by urination within 90 h.

3.9 Cooking Effect of As in Seafood

Most of the tAs and As speciation assessment of seafood has been performed with the raw (fresh) samples. However, except for a few cases, most of the seafood products are consumed after treating them with different culinary procedures such as boiling, baking, frying, grilling, etc. These treatments can alter the tAs content and the As speciation (Barciela-Alonso and Bermejo-Barrera 2016). Devesa et al. (2001a) studied the effect of different cooking procedures (grilling, roasting, baking, stewing, boiling, steaming, and microwaving) on the changes in the tAs and iAs levels in several seafood species such as hake, megrim, anchovy, sardine, Atlantic horse mackerel, bivalves, squid, crustaceans, and salted cod. They observed a significant increase of tAs after cooking bivalves and salted cod, and also iAs in the case of squid and bivalves. The same authors (Devesa et al. 2001b) studied the effect of different cooking processes (i.e. baking, frying, and grilling) and temperature on the oAs speciation (AB, TMA^+, TMAO) in several seafood species (sole, dory, hake, and sardine). The cooking temperature varied from 90–160 °C and the cooking time between 5 and 25 min. It was found that AB underwent changes in the samples during the heating, and they were transformed into another more toxic species, i.e. TMA^+. Moreover, it was observed that an increase in cooking temperature and time resulted in production of higher amounts of TMA^+. However,

Table 3.3 Bioavailability/bioaccessibility studies of tAs and As species in different seafood

Sample matrix	Bioavailability or bioaccessibility process	As species	Ref.
Fish and molluscs	[Bioavailability] 1. Mix 0.5 g powdered seafood sample with 20 mL ultra-pure water (pH 2) 2. Add 0.15 g of gastric juice solution (6% pepsin in 6 M HCl) and incubate at 37 °C (150 rpm, 120 min) 3. Add 5 mL of and intestinal juice solution (4% pancreatin, 2.5% bile salt in 0.1 M $NaHCO_3$) 4. Introduce a dialysis bag (10 kDa) filled with 20 mL of a 0.15 N PIPES solution (pH 7.5) and incubate at 37 °C (150 rpm, 120 min)	tAs, As (III), As (V), AB, DMA, MMA, AC	Moreda-Piñeiro et al. (2012a, b)
Seaweed	[Bioavailability] Same procedure as above	As (III), AB, DMA, AS-Gly, AS-PO_4, AS-SO_3	García Sartal et al. (2012)
Seaweed	[Bioavailability] Same procedure as above	As (III), as (V), AB, DMA, MMA, DMA, AS-Gly, AS-PO_4, AS-SO_3	Garcia-Sartal et al. (2012)
Seafood (*Anemonia sulcata*)	[Bioaccessibility] 1. Mix 1 g of cooked anemone with 10 mL of a gastric juice solution (100 mg pepsin + 10 mL 150 mM NaCl, pH 2.5) 2. Incubate at 37 °C (4 h, 150 rpm) 3. Add 10 mL of an intestinal juice solution (3% pancreatin, 1% amylase, 1.5 g L^{-1} bile salt in ultra-pure water), adjust pH to 7.4 4. Incubate at 37 °C (4 h, 150 rpm), centrifuge (8 g, 30 min, 4 °C)	As (III), as (V), AB, DMA, MMA, AC, $DMAS^V$, GpAsC, TMAO, TETRA, tAs	Contreras-Acuña et al. (2014)
Seafood	[Bioaccessibility] 1. Mix 5 g of cooked sample with 5 mL of artificial saliva solution (5 min) 2. Add 12 mL of a gastric juice solution and stir for 2 h (37 °C, 60 rpm) 3. Add 12 mL of a duodenal	tAs	Cano-Sancho et al. (2015)

(continued)

Table 3.3 (continued)

Sample matrix	Bioavailability or bioaccessibility process	As species	Ref.
	juice solution and stir for 5 min, and then add 5 mL of bile juice solution and stir for 2 h (37 °C, 60 rpm) 4. Separate a non-digestible fraction by centrifuging (10,000 g for 10 min, 4 °C)		
Gastropod (*Bellamya aeruginosa*)	[Bioaccessibility] 1. Mix 0.5 g of powdered sample with 6 mL artificial saliva solution (pH 6.8), incubate for 5 min (37 °C, 250 rpm) 2. Add 12 mL of artificial gastric juice solution (pH 1), incubate for 2 h (37 °C, 250 rpm) 3. Add 12 mL of a duodenal juice solution, 6 mL of a bile juice solution, 2 mL of a 1 M Na_2CO_3 solution and incubate for 2 h (37 °C, 250 rpm) 4. Separate a non-digest fraction by centrifuging (10,000 g, 10 min)	tAs, as (III), as (V), AB, DMA, AC	Lyu et al. (2020)
Seafood	[Bioaccessibility] 1. Mix 1.5–2 g of sample with 4 mL of a saliva fluid (pH 7), 5 min (37 °C, 25 rpm) 2. Add 8 mL of a gastric fluid (pH 2), incubate for 2 h, (37 °C, 25 rpm) 3. Add 8 mL of a duodenal fluid, 4 mL of a bile fluid (pH 7), incubate for 2 h, (37 °C, 25 rpm) 4. Separate the bioaccessible fraction by centrifuging (2750 g, 10 °C, 10 min)	tAs	Alves et al. (2018)
Seaweeds (kombu, wakame, nori, and sea lettuce)	[Bioaccessibility] 1. Mix 0.5 min sample with 20 mL ultra-pure water, after 20 min adjust to pH 2 (6 M HCl) 2. Add 0.15 g of a gastric solution (pepsin 6%, in 0.1 M HCl) and incubate for 2 h (37 °C, 150 rpm) 3. Add 5 mL of a gastric solution (0.4% pancreatin, 2.5% bile salt in 0.1 M $NaHCO_3$) 4. Introduce a dialysis	tAs	García-Sartal et al. (2011)

(continued)

Table 3.3 (continued)

Sample matrix	Bioavailability or bioaccessibility process	As species	Ref.
	membrane (10 kDa) filled with 20 mL of a 0.15 N PIPES solution (pH 7.5) and incubate at 37 °C (150 rpm, 120 min)		
Seafood	[Bioaccessibility] 1. Mix 2 g sample with 30 mL of a stomach solution (0.6% pepsin, 0.85% NaCl, pH 2) and incubate for 2 h (37 °C, 130 rpm) 2. Add 50 mL of an intestinal juice solution (3 g L^{-1} porcine pancreatin, 6 g L^{-1} oxgall, 12.5 g L^{-1} $NaHCO_3$) and incubate for 3 h (37 °C, 130 rpm) 3. Separate the bio accessible fraction by centrifuging (10,000 g, 20 min)	tAs	Laird and Chan (2013)
Fish, crab	1. Mix 5 g of sample with 5 mL of a saliva solution (pH 6.8) and 5 min (37 °C, 60 rpm) 2. Add 12 mL of a gastric juice solution (pH 1.3) and incubate for 2 h (37 °C, 60 rpm) 3. Add 12 mL of a duodenal juice solution (pH 8.1), incubate for 5 min (37 °C, 60 rpm), and add 6 mL of a bile juice solution (pH 8.2) and finally incubate for 2 h (37 °C, 60 rpm) 4. Separate the digested fraction by centrifuging (10,000 g, 10 min, 10 °C)	tAs	Maulvault et al. (2011)

AB arsenobetaine, *AC* arsenocholine, *DMA* dimethyl arsonic acid, *$DMAS^V$* dimethylmonothioarsinic acid, *MMA* monomethyl arsonic acid, *GpAsC* glycerylphosphorylarsenocholine, *tAs* total arsenic, *TETRA* tetra-methyl-arsonium, *TMAO* trimethylarsine oxide

Rasmussen et al. (2017) studied the cold smoking process of Greenland halibut and Atlantic salmon and concluded that non-toxic oAs did not transform into carcinogen iAs during the industrial process. The same observation was reported by Schmidt et al. (2017). In their study, three different culinary treatments, i.e. boiling, frying, and sautéing with or without the addition of three spices, i.e. salt, lemon juice, and garlic on the As speciation [As (III), As (V), AB, DMA, MMA] of blacktip shark and Asian tiger shrimp were investigated. It was confirmed that there was no interconversion of the As species due to any culinary treatment and the addition of spices.

The extraction efficiency was not changed; only in case of boiling was a 15–45% loss of As observed.

The effect of four cooking methods (baking, grilling, microwaving, and frying) on the element profile in sea bass fillets (*Dicentrarchus labrax*) was studied by Ersoy et al. (2006). It was found that the As concentration of fried and microwaved samples was increased significantly, hence these culinary processes were concluded not to be suitable for seabass. Laparra et al. (2004) studied the cooking effect on commercially available edible seaweeds, *Hizikia fusiforme,* which had a high content of tAs and iAs. It was established that boiling at 100 °C for 20 min caused a significant reduction in the concentrations of tAs (30–43%) and iAs (46–50%). A reduction in tAs was also observed by García Sartal et al. (2012) in seaweed samples following boiling. It was demonstrated that 69% of tAs in Kombu, 50% in Wakame, 71% in Nori, and 34% in sea lettuce were released into the boiling water. Furthermore, it was suggested that the heat treatment and acidic environment and enzymes used in the in vitro gastrointestinal digestion did not produce any changes in the As speciation of the four seaweeds studied. In another study conducted by Contreras-Acuña et al. (2014), the cooked anemones (*Anemonia sulcata*) were prepared in wheat flour and fried with olive oil. This treatment resulted in a 54% loss of tAs. Thus, the increase or the decrease in the As content of seafood species is both species and culinary treatment specific.

3.10 Risk Assessment of As and Seafood

An increasing concentration of As in the environment is a major threat to human health from exposure through inhalation, ingestion, and dermal contact (Ferrante et al. 2019). Oral consumption of seafood is primarily the major route for human exposure to As (Lorenzana et al. 2009). The Agency for Toxic Substances and Disease Registry (ATSDR) of the United States of America categorized As as number one in their substances priority list in 2017; furthermore, it is also categorized as a human carcinogen by the International Agency for Research on Cancer (IARC) (Jinadasa and Fowler 2019). Health risk associated with exposure to As is a significant global health issue that affects millions of people. The symptoms of acute exposure to As include vomiting, abdominal pain, and diarrhoea. Chronic exposure to As is associated with cancer, skin diseases, developmental effects, morphological alterations, cardiovascular disease, neurotoxicity, epigenetic changes like DNA methylation, increased risk of diabetes mellitus, adverse pregnancy outcomes, and a variety of complications in body organ systems (Hsueh et al. 2016; Upadhyay et al. 2018). Hence, the determination of As speciation in seafood is a more important factor to be considered in human health and risk assessment studies than the tAs measurement.

Seafood contains both iAs and oAs species, but the iAs species are considered more toxic than the oAs species. The main oAs species in seafood, such as AB, is not metabolized by humans. Hence, it is excreted unchanged and assumed to be of no toxicological concern (Ferrante et al. 2019). The United States Environmental

Protection Agency (USEPA) published a consensus toxicity value of oral exposure dose (RfD) for the iAs species, but not for the oAs species (Lorenzana et al. 2009). However, there is a lack of metabolism pathways and toxicity studies regarding such As species as AL, etc. (Taylor et al. 2017). Most of the available health risk assessment studies dealing with As in seafood have used the following measures; provisional tolerable weekly intake (PTWI) or average daily intake (ADI), target hazard quotient calculation (THQ) for non-carcinogen risk analysis, and the cancer risk (CR) calculation. When a THQ is lower than 1, it means that there is no adverse effect coming from the oral exposure to As. A value greater than 1 means that there is a statistical possibility of developing chronic systemic effects, but it does not provide a risk quantification. In the case of CR, when its value is above an acceptable lifetime risk (ALR) or equal to 1×10^{-5}, there is 1 chance in 100,000 that a person could develop cancer from the oral exposure to iAs. Such results depend not only on the As concentration in seafood, but also on the amount consumed, the culinary pattern, season, consumer body weight and age, etc. (Ferrante et al. 2019). Even with the limitation of available data, some researchers have concluded that there is a health risk associated with long-term consumption of some seafood species having a high iAs content, and some potential risk to certain age groups and in some areas where seafood is highly consumed (Lyu et al. 2020; Omeragic et al. 2020; Jia et al. 2018b; Ahmed et al. 2016).

3.11 Conclusions

The accumulation of arsenic in seafood and the analytical techniques for the routine extraction, or micro extraction, and detection of total As (tAs) and various As species are presented and evaluated in this chapter. Related to these topics, recent publications, international regulations, and aspects of bioavailability and bioaccessibility of As from seafood, cooking effects on As content, and bioavailability and risk assessment related to oral As exposure are also discussed in detail. Sample pre-treatment and pre-concentration techniques, such as SPE and LPE, are deemed important when As speciation analysis is carried out in seafood. The hyphenated techniques, combined HPLC or IC separation with ICP MS and ICP OES detection, or GFAAS and HGAAS are reliable analytical methods used for the determination of tAs as well as separated inorganic (iAs) and organic (oAs) arsenic species. It seems that the most common and frequent hyphenated technique is HPLC-ICP MS which possesses a high specificity and high sensitivity, in addition to the possibility of multi-element analysis. However, in the risk assessment analyses, transformation pathways of most As species and culinary effects on As content in seafood still remain unclear. Therefore, further studies are necessary to find the solutions for filling these gaps. Certainly, standards of individual oAs species and certified reference materials that represent particular matrices of seafood samples and contain these oAs compounds will help in this type of research. Their role in a proper selection of the conditions for sample preparation before measurements, chromatographic separation of individual arsenicals during, and

finally confirmation of the reliability of the results of the speciation analysis cannot be overestimated.

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Dietary Arsenic Exposure: Sources and Risks

4

Anamika Shrivastava

Abstract

Arsenic occurs in both organic and inorganic forms and is contributed by natural as well as anthropogenic sources. Inorganic arsenic, due to its high toxicity, is very critical for toxicological risk assessments from dietary exposure. It had been reported that when water has under low-arsenic concentration, food becomes the primary contributor to arsenic exposure in general population. Arsenic has been found in many food varieties such as rice, wheat, vegetables, fruits, beverages fishes, seafoods, etc. throughout the world, in different forms. Of all, rice plays a dominant role in contributing to the overall dietary exposure to inorganic in most parts, particularly where rice is a staple dietary source. In terms of the vulnerability, younger population is found to have more dietary exposure, which may be attributed to high food consumption on body weight basis and less variation in diet, mostly rice-based products. Although this high food consumption does not reflect a greater risk of adverse effects in them as most of the health effects of arsenic are a result of chronic exposure and only a few have been associated with acute arsenic exposure. Epidemiologic studies have linked chronic or acute dietary arsenic exposures with various adverse health effects such as cancer and many non-malignant manifestations like cardiovascular disease, type II diabetes, skin lesions, respiratory, haematological, immune, reproductive, endocrine, and neurological disorders. The risks associate with the dietary arsenic exposures have become a public health concern and it call for effective intervention to lower the exposure, especially to vulnerable populations.

Keywords

Dietary exposure · Arsenic · Risks · Vulnerability · Public health

A. Shrivastava (✉)
Amity Institute of Environmental Sciences, Amity University, Noida, Uttar Pradesh, India

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4.1 Introduction

Arsenic (As) is a ubiquitous metalloid occurring in the environment as a result of natural as well as anthropogenic processes (Davis et al. 2017; Yager et al. 2015; Shrivastava et al. 2020). Arsenic occurs both in organic and inorganic forms, in over 50 recognized naturally occurring species, major arsenic forms are shown in Table 4.1 (Pétursdóttir 2010). Different forms of arsenic vary in terms of toxicity, which depends on its complex chemical species and thus contributing to public concerns regarding risks (Pétursdóttir 2010; Nachman et al. 2017; Ciminelli et al. 2017; EFSA 2014; JECFA 2011; ATSDR 2007).

The inorganic forms of arsenic (iAs) (arsenite, As (III) and arsenate, As (V) derived from H_3AsO_3 and H_4AsO_4, respectively) are the most toxic. Furthermore, simple methylated forms such as methylarsonic acid (MA) are slightly toxic and are found as an intermediate form in the process of detoxification of iAs in human body (Leermakers et al. 2006), whereas the organic forms such as arsenobetaine (AsB) are considered to be non-toxic (Pétursdóttir 2010). Generally human exposure to As is primarily through consumption of As-contaminated water and food but in areas where As level in water is less than 10 ppb [Maximum Permissible limit (MPL) given by WHO 2010], food becomes the main source of dietary exposure (Xue et al. 2010; IARC 2012a, b; Baker et al. 2018; Yager et al.

Table 4.1 Major arsenic forms

Arsenic forms	Name/abbreviation	Chemical structure	Relevance
Total arsenic	tAs		Sum of inorganic and organic arsenic
Inorganic arsenic (iAs)	As (III)	$As(O^-)_3$	Highly toxic, found in reduced condition
	As (V)	$O = As(O^-)_3$	Toxic, favoured by oxidizing conditions
Organic arsenic	Arsenobetaine (AsBe)	$(CH_3)_3As^+CH_2COO^-$	Relatively non-toxic, main source of arsenic found in seafoods
	Arsenocholine (AsCho)	$(CH_3)_3As^+CH_2CH_2OH$	Potentially toxic compound, source of arsenic found in seafoods
	Methylarsonic acid (MA)	$CH_3AsO(O^-)_2$	Slightly toxic, an intermediate in the detoxification of inorganic arsenic in human body
	Dimethylarsinic acid (DMA)	$(CH_3)_2AsO(O^-)$	Considerably less toxic, reduced and methylated form of MA
	Trimethylarsine oxide (TMAO)	$(CH_3)_3AsO$	Potentially hazardous, minor as species in seafoods
	Tetramethylarsonium	$(CH_3)_4As^+$	Intermediate in as metabolism

2015; Kurzius-Spencer et al. 2014; Halder et al. 2013). A recent study (2003–2004 NHANES) has also found that among population with drinking water As concentration above the MPL, food contributed to 30% of iAs exposure. The same was found to be between 54 and 85% where drinking water As concentration was below MPL (Kurzius-Spencer et al. 2014; Nachman et al. 2017). In some cases, the exposure can also be by dermal route or respiratory inhalation, which in general is much less than the oral. The dermal route or respiratory inhalation can become a primary route mostly in case of occupational As exposure (Pétursdóttir 2010; Baker et al. 2018). The human exposure to As is also increased by the lifestyle of a person, for example, by cigarette smoking, even then food is found to be the primary contributor (ATSDR 2007).

The As exposure varies as per the local geochemistry, level of pollution, living conditions, etc. (Xue et al. 2010). In general, low background levels of As are present in natural water expect a few areas, in the world, e.g. West Bengal, Bangladesh, South-east Asia, etc. (Shrivastava et al. 2017). People most exposed to arsenic are those living in As- affected low-income areas who mostly rely on locally grown food and contaminated groundwater source for daily purposes such as drinking, irrigation, and cooking (Cubadda et al. 2017; Baker et al. 2018). It has been reported that the overall iAs exposure to people living in these areas is almost 10 times more compared to other places (Cubadda et al. 2017). As a result, As-contamination of water and food has become a serious problem which is putting the health and well-being of more than 150 million people worldwide, in danger (Shrivastava et al. 2015; Majumder and Banik 2019; Upadhyay et al. 2020). Additionally, some reports have also mentioned As exposure through sea foods but that mostly is in the relatively non-toxic organic forms (Pétursdóttir 2010). Due to this reason, scientists, researchers, and food related health surveys have now started to focus more on estimating iAs in food items rather than tAs alone (Xue et al. 2010; Wong et al. 2013; Oguri et al. 2014; Yager et al. 2015).

In humans, iAs forms are rapidly absorbed when consumed orally (50% to >95%) (Rose et al. 2010; Pétursdóttir 2010), whereas the in case of organic As forms the absorption value is generally more than 70% (Yager et al. 2015). After absorption, these find their way to almost every organ of the exposed person (EFSA 2009). The resulting human exposure has been associated with a wide range of adverse outcomes (Sharma et al. 2014; UN FAO/WHO 2011).

iAs has been classified as Group I carcinogen and in addition to cancer, it has been linked with many other adverse health outcomes such as skin lesions, reproductive, hepatic, cardiovascular, respiratory, neurological disorders, and more (Melkonian et al. 2012; National Research Council 2014). Studies have also reported a twofold increase in risk of diabetes mellitus when consumed orally (Lim et al. 2014). Moreover, iAs has also been linked with the neurodevelopmental effects on new born and in early life, making it a matter of high public concern in terms of dietary risk assessment and management (Nachman et al. 2017; Cubadda et al. 2017).

Despite above-mentioned outcomes of As exposure and significant number of exposed population via ingestion of contaminated food and water, focus of

regulatory bodies, in the past has been on limiting iAs in drinking water and soil (Kurzius-Spencer et al. 2014; Carlin et al. 2015). However, only recently the need for regulatory limits of iAs in food has been recognized by many national and international agencies (Nachman et al. 2017). Additionally, the importance of assessment study of dietary iAs exposure in humans and characterisation of food related risks have also been acknowledged (Marcason 2015; Cubadda et al. 2017).

Rare but another risk associated with As is the accidental ingestion of As containing pesticides or insecticides, which can eventually lead to acute As exposure that can become fatal if consumed above 100 mg (Duarte et al. 2009). The most common symptoms of acute As exposure are abdominal pain, cramping, nausea, vomiting, and diarrhoea. These can progress to serious issues like kidney failure, respiratory issues, etc. and sometimes may lead to shock, coma, and death of the victim (Lim et al. 2014; Duarte et al. 2009; Ratnaike 2003).

Although the concern on levels and effects of iAs in food are now being recognized as a public health concern (EFSA 2014; JECFA 2011; ATSDR 2007), general population are still not much aware to make informed choices regarding their diet and food of preference (Lai et al. 2015).

4.2 Arsenic Sources in Foodstuffs

Arsenic being ubiquitous in nature can enter foodstuffs after getting released in soil and water by various natural and anthropogenic processes (Nachman et al. 2017). In some parts of the world, As is primarily released into soil and water by geogenic processes like weathering and volcanic activities (Aiuppa et al. 2006; Nachman et al. 2017; Haque et al. 2019; Shrivastava et al. 2020). However, it has also been observed that in some cases human activities become the main source to As in soil and water and ultimately reaching the food system. The most common anthropogenic sources for As release are reported to be industrial activities (Baker et al. 2018), smelters (Pershagen 1985), arsenical drugs in animal agriculture (Nachman et al. 2013, 2016), and chemical weapons (Fox et al. 2010). Furthermore, the use of arsenic based pesticides in agriculture and the subsequent runoff to water are other potential sources (Li et al. 2016). On the one hand, the crops grown in contaminated soil pose a threat to food safety, the use of contaminated groundwater for irrigation makes the situation worse by further adding up to the overall load of As in soil and thus reaching to cultivated crops (Baker et al. 2018).

Moreover, as a consequence of increasing food demands in countries like India and Bangladesh coupled with the “Green Revolution,” farmers are now cultivating the same land three to four times a year, which has made them to rely on the As-contaminated shallow groundwater sources for irrigation (Shrivastava et al. 2014). Reports have shown that in these regions, to fulfil the increased water demand, thousands of pumps abstracting water from shallow aquifers have been installed in the last few decades. These aquifers are proven to be highly contaminated with iAs of geogenic origin (Halder et al. 2013; Barla et al. 2017). This continued use of As-laden groundwater for irrigation accumulates iAs in the

upper surface of soil of the irrigated lands, affecting the topsoil strongly (Heikens 2006; Roberts et al. 2007; Baig et al. 2011; Shrivastava et al. 2014; Sahoo and Mukherjee 2014; Baker et al. 2018). This increase of As in the topsoil has ultimately resulted in increase in reported cases of As accumulation in locally grown food crops (Halder et al. 2013; Cubadda et al. 2017; Shrivastava et al. 2020).

Although contaminated soil has a big role in the accumulation of As in cultivated food crops, (Nachman et al. 2017), As present in them are not always available for plant uptake (bioavailable) due to their presence in different forms in the soil. The fraction of soil As which is bioavailable depends on various factors like As species, pH, redox potential, organic matter, biotic factors, etc. playing a significant role (Shrivastava et al. 2014, 2015; Majumdar and Bose 2018; Cubadda et al. 2017). Moreover, the rate of As uptake and its accumulation also varies from crop to crop and it is more concerning for rice in terms of As accumulation in grains, as the cultivation field requires 3/4th of its time to be fully inundated with water (Shrivastava et al. 2020). This condition leads to soil As build-up when contaminated water is used for irrigation and also provides a reduced condition that favours conversion of As (V) to As (III), the latter being more bioavailable and toxic at the same time (Upadhyay et al. 2019; Shrivastava et al. 2020). It has been reported that plants grown in As-rich environments can take up substantial amounts As and accumulate it in its edible portions (Signes-Pastor et al. 2012; Williams et al. 2007). The dietary As exposure from food of animal origin is of less concern as reports have found that animals metabolize and excrete excess As, efficiently (Cubadda et al. 2017).

In addition to As concentration in cooking medium (typically water), dietary exposure to As is also affected by the food preparation and cooking methods, which play a major role determining the As content of the final product (Cubadda et al. 2017). Generally, most food prepared using As-contaminated water are expected retain As contributed by water, thus become more concerning than when cooked using low As water (Halder et al. 2014). This has been proven by many other studies on different food items such as soups, lentils, etc. (Del Razo et al. 2002), rice (Torres-Escribano et al. 2008; Halder et al. 2014), and vegetables (Diaz et al. 2004). However, there are a few studies which have also observed that high As containing food have a tendency to show a decrease in the overall iAs in the final product when prepared using low As containing water (Bundschuh et al. 2012). Although this is not same for the food that require large volume of water or longer cooking time, here they tend to retain more As from the water (Laparra et al. 2005).

Furthermore, in case of rice, additional steps such as rinsing raw rice multiple times with water, boiling in excess water to be discarded later, have proven to be quite effective in the reduction of dietary As exposure for people consuming rice as a staple diet (Halder et al. 2014; Cubadda et al. 2017; Mihucz et al. 2010; Rahman et al. 2006; Sengupta et al. 2006). For other food items which requires more cooking time, it tend to lose their moisture and the As concentration per unit mass increases. Similar trend was reported by Ersoy et al. (2006) and Devesa et al. (2001) in sea bass and bivalves, respectively, when food items were microwaved and fried. The same showed a net decrease in As content as the cooking method was changed to steaming

(Cubadda et al. 2017). Similar result was also reported by Raab et al. (2009) although there was a slight reduction in his study.

Other sources of As in foodstuffs can be the use of arsenic containing compounds as herbicides (e.g. sodium methanearsonate), pesticides (e.g. arsenate and arsenic trioxide), and in some countries, As containing feed additives (e.g. Roxarsone) (EFSA 2009).

4.3 Health Effects of Dietary Arsenic Exposure

4.3.1 Chronic Exposure

Epidemiologic studies have linked chronic or acute As exposures due to ingestion of food and water with various adverse health effects (IARC 2004; UN FAO/WHO 2011; Sharma et al. 2014; NRC 2014; Carlin et al. 2015; Nachman et al. 2017). Although a wealth of epidemiologic evidences supports that chronic exposure of As is linked to an increased risk of diverse types of cancer such as lungs, bladder, and skin (IARC 2012a, b), only a few have shown conclusive evidence of connection with cancer of other organs such as kidney, liver, and prostate (ATSDR 2007; Cubadda et al. 2017). The non-malignant manifestations of chronic As exposure ($\geq$0.02 mg/kg BW/day) have also been reported and are associated with numerous organ systems, ranging from cardiovascular disease, type II diabetes, skin lesions, respiratory, haematological, immune, reproductive, endocrine to neurological disorders (WHO 2010; ATSDR 2007; James et al. 2015; Moon et al. 2017; Cubadda et al. 2017; Smith et al. 2006; WHO 2011a, b; Liaw et al. 2008; Yorifuji et al. 2011; US FDA 2016; EFSA 2009).

4.3.1.1 Skin Manifestations

Studies have reported that the one of the most prevalent and typical signs of chronic iAs exposure is the dermal effects (ATSDR 2007; EFSA 2009; WHO 2010; US FDA 2016). Here the most sensitive indicator is the generalized hyperpigmentation, which can progress to Palmoplantar hyperkeratosis with the continued exposure of high-dose As (0.04 mg/kg BW/day) for 6 months to 3 years or chronic exposure of low dose ($\geq$0.01 mg/kg BW/day) As for 5–15 years (US FDA 2016; ATSDR 2007; EFSA 2009). These may vary in some cases where the exposed person can show hypopigmentation or sometimes it may appear as mix of both hyperpigmentation and hypopigmentation on the face, neck, and back (WHO 2010; EFSA 2009). Some studies have also reported the occurrence of benign cutaneous warts or thickening of the outer layer of feet, palms, or other body parts (Baker et al. 2018). These skin manifestations are the diagnostic of chronic arsenicosis, which at later stage may progress to nonmelanoma skin cancers in most of the exposed population with repeated oral ingestion of As (Mazumder 2000; Chakraborti et al. 2003; ATSDR 2007).

4.3.1.2 Cancer

Arsenic, a class I carcinogen has been proven to cause human malignancies of many forms (EFSA 2009). The initial evidences were based largely on reported skin and respiratory cancers occurring due to the occupational exposures to people from activities like mining and smelting (Baker et al. 2018). Numerous studies on lower As exposure have shown increased risks of bladder cancer (IARC 2012a, b). While many studies from south Asia, south America, and the USA have reported exposed population to develop lung, prostate, kidney, and liver cancer. Additionally, reports of relation between iAs exposure and smoking in increasing the lung cancer risk are also present (Chen et al. 2010a, b; Ferreccio et al. 2013). These evidences are consistent in all these studies and thus have also been included in the IARC report (IARC 2012a, b).

4.3.1.3 Respiratory Disease

Chronic As ingestion has also been associated with many respiratory diseases such as injury to the pulmonary vasculature affecting the blood vessels along the route between the heart and lungs (Chen et al. 2009; Farzan et al. 2013). Additionally, some cases of bronchitis and other pathological conditions such as bronchopneumonia have also been found in the exposed population (ATSDR 2007; Guha Mazumder et al. 2010).

4.3.1.4 Liver Disease

The effects of chronic As ingestion in liver can range from serious hepatic injury to renal cancer. Studies have shown that patients with repeated oral As exposure (0.01–0.1 mg As/kg/day) have been examined with swollen and tender liver, often time (Liu et al. 2015). Many detailed studies of blood analysis and histological examinations have also reported increased levels of hepatic enzymes and portal tract fibrosis, respectively (Guha Mazumder et al. 2010; Shi et al. 2014). Additionally, in some cases hepatic damages like cirrhosis and internal bleeding from esophageal varices have also been observed in the exposed population (Tan et al. 2011).

4.3.1.5 Cardiovascular Diseases

The study on association between chronic As exposure via oral route and cardiovascular disease has shown adverse effects of exposure on the cardiovascular function, ranging from peripheral vascular disease prevalence, black foot disease (BFD), coronary heart disease (CHD), myocardial infarction to stroke (Navas-Acien et al. 2005; Mazumder 2008; Tseng 2008). Although the observed associations between As exposure and cardiovascular outcomes still call for more detailed studies (Chen et al. 2009; Moon et al. 2017).

4.3.1.6 Nervous System

Several studies have shown an association between exposure to iAs and nervous system injury (Mazumder 2008). One of the signature effects of iAs exposure is the symmetrical peripheral neuropathy which has been reported in most of the cases with repeated chronic ingestion of lower levels (0.03–0.10 mg/kg/day) although this

can also occur in case of acute exposure (EFSA 2009; Mazumder 2008). The distinct symptoms of As exposure begin with numbness in hand and feet, which may later progress to pricking sensation (ATSDR 2007). Some studies have also reported the effects on both sensory and motor nerves along with weakening of muscles and reduced sensitivity to stimuli in addition to abnormal patellar reflexes (EFSA 2009; Rodrıguez et al. 2003). Studies on the histology of nerves from affected person have shown axonal peripheral neuropathies with damage to the myelin sheath (EFSA 2009; Sińczuk-Walczak et al. 2010). Furthermore, a detailed histological study of exposed population has shown inconsistency in peripheral neuropathy between acute and chronic As exposure, suggesting different mechanisms in their pathogenesis (Tseng et al. 2006).

4.3.1.7 Reproductive Effects

The chronic exposure to As has mostly been reported in case of drinking water as a source. The outcome of these studies has reported many adverse reproductive effects such as increase in spontaneous abortions, stillbirth, and preterm birth compared to non-exposed women (Gilbert-Diamond et al. 2016; Milton et al. 2005). There are studies which also suggest that exposure of pregnant women to iAs can pose negative impacts on foetal development (Gilbert-Diamond et al. 2016; Raqib et al. 2009; Vahter 2008; Davis et al. 2017).

4.3.2 Acute and Intermediate Exposure

iAs is very toxic and ingestion of it in high doses can result in death (ATSDR 2007; Mazumder 2008). Many studies have established the oral lethal dose of iAs to be between 70 and 180 mg/day (US FDA 2016). The adverse health outcomes of iAs can occur in many different organs depending upon the dose and duration of iAs exposure. In case of intermediate to acute exposure ($\geq$0.2 mg As/kg BW/day) the symptoms can be range from diarrhoea, vomiting, blood in the urine, muscle cramps, stomach pain to convulsions (US FDA 2016).

The studies on intermediate exposure in terms of duration (weeks to months) have reported outcomes such as gastrointestinal effects (common symptoms like abdominal pain, vomiting, diarrhoea, and cramping), peripheral neuropathy (common symptoms like numbness, burning, or tingling sensations), and haematological effects (common symptoms like anaemia and leukopenia), somewhat similar to the chronic expose (ATSDR 2007).

Several other studies on acute iAs ingestion ($\geq$8 mg As/kg) have reported serious adverse outcomes on respiratory system, such as respiratory distress, haemorrhagic bronchitis, and pulmonary oedema (Mazumder 2008). There are also reports where gastrointestinal system may be affected, with symptoms like vomiting, diarrhoea, and severe abdominal pain, with short-term high-dose ($\geq$0.01 mg/kg/day) ingestion of iAs (Vantroyen et al. 2004; US FDA 2016). However, these symptoms generally tend to fall-off soon as the exposure stops (ATSDR 2007). Additional outcome of acute iAs exposure ($\geq$2 mg As/kg/day) includes hepatic effects like liver failure

(Vantroyen et al. 2004; Shi et al. 2014) and neurological effects like headache, confusion, seizures, coma, etc., a major indication of encephalopathy (Vantroyen et al. 2004).

4.4 Vulnerable Populations

In case of As, most of the results of adverse health outcomes have come from numerous reported cases in humans rather than animal studies and this makes unique as compared with other hazardous chemicals (Baker et al. 2018). These outcomes have shown a high variability between individuals and populations, due to varying iAs metabolism mechanism and other aspects of toxicokinetics (Carlin et al. 2016; Nachman et al. 2017). The difference in iAs metabolism and toxicokinetics has been found to depend on factors like age, sex, life-stage, lifestyle, nutritional status, etc. (EFSA 2009; Nachman et al. 2017). Similar observations came from the study conducted by Lindberg et al. (2008) on dietary iAs exposure where a 30% variation was observed in As metabolism due to difference in age, sex, and exposure level of the participants (US FDA 2016).

There are also a few emerging studies that show role of gut microbiota in causing the variations (Carlin et al. 2016). Additionally, many studies have also shown that underlying genetic or metabolic factors are responsible for distinctive susceptibility to iAs toxicity. The varying effects of dietary iAs exposure are also influenced by factors like the food preferences, dietary restrictions, and cultural choice of food (Baker et al. 2018; Nachman et al. 2017).

It is important to recognize the vulnerable population who are at increased risk of iAs exposure and more susceptible to adverse health outcomes (Baker et al. 2018). The contribution of iAs causing many adverse health effects and its variation in outcomes has led the scientists to do the risk assessments for iAs separately for the general and vulnerable populations for different life stages (US FDA 2016; Nachman et al. 2017).

In these regards, a European study found that the dietary exposure to iAs was almost 3 times more in infants (<3 years) compared to the adults (EFSA 2014). This was directed to the fact that in general infant food contains more restrictive pattern of rice and rice products and there is a high food to body weight consumption rate in them (EFSA 2009). A few studies have also shown that a certain ethnic group such as Asian/other, Mexican, and African children (6–17 years) may be more vulnerable to adverse health outcomes of dietary iAs exposure than other of same age range, due to their higher average rice consumption (Lai et al. 2015).

4.4.1 Effects on Foetal Development and Infants

The dietary iAs exposure to pregnant women has been evaluated extensively and found that even moderate exposure iAs during pregnancy can cause negative health outcomes in the foetus (Rahman et al. 2006; Gilbert-Diamond et al. 2011; Davis

et al. 2014; Karagas et al. 2016; US FDA 2016). Reports have also shown an increase chance of miscarriage, stillbirth, and risk of infant mortality for the exposed pregnant women (WHO 2010; Quansah et al. 2015). Furthermore, there are many evidences establishing that material iAs exposure during pregnancy has led to the crossing of iAs through the placental barrier and has appeared of iAs in foetal tissues (US FDA 2016; Davis et al. 2017; Nachman et al. 2018). One such study was conducted in New Hampshire Birth Cohort Study (NHBCS), where consumption of As containing food product by pregnant women led to the accumulation of iAs in the toenail of the new-borns, proving the exposure of foetus to iAs through mother's diet (Davis et al. 2014; Karagas et al. 2016).

iAs has also been reported at low levels in breast milk of nursing mothers and exposure is thought to be low from breast milk to the infants (EFSA 2009). However, another study on association of iAs ingestion and its effects on the infants showed an increase in iAs exposure when the diet shifted to rice and rice products followed by fruits and vegetables (Signes-Pastor et al. 2018). Generally different infant foods like cereals, purees, drinks are fortified with rice and rice-based products such as starch, syrup, etc. (Jackson et al. 2012c) and these have been reported to have the maximum contribution towards high iAs exposure (1.6 mg As/kg per day) to infants (EFSA 2014; WHO 2011b).

There are numerous evidences showing negative impacts on the foetal development and infants due to iAs exposure (Gilbert-Diamond et al. 2016; Raqib et al. 2009; Vahter 2008). The exposure of iAs during foetal development and in the early stage of childhood is particularly concerning due to their susceptibility to environmental contaminants (IARC 2004; Farzan et al. 2013). This particular risk may be because of developing organ systems and exposure to iAs during early stage may affect the growth and well-being of the infants in the later stage of life (Farzan et al. 2013; Davis et al. 2017). Studies have also shown that in exposed infants this also increases the risk of impaired development (NRC 2013). It has also been reported that young individuals exposed to iAs early in life have an increased risk of diseases like bronchiectasis and lung cancer (WHO 2010; Smith and Steinmaus 2009a, b).

A study conducted in Chile observed the same trend where an early exposure to iAs during foetal development or postnatally leads to a dramatic increase in rates of death from bronchiectasis (Smith et al. 2006). Moreover, at a later stage of life this can also led to an increased rate of occurrence of cancer in different organs such as lung and bladder, even if the iAs exposure had occurred as long as four decades back (Steinmaus et al. 2013). Similar result was observed by Steinmaus et al. (2014a) in another case study in Chile where individuals were exposed to moderately elevated iAs in uterus of during infant stage (Nachman et al. 2017).

4.4.2 Effects on Children and Adults

Dietary exposure to iAs in childhood days also has a possibility to cause chronic health effect such as development of cancer and other respiratory diseases in the later stage of life (WHO 2011a, b; Yorifuji et al. 2011). However, there are studies

suggesting that children metabolize As at a slower rate, while a few studies have also established that the conversion of As to its lesser toxic organic form (methylated) is done more efficiently in them as compared to the adults (ATSDR 2007; US FDA 2016).

Children generally have a less-diversified diet and on an average consume food about 3 times more on body weight basis compared to adults, leading to greater chance of dietary iAs exposure (EFSA 2009). Thus, elevated levels of iAs through food become the primary source of iAs exposure in children (ATSDR 2007; EFSA 2009). In a study conducted in the USA on mean childhood dietary iAs exposure, it was found that on an average 3.2 mg As per day is consumed by the children through food (Smith et al. 2006). This value was later adjusted on the dose to body weight basis and it was found that children may show similar response for acute and chronic exposure as adults (Lindberg et al. 2008).

Studies have observed from temporal evidence from episodic exposures that iAs exposures earlier in life are likely to play an important role than exposures later in life, for cancer risks (US FDA 2016; Steinmaus et al. 2014b). A few studies have also shown an impaired cognitive function in iAs exposed children (Hamadani et al. 2011) although there is a need for further data supporting identification of dose–response relationships.

4.4.3 Effects Due to Gender Difference

Various studies on association of iAs and its effects on different genders have also been conducted all around the world (Lindberg et al. 2008). The results of these studies have shown men to exhibit more As-induced outcomes as compared to women, based on the more dimethylarsinate and low methylarsonate in the urine of women and men, respectively (Fischer et al. 2007). This level of dimethylarsinate in urine of women points to the production of methyl donor choline, regulated by oestrogen which may attribute to an efficient iAs metabolism in them (Fischer et al. 2007; Lindberg et al. 2008). In a separate study it also has been observed that expecting mothers in their third trimester excrete more than 90% dimethylarsinate in their plasma and urine, which also supports the study of efficient methylation of As in the childbearing years (EFSA 2009). Moreover, there are certain outcomes like higher rate of anaemia and delayed onset of menstruation which have also been found in women and girls, respectively, with dietary iAs exposure (Vahter 2009). Although a few studies have tried to check the relation, a detailed study on the mechanism involved in sex difference is much needed.

4.4.4 Effects Due to Nutritional Variation

Several sources have shown results to support the role of diets as a primary source of iAs burden of population (Nachman et al. 2017), hence it is very important to show the association of iAs related health outcomes with indicators of food and nutritional

status (EFSA 2009). Out of the limited reports available, a study of Vahter (2007) has also shown that a malnourished person or a person with poor nutrition is more vulnerable to adverse outcomes of As exposure. The authors have given a possible explanation which shows As metabolism to be closely linked to one-carbon metabolism and factors like requisite intake of vitamin B12, folic acid, and choline required for proper functioning of one-carbon metabolism (EFSA 2009).

4.5 Estimating of Arsenic and Its Species in Food

Estimation of As and its species is of much importance owing to the need to check the variability, extent of exposure, and to know the foodstuff associated with high exposure to general and susceptible populations (Cubadda et al. 2017). It is difficult to characterize the dietary As exposure as only a handful of the studies have reported As contamination in selected foodstuffs, far less have done the As speciation in them (Nachman et al. 2018). For many years, As in foodstuff was targeted to estimate total arsenic content (tAs, sum of different As forms present) as it was analysed conveniently in the laboratories equipped with instruments used for trace elements analysis (EFSA 2009). However, monitoring of As speciation is more important due to the variable toxicity of different As forms which can be present in any form in different food items (Haque et al. 2019). Estimation of iAs or other As species was not so frequently done in the past due to lack of specialized instruments and expertise (EFSA 2009; Cubadda et al. 2017).

Estimation of tAs in foodstuffs using modern analytical methods usually consists of two parts: sample preparation and analysis using instrumental technique. The first step usually involves processes like mineralization, derivatization, which is followed by the running of samples through instruments. The major types of instruments used for tAs estimations are atomic fluorescence spectrometry (AFS), atomic absorption spectrometry (AAS), inductively coupled plasma atomic emission spectrometry (ICP AES), and inductively coupled plasma mass spectrometry (ICP MS) (EFSA 2009; Haque et al. 2019).

In the past few years due to the growing concerns over the effects of different As species, many sophisticated analytical methods for determination of As species have come up in practice (Cubadda et al. 2017). The prerequisite for speciation analysis is to do the first step of sample preparation without changing the chemical speciation. As species can be water or fat soluble and owing to their different properties, they require different extraction strategies. For extracting water soluble As species from foodstuffs water, acid, base, methanol, and enzymatic extractions are generally used (Conklin et al. 2012; Liu et al. 2015; Maher et al. 2015; Nookabkaew et al. 2013; Pétursdóttir et al. 2014; Sadee et al. 2016). During sample preparation it has been noted that the organic As species remain fairly stable in dilute acids or base; however, iAs (As (III) and As (V)) are easily interconvertible (Cubadda et al. 2017).

Irrespective of the toxicity potential of As (III) and As (V), human risk assessment is based on iAs as a whole (EFSA 2009) and thus generally they all are converted to As (V) by adding an oxidant (usually H_2O_2) (Raber et al. 2012) for

further evaluation as iAs. For As speciation most frequently used analytical technique is high performance liquid chromatography (HPLC) coupled to either ICP-MS or AFS. Furthermore, for water soluble As species including iAs, anion exchange chromatography is the most commonly adopted method (Fig. 4.1). Whereas for complex As species such as organic form arsenosugar, additional chromatographic separations such as cation exchange are needed (Fig. 4.1) (Taylor et al. 2017).

Even with the advancement of different methodologies and techniques for the estimation of As and its species in common foodstuffs, the estimation of iAs in seafood remains a big challenge (Baer et al. 2011; Pétursdóttir et al. 2014). This is due to the small contribution of iAs to the tAs and other factors like species interconversion, etc. (Cubadda et al. 2017).

4.6 Arsenic Exposure from Different Foodstuff

Health impacts of As intake via drinking water have been studied extensively in the past (NRC 2014). Although the reports from the existing studies have suggested same effects when it is entering via food, the level of iAs in foodstuff and estimation of its daily intake have been studied less (Nachman et al. 2018).

The dietary exposure and outcomes of iAs are directly related level of iAs in food and the amount of contaminated food consumed (US FDA 2016). Different scientist have reported varying levels of iAs in a wide range of foodstuffs (Jackson et al. 2012b) but in general, terrestrial food have higher proportion of iAs (range from 50 to 100%) as compared to the fishes and seafood (Baker et al. 2018; Pétursdóttir 2010; EFSA 2009). In fishes and seafood, depending upon the seafood type, the overall iAs is less, this value also decreases with the increase in tAs concentration (EFSA 2009; Pétursdóttir 2010).

Many scientists have also shown that iAs exposure from food becomes the primary contributor towards daily As intake when level of As is less in water (Baker et al. 2018). Studies have also shown that the level of daily dietary iAs exposure also varies in different age groups, where the average and high level values of dietary exposure to tAs for adults were 1.3 and 4.4 mg/kg BW/day, respectively. Moreover, the estimates were higher for children compared to adults, owing to their higher food consumption relative to body weight basis (Rose et al. 2010).

4.6.1 Rice and Rice Products

Epidemiologic evidence suggests that rice is a primary contributor to dietary iAs exposure (Davis et al. 2017) as it is a major part of the diet for a majority of world's population with regard to nutrition and caloric intake (Schmidt 2015; Shrivastava et al. 2017, 2020). Rice is a major component of many infant food and many breakfast cereals consumed by children in different parts of the world, making them more susceptible to adverse health outcomes of iAs exposure (Mazumder 2008; Farzan et al. 2013; Jackson et al. 2012a; Signes-Pastor et al. 2016). Concerns

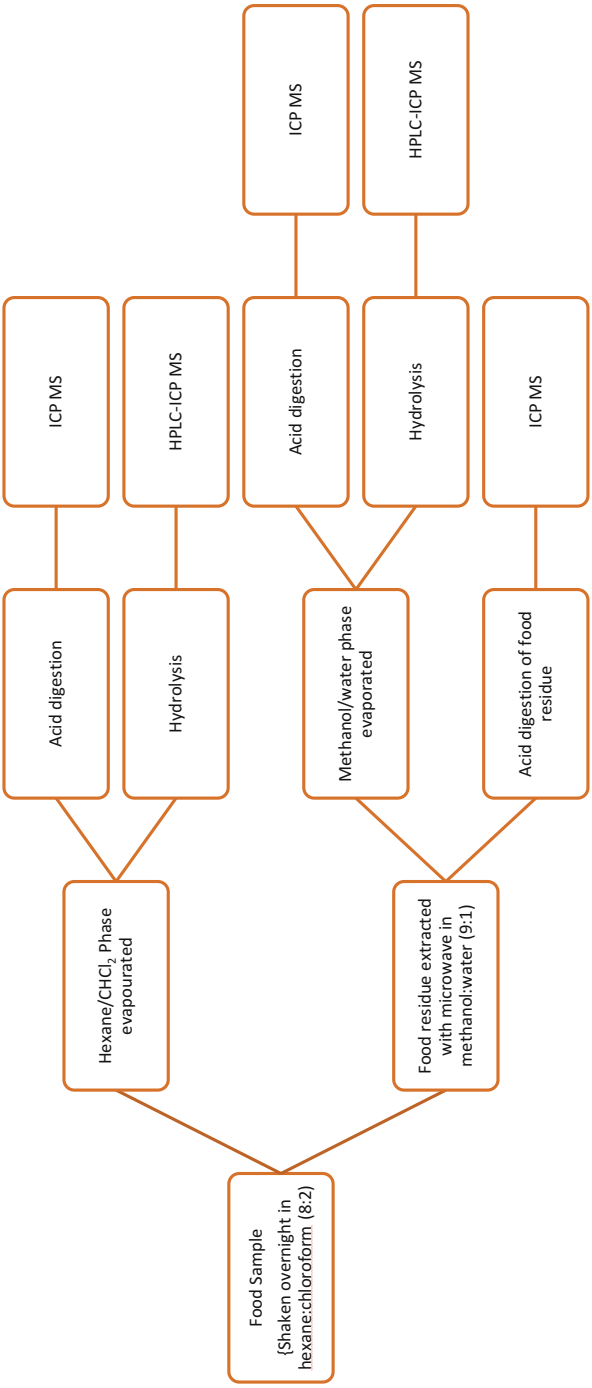

Fig. 4.1 Extraction and detection methods of arsenic species in food (modified after: Pétursdóttir 2010)

have also been raised for regarding the bioaccessibility of As present in rice. The in vitro gastrointestinal digestion simulation procedures have revealed that in rice the bioavailable fraction of tAs is between 53 and 102% (He et al. 2012; Signes-Pastor et al. 2012).

The evidences of higher iAs level in rice crop come from the fact that it is grown in anaerobic conditions of flooded rice paddies which can result in high tAs availability by facilitating the conversion of immobile As (V) into mobile As (III), thus increasing the uptake (Barla et al. 2017). Furthermore, rice plant has a unique physiology that leads to uptake and accumulation of more As from the environment, assimilating it to a greater extent than the soil (Hojsak et al. 2015; US FDA 2016). Supporting evidences show that iAs is an analogue of the phosphorus (one of the plant micronutrients) and silicic acid, which are captured very efficiently by plants from soil solution due to the evolved mechanism (Zhao et al. 2010). It has also been found that rice can bioaccumulate iAs at 10 times higher rate compared to other grains such as wheat and barley (Williams et al. 2007; Ma et al. 2008; Meharg et al. 2009; Mitani et al. 2009).

A variation in the amount and type of As is found in rice depending on the rice cultivar, soil type, and the geographical location of cultivation (Bastias et al. 2010; Norton et al. 2009, 2012; Signes-Pastor et al. 2016; Williams et al. 2005, 2007; Torres-Escribano et al. 2008). Moreover, the iAs levels in rice also change when contaminated water is used in crop irrigation as well as during different stages of processing and food preparation (Carbonell-Barrachina et al. 2009). For example, the iAs content in brown rice is found to be more than the white rice and cooking rice using uncontaminated water can lead to a reduction in the rice As content (Jackson et al. 2012a; Diaz et al. 2004). In general the rice grown in parts of India and Bangladesh has more iAs which can even reach up to 90% of tAs (Hojsak et al. 2015), whereas those cultivated in the USA has higher level of dimethylarsinic acid (DMA) (Meharg et al. 2009; Williams et al. 2005). In a study conducted in UK, pure baby rice it was found that the tAs concentrations ranged between 0.120 and 0.470 ppm, whereas iAs concentration ranged between 0.060 and 0.160 ppm (33–68% of tAs) (Meharg et al. 2008).

In the studies conducted to estimate iAs in different parts of the rice plants (e.g. root, shoot grains, husk, or bran), it was found that the iAs level in husk is 10–20 times higher than grains (Sun et al. 2008; Meharg et al. 2008). Thus, the dietary exposure from the rice drinks prepared from rice bran is found to be much higher than exposure from rice grains (Meharg et al. 2008a). Another study on rice flour, a primary ingredient of processed food and brown rice syrup showed higher iAs content, making rice and its product a potential source for dietary exposure (Baker et al. 2018; Upadhyay et al. 2020).

4.6.2 Seafood

Scientific studies have reported that although a large amount of As is present in seafoods, most of it is present in the organic form as arsenobetaine (AsB) and to a

lesser extent, as arsenocholine (AsCho) and arsenosugars (Caldwell et al. 2009; US FDA 2016) and only 0.4–5.3% of As is present in inorganic form (Borak and Hosgood 2007; Sirot et al. 2009). Organic As being relatively non-toxic poses no harmful effects when dietary exposure occurs due to consumption of seafoods (Sirot et al. 2009). As is present as AsB in the fishes and crustaceans and as arsenosugars in seaweed, marine algae, commonly consumed bivalves, etc. (Leffers et al. 2013). Some studies on As in seafood have also found that the arsenosugars present in them may metabolize to dimethylarsinic acid (DMA) and thio-dimethylarsinic acid. Although studies have shown the cellular toxicity and genotoxicity of these compounds, the overall human health impacts have yet not been studied in detail (Leffers et al. 2013).

It is very important to have a clear idea about the differentiation between tAs and iAs as some food such as fishes and seafood may show a very high tAs value but will have low fraction of iAs, the toxic form (EFSA 2009). For the population that consume more seafood, it becomes the significant source of iAs exposure but due to its presence as organic AsB, other sources such as fruits and grains become primary sources of dietary iAs exposure (Taylor et al. 2016; Xue et al. 2010).

Among the seafoods, the highest tAs concentrations were found in bottom dwelling fish species (12–34 ppm), with concentrations of iAs varying from 0.068 to 0.073 ppm (Sirot et al. 2009). Similarly, crustaceans also showed high concentrations of tAs, however, Lynch et al. (2014), in his study observed that a few crustaceans such as molluscs may constitute a considerable level of iAs (0.1–6% of tAs) which normally varies between 0.1 and 3.5% in other seafoods. Moreover, for marine food like seaweeds, the level of iAs varies from around 1% in most consumable forms to >50% in some brown algae (EFSA 2009).

4.6.3 Vegetables

In vegetables, As is present as iAs but it has been found that consumption of vegetables alone does not pose a health risk to the people. However, vegetables when grown in contaminated soil or irrigated using contaminated water, generally accumulate more iAs and become a matter of concern (Halder et al. 2013). In the absence of As in soil or water, these have less iAs (10–20 ppb) but still can be of concern for dietary iAs exposure due to their high consumption level (Cubadda et al. 2017).

Many scientists have also conducted studies to assess the level of iAs in different vegetable types. In a study conducted on the comparison of As accumulation by different vegetables in Bangladesh, it was found higher accumulation of As in leafy vegetables such as spinach and amaranth leaf (average 0.21 ppm) as compared to the non-leafy or root vegetables (average 0.07 and 0.1 ppm, respectively) (Halder et al. 2013). Similar results were found by Williams et al. (2006) and Roychowdhury et al. (2002) in studies conducted in Bangladesh and India, respectively. However, a few studies have also shown a higher accumulation of As in the underground vegetables such as taro, arum tuber, potato, and elephant foot (Williams et al. 2006; Guha

Mazumder et al. 2010). Thus, a detailed conclusive study on vegetables is still needed.

4.6.4 Other Foodstuffs

There are several other studies that have shown the presence of As in different food like fruits and fruit juices, chicken meat, etc. One such study conducted on samples from Slovak Republic found average As concentration in chicken meat to be 0.028 ppm, although majority of the As was in the organic form arsenobetaine (Lindberg et al. 2006).

Another study conducted by FDA in the USA on As in fruit juices found that apple juice has a more threat for dietary iAs exposure especially in children due to their dietary pattern (Carrington et al. 2013). This was followed by grape juice (9 ppb) and cooked spinach (6 ppb) (EFSA 2009). Another study on poultry has found that chicken meat can also become a potential source of dietary iAs exposure due to the use of roxarsone, an approved animal drug that containing organic As. The organic As could get converted to iAs in the roxarsone treated chickens (JECFA 2011). This has not only potential to affect the direct consumers, but the litter of the poultry has also been found to contain iAs due to the use of organo-arsenical feed additives. As these are used in the agriculture, iAs gets released and may result in accumulation in soil hence can be up taken by the crops, reaching to the cultivated food (Rutherford et al. 2003).

4.7 Dietary iAs Intake: Status of Toxicological Assessments

Despite the adverse health effects and classification of iAs as carcinogen, not many countries consider the need for regulatory limits for iAs except the USA and Europe, who recently recognized it (Cubadda et al. 2017). This delay could possibly be due to complexity in toxicological risk assessment of iAs, which depends on As speciation analysis (Cubadda et al. 2017). Due to the latest toxicological studies of dietary As raising concerns on the health outcomes and as analytical speciation techniques continue to improve, scientists now have started to focus more on iAs (Sirot et al. 2009).

Initially with the limited data available, the provisional tolerable weekly intake (PTWI) of 15 μg/kg body weight (BW) for As was given by the World Health Organization (WHO 1989). After the studies that establish that iAs causes cancer, dermal, cardiovascular, and many other adverse effects, at even lower levels of exposure, the PTWI of 15 μg/kg was no longer considered suitable (Pétursdóttir 2010).

Another way for toxicological assessments of iAs is to calculate the total daily intake of inorganic As (TDI-iAs) (Eq. 4.1), which is essentially the sum of daily intake of iAs (Eqs. 4.2 and 4.3) from different dietary sources (e.g. drinking water,

rice, fruits, and vegetables) for an exposed person, which can be calculated using the equation as given below (EPA, 200; Halder et al. 2013):

$$\mathrm{TDI} - \mathrm{iAs} = \mathrm{DI_w} - \mathrm{iAs} + \mathrm{DI_f} - \mathrm{iAs} \tag{4.1}$$

$$\mathrm{DI_w} - \mathrm{iAs} = (\mathrm{Cw} \times \mathrm{Fi} \times \mathrm{W})/\mathrm{BW} \tag{4.2}$$

$$\mathrm{DI_f} - \mathrm{iAs} = (\mathrm{Cs} \times \mathrm{Fi} \times \mathrm{W})/\mathrm{BW} \tag{4.3}$$

where $\mathrm{DI_w} - \mathrm{iAs}$ = daily intake of iAs from drinking water (μg/day/kg BW), $\mathrm{DI_f} - \mathrm{iAs}$ = daily intake of iAs from solid foods (μg/day/kg BW), Cw = concentration of total As in drinking water (μg/L), Cf = concentration of total As in solid foods (μg/kg), Fi = fraction of inorganic As content in the medium, W = the amount of daily consumption of the exposure medium (L/day for drinking water and kg/day for solid foods), BW = body weight of exposed person (kg).

Similar to PTWI, the provisional tolerable daily intake (PTDI) value for iAs intake (2.1 μg/day/kg BW) was also withdrawn at the 72nd meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), as the value observed to be in the lower range of the BMDL0.5 (bench mark dose level for 0.5% increased prevalence of lung cancer) (JECFA 2011).

So far the key evidences for risk assessment of iAs have come from people with chronic exposure to high level of As especially through drinking water (>50 ppb) in several regions like Bangladesh, India, South Asian countries, parts of South America (Chen et al. 2010b; Halder et al. 2013; Shrivastava et al. 2014; Cubadda et al. 2017). As of now, no established guidelines for risk assessment of iAs from dietary sources have been given. Furthermore the Codex Committee on Contaminants in Foods (CCCF) has suggested that a TDI-iAs level observed below BMDL0.5 does not guarantee safety and should not be considered as the safe limit (JECFA 2011).

Schoof et al. (1998) conducted a study long back in Taiwan to assess the mean dietary iAs exposure from food in Asian people and found out that on an average the $\mathrm{DI_f}$-iAs for the adult population was 50 μg/day, which was much above the recommended dose (EFSA 2009). Many other studies conducted in Bangladesh, West Bengal, and other places found similar results where the iAs level ranged between 34 and 97 μg/day (Halder et al. 2014; Shrivastava et al. 2017). Another study conducted in Europe found that the DI-iAs in adults (average body weight 58 kg) ranged between 22 and 70 μg/kg. The study was also conducted on certain ethnic groups with specific diet preferences and found that those who consume rice and algae-based products had more DI-iAs (EFSA 2014). In a probabilistic exposure modeling study combined with food intake data conducted by NHANES, in the USA, it was found that on an average DI-iAs of 1.96 μg/day is accounted by US diet, which is not as high as the previous ones but was two times the average iAs contribution through drinking water and significant for a nation where severe As contamination has not been reported (Xue et al. 2010).

4.8 Dietary iAs Exposure Assessment

For the dietary iAs exposure assessment, a clarity in amount of contaminated food consumed and the measure of internal dose are very important (Davis et al. 2017). So far numerous studies have focused on understanding the association between dietary iAs exposure and As biomarkers concentration (Gilbert-Diamond et al. 2011).

Most frequently used method for estimating iAs in foodstuffs has already been discussed in the previous section. Next step is to estimate the absorption of ingested arsenic forms, which is supposed to differ depending on factors like the soluble fraction of different As forms in food, association with food constituents and nutrients in the gastrointestinal tract, etc. (EFSA 2009). This has been explained in a study conducted by Juhasz et al. (2008) in a swine model. The authors found out that although the bioavailability of iAs in different foodstuffs varied greatly such as 100% in mung beans, and only 50% in leafy vegetables, supporting the influence of other component of the vegetable on gastrointestinal absorption of iAs.

4.8.1 Biomarkers of Human Arsenic Exposure

Biomarkers have widely been preferred for estimating the internal dose of As exposure and the most frequently used biomarkers are urine, nails, hair, and blood (Marchiset-Ferlay et al. 2012; Meharg et al. 2014).

After the exposure, As is absorbed and iAs fraction starts to get methylated (MMA and DMA) within the body and the sum of iAs and its metabolites in the urine are reported as the total urine As (Hughes 2006; Baker et al. 2018). This value is the most frequently used to interpret As exposure (Hughes 2006; Normandin et al. 2014). The sum of iAs and its metabolites in urine samples have been found to reflect human exposure from all the sources (dietary and other sources) and if other sources such as air, dermal, etc. are insignificant, urine can play an important role as a biomarker of dietary exposure (Gilbert-Diamond et al. 2016; García-Esquinas et al. 2013; Moon et al. 2013; Zheng et al. 2013; Hamadani et al. 2011). The distribution of iAs and methylated As forms excreted in urine shows an individual's potential to metabolize iAs (Nachman et al. 2017).

Many supporting studies conducted in Europe, the USA, South America, and southeast Asia have reported the ratio of total urine As to iAs level in the exposure medium to be 1:1 although it was conducted considering level of As only in water. This ratio was found in cases where water was the primary contributor to As exposure (UN FAO/WHO (2011)). For cases where food was the primary As contributor, the ratio was found to be higher than 1 (Cubadda et al. 2017).

In addition to assessing dietary exposure, assessment of As speciation in urine is also useful understand As metabolism (Davis et al. 2017; Fängström et al. 2009; Hughes 2006; Baker et al. 2018). Different studies have found that in the body iAs first metabolizes to MMA and then to DMA. Evidences have shown that cases where people have excreted more MMA in their urine have been found to have an increased risk of different types of cancer. This is mainly due to an inefficient methylation

capacity converting iAs to DMA although this may vary from person to person (Smith and Steinmaus 2009a, b). Furthermore, a few studies have also suggested that a high level of DMA observed in the urine is associated with an increased risk of type 2 diabetes (Chen et al. 2010b, 2012; Gribble et al. 2013; Kuo et al. 2015).

As a best practice the urine As concentration should be analysed within 24 h of sample collection for the accurate result. However, spot urine samples have also indicated a good correlation with dietary As exposure (Davis et al. 2012). One important factor to consider is that As in urine only starts to appear after 3–5 days of As ingestion (Meharg et al. 2014) and not necessarily show the exact estimate of As exposure as it can also accumulate and get release from other routes (hair, nails, faeces) (Yager et al. 2015).

Other biomarkers used extensively to assess long-term chronic exposure to iAs in humans are hair and nails (Marchiset-Ferlay et al. 2012; Slotnick and Nriagu 2006; Davis et al. 2017) and have a very slight effect of organic As ingestion (Cubadda et al. 2017). This is because of presence of high keratin that has sulphydryl groups which can bind iAs although they have a high potential for external contamination which poses some limitation (EFSA 2009). Despite this, hair and nails specimens have some advantages like being convenient to collect and store but is preferred less over urine as these are less sensitive than later (Davis et al. 2017). These are preferred only when the measurement of long-term exposure is required, as they tend to provide better estimate due to their growth rate (Mandal et al. 2003). Moreover, interestingly the blood As was not found to be a well-founded biomarker of As exposure as these are rapidly eliminated from the blood thus have shown an inconclusive relation with As exposure (Hughes 2006; Munday 2015).

4.9 Regulatory Policies Concerning Arsenic in Food

The existing regulatory system focuses on the As levels in soil, water, and irrigation water, they do not address the same in the food nor do they address the maximum dietary intake value of iAs (Nachman et al. 2017). There is available value for maximum tolerable level of tAs in drinking water given by the World Health Organization (WHO, 10 ppb) (WHO 2011a, b), limit for maximum dietary intake or maximum limit of As (tAs or iAs) in food items are not available from any of the major agencies like WHO, European Union (EU) or the USA, Food and Drug Administration (US FDA) (Francesconi 2007). Although the dietary As exposure has proved to be a serious issue in many areas all around the globe, current regulatory approaches regarding dietary exposure are limited. The possible reason for this could be the variation of iAs levels across various foodstuffs, different food choices, and a varying rate of food consumption, making it hard to focus on a specific foodstuff as a reference for regulatory limits and widespread awareness (Nachman et al. 2017). This has resulted in only a minor success in controlling dietary iAs exposure, moreover has created a gap in the communication about risks to the consumers (Nachman et al. 2018). Moreover, the information available to the

consumers based on the research does not give them a clarity to take informed choices regarding possibility of dietary iAs (Lai et al. 2015).

Few countries do have regulatory limits for As in certain food items, but value, food item, and the assessment associated with the limits differ drastically amongst different countries (Nachman et al. 2017). Rice has ever been a focus for the several agencies to regulate iAs limits as a measure to check dietary As exposure (Halder et al. 2014; Shrivastava et al. 2020). However, no recommendation has been given regarding limits of As in fish due to the evidence of presence of organic As in them which are relatively non-toxic and easily metabolized (EFSA 2009).

Previously China regulated the iAs level in rice where the maximum contaminant level permitted was given to be 0.15 ppm (Zhu et al. 2008). However, with further study, iAs was found to be a non-threshold carcinogen and exposure of any level constituted risk, thus, a limit on dietary intake could not be established (Hite 2013). This was also the reason for taking down the limit provisional maximum tolerable daily intake (PMTDI) for iAs (2 mg/kg (bw)/day), proposed back in 1983 by Joint FAO/WHO Expert Committee on Food Additives (JECFA) (WHO 1983). Later JECFA determined the value for benchmark dose confidence limit (BMDL) to be 3.0 mg/kg (bw)/day (WHO 2011a), however Contaminants in the Food Chain (CONTAM) Panel of the European Food Safety Authority (EFSA) determined the same for a 1% increased risk of different types of cancer to be and 0.3–8 mg/kg (bw)/day. They also gave recommendation to use the same range for the risk characterization for dietary iAs exposure (EFSA 2009).

Recently at the Codex Alimentarius level, regulatory limits for iAs in polished rice have been proposed (UN FAO/WHO (2011)) and at the European Union level, the regulatory limits for the same have been adopted for rice and rice-based products (EU 2015). The maximum limit in EU has set to be 200 ppb for white rice and 100 ppb for rice used for the production of rice-based food items especially for infants and young children (EU 2015).

The problem remains the same in the USA also, where on the one hand United States Environmental Protection Agency (US EPA) regulates As level in public supply of drinking water, there is no regulatory agency directly involved in monitoring of As content in irrigation water (contributing to As accumulation in agricultural soil and food crops) and food (Heikens 2006). Although the various assessments of FDA address the risks associated with As exposure in the early life due to high food consumption, it fails to address the effects of long-time dietary iAs exposure (Nachman et al. 2017). The FDA attention towards the iAs in food and beverages has become more serious in recent years after public attention and interest of the legislators (Consumer Reports 2012). As a result, the safe limits as adopted by EU are consideration by the US FDA (2016).

On the global level, policy and limits on As in foodstuffs are a matter that needs more attention for many countries and international agencies (Nachman et al. 2017). Unfortunately, many countries such as Bangladesh, India, South Asian countries, Argentina with a significant population exposed to iAs exposure via food and water, has not set any limit for dietary As exposure. This may be due to the fact that there are certain gaps still existing in understanding the complete picture which once

filled, would help in setting limits for public health safety and reducing dietary exposure (Nachman et al. 2018). Thus, a detailed study and regulatory advances are much needed for an effective intervention and implementation of necessary steps for reducing dietary iAs exposure.

4.10 Prioritizing Intervention Opportunities

Many reports from all across the world have given enough evidence to establish the fact that diet can play a crucial role in human iAs exposure. Also, a vast variation in iAs level across different foodstuffs, their consumption pattern, and its countless outcomes makes research, regulatory intervention, mitigation plans and effective risk communication, the need of the hour. Furthermore, the consideration to evaluate the dietary exposure to organic As species, in addition to iAs, would also add to the knowledge in understanding true health burdens resulting from exposure (Li et al. 2009). The research and intervention strategies of dietary iAs exposure may best focus on minimizing the exposure risks from common food items, in addition to commonly used risk-based approach such as cancer risk (Nachman et al. 2017). More research and meta-analysis of other health outcomes of iAs exposure such as cardiovascular diseases, neurodevelopmental issues, diabetes, renal disease, etc. are also much needed. Furthermore, research on interactions of As exposure with different genetic factors and association with other contaminant can also help in such studies.

Additionally, there can be other intervention strategies for reducing dietary iAs exposure such as the adoption of better cultivation practices (e.g. intermittent irrigation method in case of rice) that could limit As uptake by the food crop, prioritizing food of concern and their detailed evaluation (Norton et al. 2017; Shrivastava et al. 2020). There are instances where reduction in As exposure is not possible by the limiting As content of food, then alternative way such as focusing on influencing consumers preference of food purchase may be warranted. Consumer awareness and providing dietary advice on regulating the dietary iAs intake can also be very useful in this scenario (Shrivastava et al. 2020). For similar concern, Nachman et al. (2017) has also suggested the option of developing a relative source contribution (RSC) approach in the food which can ensure that no particular food contributes a disproportionate amount to aggregate dose.

In a recent report Codex Alimentarius international food standards codes of practice (Codex 2017) summarized simple ways for reducing iAs content in rice, namely, source-directed measures, agricultural measures, and monitoring and risk communication step. The first step focuses on ways to make sure that As in soil and irrigation water is good for cultivation purpose. If this is difficult to achieve, then the second step focuses on taking necessary measure to reduce iAs uptake by crops like alternative irrigation methods or selection of low-arsenic cultivars. In case of rice a few studies have also observed that cooking rice in excess of As safe water ($<$10 ppb of As) and draining resulted in the net decrease in tAs content in the finished product, which could also be adopted (Munera-Picazo et al. 2015). The final step focuses on

proper monitoring and public awareness to make sure the consumers are at lower risk of exposure (Nachman et al. 2018).

All the above interventions can be made more useful with the integration of population-level health surveys of the exposed or vulnerable population, their dietary patterns and consumption rate (Nachman et al. 2017). Thus, reducing dietary As exposure requires a multi-sectorial, inter-agency, and public health systems approach across the globe.

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Effects of Arsenic: Neurological and Cellular Perspective

5

Anushree and Jawaid Ahsan

Abstract

Arsenic in combination with oxygen, sulphur and hydrogen is highly toxic and even regarded as a xenobiotic compound. Inorganic arsenic has become a global health concern for its easier availability in nature. Most commonly accessible source being groundwater which is being used for drinking as well as irrigation purposes in various parts of the world where it is released due to several geological processes like erosion. It induces toxicity through various mechanisms but in this chapter arsenic induced neurotoxicity is analysed. Cognitive impairment in the nervous system is one of the critical implications of its toxicity which may further lead to various neurological as well as neurodegenerative disorders. The potential neurotoxicity and the mechanisms involved at molecular level with arsenic neurotoxicity are investigated in this chapter which includes cognitive dysfunctions, neurochemical alterations and neurodevelopmental alterations. Arsenic exposure may be toxic for cholinergic and dopaminergic system development which may be the cause for various other adverse effects specifically in perinatal.

Keywords

Inorganic arsenic · Neurotoxicity · Acute toxicity · Chronic toxicity · ROS · Neurodegeneration · Oxidative methylation · Arsenic metabolites

Anushree · J. Ahsan (✉)
Department of Biotechnology, Central University of South Bihar, Gaya, Bihar, India
e-mail: jahsan@cub.ac.in

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5.1 Introduction

Arsenic in its inorganic form is distributed all over the environment which includes land, air and water. It manifests the properties of both metal and non-metal. Hence, it is often referred to as metalloid. Elemental sulphide and carbonate allotropic forms of arsenic have usage in the industries (Henke 2009). It has been used in past as a homicidal agent and as a pigment. Lately for its chemical properties arsenic salts have been used naturally in traditional medicines to treat ulcers and leukaemia (Ernst 2002; Cooper et al. 2007). Arsenic is also being used in pesticides, fertilisers and in various industries (Hughes et al. 2011).

Arsenic concentrates leaches into drinking water from the earth's crust, bedrocks (Vahter 2008). Globally people are exposed to arsenic mostly from the contaminated water which is used for drinking, irrigation as well as in food preparation. According to World Health Organization (WHO) the recommended arsenic contamination in drinking water is 10 ppb. The drinking water containing arsenic has been reported to be one of the major cause for health problems in several countries such as Argentina, Chile, India, Taiwan, Bolivia, Japan, Bangladesh, Columbia and Mexico (Brinkel et al. 2009; Chen et al. 2011; Duker et al. 2005; Gonzalez-Horta et al. 2015; Hughes et al. 2011; Liu and Waalkes 2008) contained arsenic above 10 ppb. According to the data available arsenic contaminated drinking water containing more than 10 ppb of arsenic has affected about 140 million people residing in more than 50 countries of the world (Ravenscroft et al. 2009).

It can easily cross blood–brain barrier and may even accumulate in brain to cause neurobehavioural deformities (Itoh et al. 1990). Serious health impact due to long-term arsenic exposure in low doses includes skin cancer liver cancer, kidney cancer, cardiovascular disorders and neurological disorders (Vahidnia et al. 2008). McCarty et al. (2011) referred these medical conditions due to low dose and of term of arsenic exposure as "arsenicosis". The heavy metal arsenic along with its inorganic form is known to be neurotoxic and exhibits neurological effects within few hours after exposure but most commonly seen after 2–8 weeks of arsenic induction (Kishi et al. 2001; Jha et al. 2002). Arsenic exposure leading to peripheral neuropathy has been studied by many scientists (Chhuttani and Chopra 1979; Brouwer et al. 1992; Heaven et al. 1994). It is hypothesised that arsenic may be the causative agent for neurological disorders based on the research reporting that arsenic ingestion is responsible to increase risk of microvascular diseases (Chiou et al. 2005). Arsenic induces neurotoxicity by altering the levels of several neurotransmitters including acetylcholine, dopamine and serotonin which suggested that neurotoxicity involved biogenic amines due to arsenic encounter (Tripathi et al. 1997; Kannan et al. 2001). Shila et al. (2005) reported that the specific brain areas like corpus striatum, cortex and hippocampus display effects of arsenic.

It has been reported that arsenic presence in breast milk may cause adverse effects on infant growth and development (Fängström et al. 2008). Arsenic chronic exposure decreases the signal transmission speed in peripheral nerve (Blom et al. 1985; Vahidnia et al. 2007). Gharibzadeh and Shahabuddin (2008) researched that arsenic

presence within the vertebrate body may induce cortical neurons apoptosis leading to neurodegenerative disease like Alzheimer's disease.

This chapter focuses mainly on the arsenic induced neurotoxicity thoroughly for its toxicity and epidemiological relevance. And an effort is made to understand the mechanisms involved in causing neurological disorder due to long-term arsenic exposure, specifically its inorganic forms.

5.2 Natural and Anthropogenic Sources of Arsenic and Their Exposure

Arsenic is present naturally in the environment including water, air and soil either by natural means or in anthropogenic ways in its inorganic form which are highly toxic. Arsenic leaches from several natural geological resources into the environment. Mining and industrial processes are also responsible for arsenic presence in the environment. There are two inorganic forms which are most commonly found in the environment, namely trivalent arsenic (iAsIII) form and pentavalent arsenic (iAsV) form. In deep water sources arsenic is mostly found in its iAsIII form. Its concentration in seawater is approximately 2 ppb (Onishi and Sandell 1955), while in rain and river water is 0 ppb (Mochizuki et al. 2019). In seafood 0.78–25 ppm of arsenic is found in less toxic organic form (Lunde 1977).

Arsenic contaminated underground water is used by people in daily life like cooking, drinking, etc. as well as for agricultural purposes through which it enters the human body. Arsenate insecticide was used in the past to treat tobacco plant from which arsenic was taken up by plant easily. This tobacco exposed natural arsenic to smokers in their inorganic form. Agricultural products and soil readily allowed arsenic to enter the food chain of plants (Tamaki and Frankenberger 1992). When a pregnant female ingests arsenic contaminated water, arsenic can easily cross placenta as well as blood–brain barrier (BBB) in human (Jin et al. 2006; Hirner and Rettenmeier 2010; Rudge et al. 2009; Sanders et al. 2014; Willhite and Ferm 1984). When high amount of arsenic is consumed by a pregnant female it may lead to foetal fall, defective neural tube, abortion and neonatal death (Mazumdar 2017; Milton et al. 2017; Rahman et al. 2010, 2016).

Various industries manufacturing wood preservatives, electrical products like semiconductors, lasers, etc., fertiliser, cotton desiccants, agricultural chemicals, etc. are those where arsenic is used. Arsenic exposure through inhalation directly from the air especially in the proximity of mines, smelters and industrial hotspots is also absorbed by human body. The concentration dependent response relationship of arsenic exposure to various organs causing diseases is reported to be linear in previous studies (Yoshida et al. 2004; Lubin et al. 2000; Yuan et al. 2018). According to WHO, as the exposure time increases the threshold value of arsenic causing organ impairment is low (Ratnaike 2003). To cause cancers, the threshold value of arsenic in drinking water lies between 50 and 150 ppb (Tsuji et al. 2019). While long exposure period of arsenic contaminated water is reported to cause diabetes mellitus and hypertension (Chen et al. 2007).

5.3 Arsenic Toxicity: Clinical Manifestations

There are mainly two types of clinical features of arsenic toxicity, namely acute toxicity and chronic toxicity. These two types of clinical features are based on concentration and duration of dose. Significant features of both acute and chronic acute toxicity are mentioned in Table 5.1.

5.3.1 Acute Toxicity Due to Arsenic Exposure

Acute arsenic toxicity occurs when high concentration of arsenic is either ingested or inhaled or absorbed. Rare occurrence of acute toxicity is observed as it is considered as wilful suicide or homicide condition due to accidental ingestion of arsenic. Acute toxicity concentration range of arsenic lies between 100 and 300 mg (Schoolmeester and White 1980) and for humans the lethal dose of arsenic is reported to be 0.6 mg/kg/day (Opresko et al. 1993). A person dies if consumed a quantity higher than lethal dose within 24 h.

Arsenic exposure associated with several other medical symptoms involving gastrointestinal system like nausea, vomiting, severe diarrhoea and abdominal pain can become severe initially but may lead to death lately. Metabolism is affected due to arsenic toxicity. Its impact is reported to cause abnormalities in cardiac and respiratory system as well. These abnormalities include pulmonary oedema, respiratory failure (Lerman et al. 1980), toxic cardiomyopathy (Ghariani et al. 1991; Greenberg et al. 1979), hypotension, cardiac arrest and seizures (Campbell and Alvarez 1989). Delirium, weakness, peripheral neuropathy, encephalopathy are some of the neurological abnormalities which have been reported (Greenberg 1996). Encephalopathy occurs when arsenic enters the body system intravenously (Lerman et al. 1980). Haemorrhage is hypothesised to be the cause for encephalopathy (Beckett et al. 1986). Arsenic induced neuropathy due to toxicity led to decrement in signal conduction velocity severely (Vahidnia et al. 2007). After few weeks arsenic toxicity is observed as delayed peripheral neuropathy (Le Quesne and

Table 5.1 Significant features of acute and chronic arsenic toxicity (Adapted from Ratnaike 2003)

Acute inorganic toxicity	Chronic inorganic arsenic toxicity
• Clinical symptoms include nausea, vomiting, abdominal pain, excessive salivation and diarrhoea • Arsenic toxicity affects several organs like acute psychosis, seizures and skin rashes after diffusion, toxic cardiomyopathy, renal failure, pulmonary oedema, etc. • Neurotoxicity includes peripheral neuropathy as well as encephalopathy • Recent acute arsenic toxicity is detected by determining arsenic concentration in urine within 1–2 days	• Arsenic absorbed gets accumulated into various body organs including liver, kidney, nervous system, gastrointestinal tract, lungs and spleen • Keratin rich tissues are highly prone for arsenic accumulation like nails, hair and skin • Clinical symptoms include malignant modifications in various organs, dermatological modifications like hyperpigmentation, cardiovascular diseases, peripheral vascular disease and neutropenia • No effective treatment yet developed

McLeod 1977). Arsenic concentration within 2 days in urine can be used as an indicator for arsenic acute toxicity.

5.3.2 Chronic Toxicity Due to Arsenic Exposure

Chronic arsenic toxicity occurs when low concentration of arsenic is either ingested or inhaled or absorbed for a very long time. It imposes a serious health threat globally as arsenic availability in the environment becomes much easier and from where getting access to the human body. Around 35–37 million people are reported to be suffering from chronic toxicity and may even lead to their death, principally among children (Mayans et al. 2000; Mukherjee et al. 2006).

According to WHO, initial symptoms after the chronic arsenic exposure for a duration of at least 5 years are seen in the skin which includes hyperkeratosis, pigmentation alteration and skin lesions. Developmental effects, cardiovascular diseases, diabetes and pulmonary disease are some of the other symptoms of chronic arsenic toxicity.

Arsenic chronic toxicity has adverse effects on pregnancy as well as on mortality rate of infant. Due to the arsenic exposure during pregnancy, it is likely to have high mortality among young adults (Quansah et al. 2015). Occurrence of multiple cancers, kidney failure, lung disease and heart attack in early childhood due to exposure within the uterus may be the reason behind high mortality (Farzan et al. 2013). It has also been reported that cognitive dysfunction including memory, development and intelligence also occurred due to the chronic arsenic exposure (Tolins et al. 2014).

5.4 Effects of Arsenic on the Nervous System

Since inorganic arsenic has the potential to traverse the blood–brain barrier (BBB) with ease, brain becomes the significant organ to get affected by arsenic toxicity which further leads to cognitive impairment including learning and memory (Mundey et al. 2013). Although arsenic being distributed throughout the brain but at pituitary gland it gets highly accumulated (Sánchez-Peña et al. 2010). Sensory neurons sensitivity to arsenic in comparison to motor neurons is higher. Longer axon neuron is more affected due to arsenic than shorter ones. Arsenic neurotoxicity is one of the major causes of production of reactive oxygen species (ROS) which further leads to cause oxidative stress, even the activity of enzyme superoxide dismutase (SOD) declines and glutathione (GSH) level is also reduced (Mundey et al. 2013; Dwivedi and Flora 2011). Cytoskeletal framework disorganisation and destabilisation in addition to neuronal apoptosis are also major effects of arsenic exposure (Namgung and Xia 2001). Enzymes which are prominent for a cell to function might even get inactive due to adverse condition of arsenic neurotoxicity. Arsenic is also responsible for inducing central neuropathy as well as peripheral neuropathy (Rodríguez et al. 2003; Mathew et al. 2010). Various neurological

implications in humans due to arsenic exposure include Guillain-Barre like neuropathy, poor concentration, Parkinson's disease, cognitive dysfunction, encephalopathy, impaired memory as well as peripheral neuropathy (Piao et al. 2005; Felix et al. 2005; Yip et al. 2002; Gopalkrishnan and Rao 2006; Bardullas et al. 2009). Various neurodegenerative conditions such as Alzheimer's disease are reported to be caused due to chronic arsenic toxicity (O'Bryant et al. 2011). Arsenic metabolism and its toxicity mechanism are discussed in detail later in this chapter.

The neurobehavioural disorders and cognitive dysfunctions are also reported to be the consequences of severe arsenic exposure (Vahidnia et al. 2007). As per studies carried out these consequences occurred due to the receptors present in the hippocampus get suppressed in the presence of specific arsenic metabolites (Luo et al. 2009; Krüger et al. 2009). Concentration between 10 and 50 ppb of arsenic presence in the water is reported to be responsible for causing peripheral neuropathy (Mochizuki et al. 2019). Peripheral neuropathy outcome is the impairment of sensory neurons to a large extent than the motor neuron (Ishii et al. 2019; Kawasaki et al. 2002). Further reduction in the number of both myelinated and non-myelinated axon occurs leading to peripheral neuron axonal degeneration (Le Quesne and McLeod 1977). Arsenic concentration to cause CNS impairment is reported to be 50 ppb for children or more, while for adults with high concentration is required (Vibol et al. 2015; Mochizuki et al. 2016). CNS impairment due to arsenic exposure including encephalopathy with loss of brain functions lately is considered to be irreversible. Encephalopathy is the outcome of elevated level of pyruvate in the blood and this elevated pyruvate is contributed by arsenic important role in thiamine deficiency and enzyme pyruvate decarboxylase inhibition (Gopalkrishnan and Rao 2006).

Arsenic is also responsible for inducing apoptosis in CNS by triggering p38-mitogen-activated protein kinase (MAPK) and JNK3 pathway (Namgung and Xia 2001). The various neurotransmitters like glutamate, acetylcholine, dopamine, epinephrine, etc. level are modified along with their metabolism and synaptic transmission velocity after arsenic exposure (Kannan et al. 2001; Rodríguez et al. 2002; Ramos-Chávez et al. 2015; Nelson-Mora et al. 2018). Arsenic clinical manifestations include delusion, stroke, headache and even a state of deep unconsciousness (Bartolomé et al. 1999).

5.5 Stage Specific Arsenic Neurotoxicity

5.5.1 In Foetal and Children Development

Study conducted on mice has revealed that sodium arsenite prenatal exposure causes neurobehavioural impairment along with prelimbic cortex abnormal formation in the offspring (Aung et al. 2016). Sodium arsenite gestational exposure has the potential to impair learning and memory processes (Ramos-Chávez et al. 2015; Nelson-Mora et al. 2018).

It is reported that arsenic exposure impacts full scale intelligent quotient (IQ) and memory even at a concentration far below than recommended level (Tolins et al. 2014; Farzan et al. 2013). IQ, cognitive function, long term memory, motor skills and verbal abilities are affected after inorganic arsenic contaminated water exposure ranging between 5 and 50 ppb in children of Mexico (Calderón et al. 2001; Rosado et al. 2007), the USA (Wasserman et al. 2014) and Bangladesh (Parvez et al. 2011). In comparison to adults there is less arsenic neurotoxicity reported in children as children have effective detoxification mechanism through arsenic methylation (Lau et al. 2013; He et al. 2009). But CNS damage is severe in children than in adults due to its immature BBB defence system. Further investigation is required to be conducted to understand the gestational and developmental arsenic neurotoxicity in a better and advanced way. During development inorganic has the potential to modify the formation of BBB gap junction (Golmohammadi et al. 2019; Manthari et al. 2018). It can have an adverse effect in the development of brain.

5.5.2 In Adults

There are reports disseminating that inorganic arsenic exposure is responsible for modified adult cognitive function as well as mental health (Hong et al. 2014; Tyler and Allan 2014). Arsenic contaminated underground water not only affects peripheral neuropathy but also alters sensory functions and decreases nerve conduction velocity (Chou et al. 2007; Paul et al. 2013; Mochizuki et al. 2019; Hafeman et al. 2005). In rats it is observed that after arsenic exposure neurofilament and fibroblast proteins specifically in the sciatic nerves get disappeared (Vahidnia et al. 2006, 2008). Also, peripheral neuron axon gets modified; demyelination and increase oxidative damage are seen in rats after arsenic exposure. Further all these observations affect the neurotransmission between CNS and peripheral nervous system (García-Chávez et al. 2006).

5.5.3 Neurodegeneration

Arsenic relevance in causing oxidative stress, mitochondrial dysfunction and inflammation is an essential aspect as these molecular mechanisms play vital role in causing neurodegeneration. The Alzheimer's disease (AD) vulnerability increases when there is high level of inorganic arsenic, dimethylarsinic acid (DMA) and selenium in urine (Yang et al. 2018). Study conducted on rats revealed that due to chronic arsenic exposure neurobehaviour gets affected as level of amyloid-beta (Aβ) increased along with enzyme beta-secretase increased activity (Nino et al. 2018). Arsenic associated with other heavy metals leads to increased pro-amyloidogenic effects, this further promotes oxidative damage and neuroinflammation (Ashok et al. 2015). Arsenic in cooperation with the affected neurotransmitter dopamine leads to neurotoxicity which plays significant role in alpha-synuclein accumulation and

oligomerisation causing Parkinson's disease (PD) (Cholanians et al. 2016). These studies have revealed the relationship of arsenic with neurodegeneration.

5.6 Arsenic Metabolism and Its Metabolites

Inorganic arsenic is transported into the cell and then its metabolism occurs which leads to the formation of several metabolites as represented in Fig. 5.1. The complete mechanism is discussed in detail below.

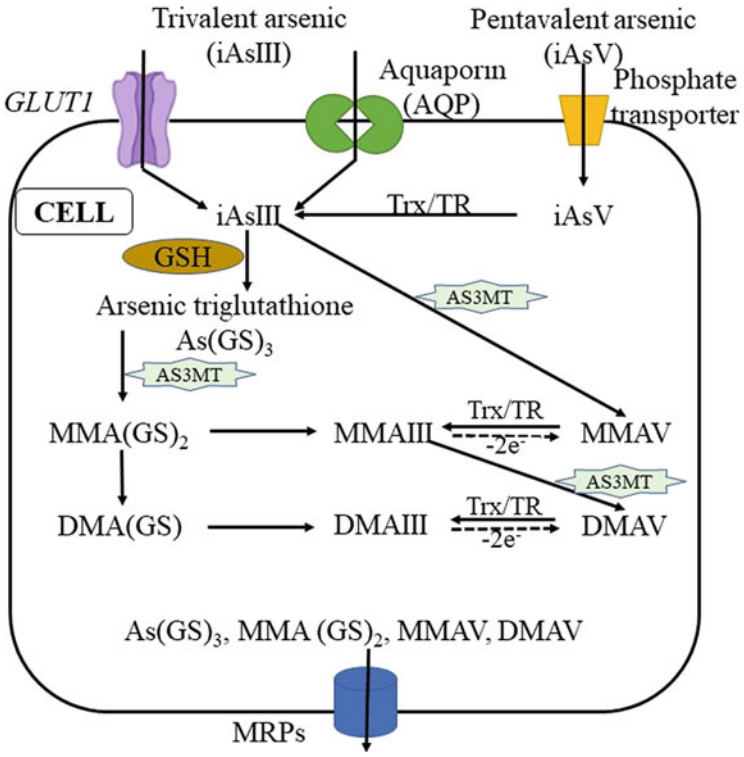

Fig. 5.1 Inorganic arsenic transport and metabolism (Adapted from Garza-Lombo et al. 2019). Trivalent inorganic arsenic (iAsIII) enters into a cell through glucose transporter (GLUT1) and aquaporins (AQP). While pentavalent inorganic arsenic (iAsV) enters through phosphate transporter. Within the cell iAsV gets reduced to iAsIII with the help of thioredoxin (Trx)/thioredoxin reductase (TR) system. Oxidative methylation of iAsIII into various metabolites is catalysed by arsenite methyltransferase (AS3MT). iAsIII combination with glutathione (GSH) in the presence of glutathione-S transferase (GSTs) results in the formation of conjugates like $As(GS)_3$. Arsenic metabolites produced within the cell are transported outside the cell through the multidrug resistance proteins (MRPs)

5.6.1 Arsenic Transportation into the Brain

As mentioned earlier inorganic arsenic exists in two oxidation states, i.e. trivalent (iAsIII) and pentavalent (iAsV). About 60–87% of both inorganic form of arsenic are bioavailable in humans. Large amount of arsenic is absorbed in the small intestine, while its small amount is absorbed by skin and through inhalation (Centeno et al. 2002; Enterline et al. 1987; Hertz-Picciotto and Smith 1993).

After entering into the blood, arsenic enters into the brain easily as it can cross the BBB. There are different types of transporter used by them to enter the cells. Aquaporin (AQP) which is an organic anion transporter glucose transporters (GLUT) is used by iAsIII to enter the cell. While phosphate transporters are used by iAsV to enter the cell wherein they are reduced to their iAsIII form (Torres-Avila et al. 2010; Liu et al. 2002; Calatayud et al. 2012). It is highly accumulated in the pituitary gland inside the brain in its methylated form (Sánchez-Peña et al. 2010). Inorganic arsenic metabolites are transported out of the brain cells through multidrug resistant protein (MRP). Mostly MRP1, MRP2 and MRP4 are used (Leslie et al. 2004; Yoshino et al. 2011; Shukalek et al. 2016).

5.6.2 Inorganic Arsenic Metabolic Pathway and Methylation

After entering the brain cells inorganic arsenic undergoes methylation through various mechanisms. iAsIII is always methylated; hence, iAsV has to be first reduced to iAsIII. Inorganic arsenic is methylated in different zones of the brain which can express the enzyme arsenic methyltransferase (AS3MT) (Sánchez-Peña et al. 2010; Rodríguez et al. 2005). The mechanisms used for methylation of inorganic arsenic (Challenger 1945; Hayakawa et al. 2005) are described below.

5.6.2.1 Oxidative Methylation

In oxidative methylation, *S*-adenosylmethionine (SAM) acts as the donor of methyl group catalysed by inorganic arsenic methyltransferase (AS3MT) enzyme to the inorganic arsenic. Various products produced due to iAsIII methylation as shown in Fig. 5.1 are monomethylarsonic acid or arsenate (MMAV), monomethylarsonous acid (MMAIII), dimethylarsinic acid (DMAV) and dimethylarsinous acid (DMAIII) (Watanabe and Hirano 2013; Chou et al. 2007).

5.6.2.2 Inorganic Arsenic Glutathione (GSH) Conjugation

Inorganic arsenic is conjugated to GSH non-enzymatically to produce arsenic tri-glutathione [$As(GS_3)$] (Leslie et al. 2004; Watanabe and Hirano 2013). Arsenic conjugated GSH is further methylated in a reaction catalysed by enzyme arsenite methyltransferase (AS3MT) to produce mono-methylarsenic di-glutathione [$MMA(GS)_2$] and di-methylarsenic glutathione [DMA(GS)]. When the presence of glutathione is less than the GSH conjugates, then these conjugates further get hydrolysed followed by oxidation to produce MMAV and DMAV (Watanabe and Hirano 2013).

In human urine DMAV (40–80%), MMAV (10–25%), and inorganic As (10–30%) are reported to be detected frequently (ATSDR 2007; Vahter and Concha 2001). LD50 concentration values of arsenic and its metabolites in human are as follows for each: iAsIII—50μM, iAsV—180μM, MMAIII—8μM, MMAV—60 mM, DMAIII—8μM and DMAV—15 mM (Himeno 2017). MMAIII and DMAIII are reported to have deleterious effects in comparison to other arsenic metabolites (Kligerman et al. 2003). Depending on the different oxidation state of arsenic the biological half-life is determined. In comparison to arsenate, arsenite has a shorter biological half-life (Sattar et al. 2016). Arsenate is reduced to arsenite in a reaction catalysed by GSH and thiols reducing agents (Buchet et al. 1981).

5.7 Arsenic Induced Toxicity Mechanism

The various arsenic metabolites as discussed above express their neurotoxic effect by inducing significant enzymes inactive which participates in catalysing necessary life processes pathways like DNA repair and synthesis pathway. More precisely trivalent arsenic metabolites in their reduced state inhibit catalytic activity of enzymes (Aposhian et al. 2004; Ratnaike 2003). There are various mechanisms through which arsenic metabolites induce their neurotoxic effects like reactive oxygen species generation, oxidative stress, shortfall of thiamine and reduction in enzyme acetylcholinesterase activity (Dwivedi and Flora 2011; Singh et al. 2011). Molecular mechanism of arsenic induced neurotoxicity is shown in Fig. 5.2. Arsenic and its metabolites play a significant role in epigenetic modification leading to neurological impairment (Kleefstra et al. 2014; Rudenko and Tsai 2014; Farzan et al. 2013; Smith et al. 2012), altering neurotransmitter homeostasis as well as

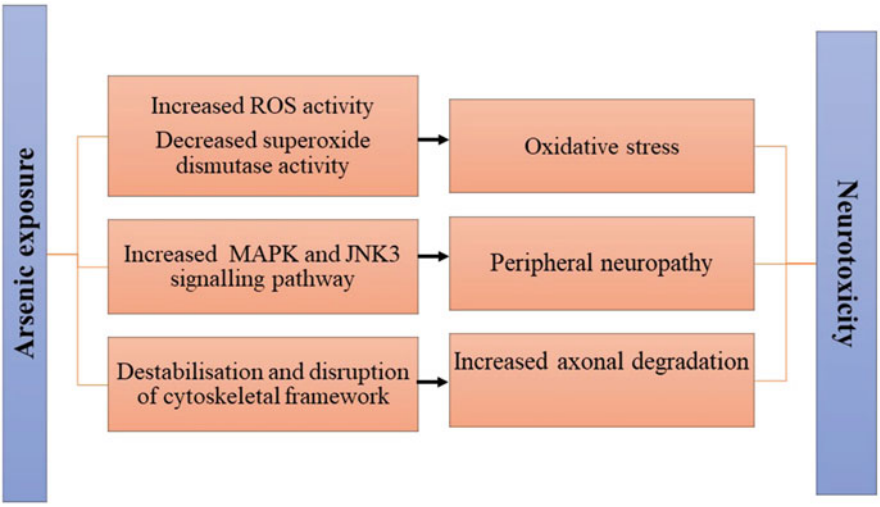

Fig. 5.2 Arsenic induced neurotoxicity (Adapted from Mohammed Abdul et al. 2015)

synaptic neurotransmission, inducing neuronal cell death and brain strong inflammatory response. These mechanisms affected by arsenic and its metabolites are discussed in detail below.

5.7.1 Mitochondrial Dysfunction and ROS Production

Mitochondrial dysfunction involvement in ROS production plays a vital role in arsenic induced neurotoxicity (Chandravanshi et al. 2019; Prakash et al. 2016) and may even induce neurodegeneration (Calì et al. 2011). Arsenic neurotoxicity major implication is observed in reactive oxygen species (ROS) generation shown in Fig. 5.3 which occurs primarily in mitochondria (Jomova et al. 2011; Flora 2011) due to the electron leak by decreasing the activities of mitochondrial complexes (I–IV) (Chandravanshi et al. 2019). It is well known that in normal conditions mitochondrial ROS level is controlled by the antioxidant systems. But in adverse

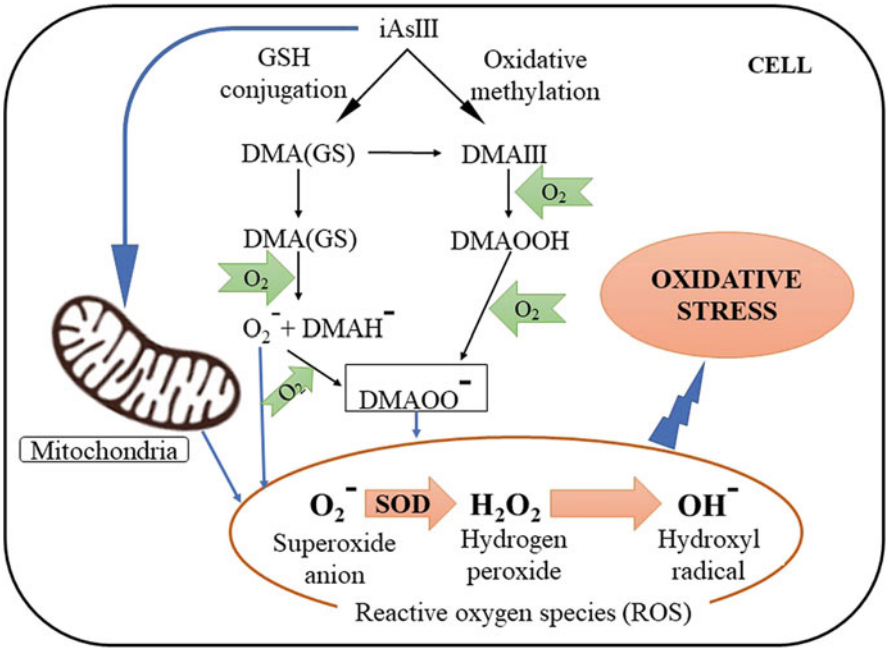

Fig. 5.3 Arsenic metabolism induces generation of reactive oxygen species (ROS) leading to oxidative stress along with mitochondrial dysfunction (Adapted from Garza-Lombo et al. 2019). Mitochondria function is altered and ROS are generated through its electron transport chain. Superoxide anion, hydrogen peroxide and hydroxyl radical act as ROS. Superoxide anion (O_2^-) forms hydrogen peroxide (H_2O_2) in the presence of superoxide dismutase (SOD). GSH conjugated arsenic [DMA(GS)] forms dimethylarsine (DMAH). DMAH after reacting with molecular oxygen (O_2) forms DMAH free radicals ($DMAH^-$) as well as the DMAH peroxyl radical ($DMAOO^-$). Dimethylarsinous acid (DMAIII) reacts with O_2 to form dimethylated arsenic peroxide (DMAOOH) which again in the presence of O_2 leads to the formation of radical $DMAOO^-$

condition which may be either due to mitochondria dysfunction or ageing which assists in the uncontrolled ROS generation, protein carbonylation and lipid peroxidation (Halliwell and Cross 1994; Olsen et al. 2013; Forman 2016). The other factors which contribute to the ROS generation include nicotinamide adenine dinucleotide phosphate (NADPH) dependent oxidase and the NO synthase enzyme activities (Culotta et al. 2006; Schrader and Fahimi 2006). Activities of certain other enzymes like cytochrome p450 enzymes, lipoxygenases, myeloperoxidases, xanthine oxidases, cyclooxygenases (COX) and the molecular mechanism of protein folding in the endoplasmic reticulum (ER) also play important role in ROS generation (Halliwell and Cross 1994; Olsen et al. 2013; Finkel 2011). Increased level of ROS in comparison to normal condition leads to oxidative stress. And this oxidative stress causes oxidative alteration of biomolecules which further leads to the functional protein loss, organelles impairment and even apoptosis (Finkel 2011; Olsen et al. 2013; Forman 2016; Reczek and Chandel 2015). There are enzymatic and non-enzymatic antioxidant mechanisms which prevent oxidative stress (Halliwell and Cross 1994; Olsen et al. 2013; Forman 2016; Finkel 2011). ROS generation induced by arsenic leading to oxidative stress is represented in Fig. 5.3.

Mitochondrial dysfunction is also responsible for reducing the amount of peroxisome proliferator-activated receptor-gamma co-activator 1-alpha (PGC-1α) as well as the transcription factor A found in mitochondria (TFAM) (Prakash and Kumar 2016). Arsenic metabolite specifically MMAIII and DMAIII produces free radicals and hence considered to be more potent toxic (Zamora et al. 2014).

5.7.2 Thiamine Deficiency

Thiamine is a vitamin which is referred as vitamin B1. Neuronal complications occur due to its deficiency. Arsenic plays a vital role in thiamine deficiency which further inhibits the activity of enzyme pyruvate decarboxylase leading to neuronal complications (Gopalkrishnan and Rao 2006). Enzyme pyruvate decarboxylase catalyses the catabolic pathway of glucose to release energy. ROS produced due to trivalent arsenic and its metabolites makes pyruvate dehydrogenase enzyme inactive by oxidising it. And for this very low concentration of arsenic is enough in comparison to arsenate concentration required for binding to the critical thiols (Samikkannu et al. 2003; Szinicz and Forth 1988). Both dry thiamine deficiency neuropathy and mild encephalopathy are considered to be the severe form of thiamine deficiency affecting the nervous system (Dieu-Thu 2015). Thiamine deficiency may be induced by arsenic exposure.

5.7.3 Decreased Acetylcholinesterase Enzyme Activity

Acetylcholinesterase enzyme (AChE) plays a significant role in cholinergic neurotransmission. It catalyses the hydrolysis of acetylcholine which functions as a neurotransmitter into acetate and choline. Hence it is crucial for proper functioning

of brain or nervous system. It was found that when rats as animal model were exposed to arsenic trioxide depending on dosage, activity of the AChE present in their serum was decreased (Patlolla and Tchounwou 2005). And further it affects the cholinergic neurotransmission in association with either peripheral neuropathy or CNS damage (Singh et al. 2011; Patlolla and Tchounwou 2005). A more detailed study is required to determine the mechanism, symptoms and association between AChE and arsenic exposure.

5.7.4 Epigenetics Modification

Epigenetics is defined as inherited altered phenotype or gene expression without the DNA sequence involvement (Eccleston et al. 2007; Nanney 1958). Nanney in 1958 coined term epigenetics. The modified phenotype or gene expression may be brought about by acetylation, ubiquitination, phosphorylation of histone, methylation (DNA as well as histone) and expression of microRNA (Collotta et al. 2013; Heerboth et al. 2014). Epigenetic modifications are reported to be associated with neurological dysfunctioning (Kleefstra et al. 2014; Rudenko and Tsai 2014). Methylation is assumed to be responsible to conciliate arsenic toxicity (Reichard and Puga 2010; Ren et al. 2011). *S*-adenosyl methyltransferase (SAM) plays a crucial role in methylation dependent epigenetic modification like DNA and histone methylation. Reduction or deletion of the SAM gene expression is the main effect of inorganic arsenic exposure.

Gene transcription is repressed mostly due to DNA methylation. Arsenic induced epigenetic disruption is also regulated by DNA methyltransferase enzyme activity and expression (Bestor 2000; Lan et al. 2010; Reichard and Puga 2010). More than 2000 newborn cord blood genes are reported in an epidemiological study that DNA methylation modifies due to arsenic exposure (Garza-Lombó et al. 2019). Gene methylation altered due to inorganic arsenic exposure modified was reported to be related to the gestational age and head circumference (Rojas et al. 2015). Studies on rats revealed that neuroplasticity regulating genes showed altered methylation due to arsenic developmental exposure (Martínez et al. 2011). Even the enzymes participating in DNA methylation demethylation processes in rat's brain, DNA methyltransferase as well as translocation enzymes were found to be suppressed due to arsenic exposure.

Inorganic arsenic is also proposed to affect the acetylation process of histone. Since enzyme pyruvate dehydrogenase (PDH) catalysed the oxidation reaction of pyruvate to acetyl-CoA which gets impaired after arsenic being introduced into the body (Samikkannu et al. 2003; Schiller et al. 1977). Acetyl-CoA acts as the donor of acetyl group required for acetylation.

5.7.5 Apoptosis

Apoptosis in nervous system basically involves neural death pathway due to inorganic exposure. Arsenic and its metabolites neurotoxicity are responsible for activating several neural death pathways. The different pathways used for inducing caspase dependent neurons and neuroblastoma apoptosis include mitogen-activated protein (MAP) kinase, serine/threonine protein kinase such as extracellular signal-regulated kinase (ERK), p38 MAPKs or c-Jun N-terminal kinases (JNK) signalling pathway (Namgung and Xia 2001; Lu et al. 2011). Secondary messenger calcium ion (Ca^{2+}) can also induce apoptosis due to arsenic exposure (Florea et al. 2007). When HepaRG cells were exposed to arsenic metabolite DMAIII, the activity of apoptosis initiator caspase-9 is reported to increase (Würstle et al. 2012). Arsenic is reported to induce apoptosis in cerebral cortex (Yen et al. 2011). Even the hippocampal neurons can be induced for apoptosis due to arsenic exposure by the antagonism of neurotrophic signalling (Pandey et al. 2017).

Autophagy is the regulated process of a cell which helps in removing the damaged cells and unnecessary components. Basically, autophagy is activated to counter stress as a defence mechanism but sometimes it may even induce cell death (Doherty and Baehrecke 2018). As such during development arsenic triggers autophagy in mouse brain by inhibiting Akt or phosphoinositide 3-kinase signalling or mTOR signalling pathway (Manthari et al. 2018). These studies provided evidence of association between arsenic induced apoptosis and neurotoxicity.

5.7.6 Inflammation

Strong inflammatory reaction is observed in the brain due to inorganic arsenic exposure. On exposing arsenic to rat's hippocampus, after culturing microglia and glial cells of the CNS, the phenotypic expression of inflammatory causing cytokines such as interleukin-1-beta (IL-1β), interleukin-6 (IL-6), interferon gamma (IFNγ) and tumour necrosis factor-α (TNFα) was increased to a large amount (Ashok et al. 2015; Firdaus et al. 2018; Mao et al. 2016). The cytokines released may enhance the chances of mediating neuronal toxicity (Mao et al. 2016).

5.8 Diagnosis and Treatment

The urine sample is used for the purpose of quantification of arsenic concentration in the body. To diagnose acute arsenic toxicity there are two parameters which are to be considered: firstly, when arsenic concentration in urine is 50μg/L and secondly when arsenic concentration in urine is 100μg within 24 h of urine collected. There is another prior condition that no seafood is ingested when the urine sample is collected. Urine sample should be kept according to the protocol to carry out the quantification. Blood, nails and even hair as biological samples can be used for chronic arsenic toxicity diagnosis.

Acute arsenic toxicity treatment should be focused on amending arsenic induced dehydration as well as restoring the functions which are vital for the body for which it is required to eliminate arsenic from the body. Gastric lavage, activated charcoal and haemodialysis are prescribed for its elimination from the body. But still there is no evidence for these methods for their efficacy. Since arsenic is a metalloid, chelators like 2,3-dimercapto-1-propanol also commonly known as British anti-lewisite (BAL), dimercaptosuccinic acid (DMSA), penicillamine and 2,3-dimercapto-1-propane sulfonic acid (DMPS) are used for their successful removal (Vantroyen et al. 2004; Tseng et al. 2006; Rahman et al. 2001; Stenehjem et al. 2007). Neurological complications of acute arsenic toxicity are reported to be not relieved after chelation (Perriol et al. 2006). But the studies conducted on rats revealed that after chelating using BAL, arsenic is depleted from tissues and even excreted through urine and faeces (Hilmy et al. 1991). Chelating agent has higher binding affinity for arsenic than endogenous ligands present within the body but the chelating is reported to be ineffective for treating arsenic induced peripheral neuropathy (Hall 2002). Still more studies are required to be carried out for treating arsenic toxicity.

5.9 Conclusion and Future Perspective

Arsenic has become a worldwide public health concern for its toxic effects. The primary focus of this chapter is to understand the various neurotoxic pathway of arsenic along with their severe consequences. After understanding the mechanism of arsenic induced toxicity specifically arsenic neurotoxicity, it has become clear that its toxic effect is far wider. Epidemiological studies have revealed that arsenic neurotoxicity impact is not only limited to adults but even to the foetus as well as children's nervous system proper development which includes their intellectual and cognitive functions (Nagaraja and Desiraju 1994; Hamadani et al. 2011; Rahman et al. 2009; McDermott et al. 2012; Grandjean and Landrigan 2006). The arsenic involvement in increasing the susceptibility to develop neurodegenerative disease, neuronal apoptosis and oxidative stress is discussed in detail in this chapter. The role of chelating agent in the treatment of arsenic induced toxicity is also discussed along with the various parameters which should be considered for its diagnosis (Vahidnia et al. 2007). Axonal degradation and neuropathy of CNS are few adverse implications of chronic arsenic neurotoxicity.

Affordable, sustainable as well as cost effective methods are required to be developed to remove arsenic from the most common accessible arsenic source, i.e. drinking water (Matschullat 2000). More study and research are required to understand the mechanisms by which neurotransmission and cognitive functions are altered by arsenic exposure during development. Also, arsenic toxicity association with neural cell population which includes neurons and glia is required to be analysed in more detail. Till now there is no cure and treatment for its toxic effect which can be an important area of study. Diagnosis of arsenic toxicity using the

potential biomarkers can transform its detection as acute or chronic and henceforth its diagnosis can become easier (Garza-Lombó et al. 2019).

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Arsenic: Source, Distribution, Toxicity and Bioremediation

6

Ghanshyam Kumar Satyapal and Nitish Kumar

Abstract

Arsenic is ubiquitous in nature and a well-known toxic metalloid. There are four oxidation states (−3, 0, +3 and + 5) of arsenic found in nature and most common forms are +3 and + 5. The main sources of arsenic in nature are anthropogenic and natural activities. The natural sources include rocks, soils, seawater, arsenic-bearing minerals, volcanic emission and river originating from Himalaya. The anthropogenic activities include mining, smelting, use in herbicides and combustion of fossil fuels. The exposure to arsenic occurs mainly by consumption of arsenic contaminated drinking water or food. Arsenic is distributed all around the world beyond permissible limits in drinking water. Such type of contamination was reported in India, Thailand, Mexico, Chile, Argentina, China, Taiwan, USA Hungary and Bangladesh. The arsenic toxicity largely depends on its physical state and chemical form of the arsenic compound. Arsenic toxicity causes bladder, prostate, lung and skin cancer, rhagades, skin lesions, oxidative stress, mitochondrial damage and may interfere with the DNA methylation or DNA repair system. The ubiquitous nature of arsenic leads microorganism to evolve several plan of action for their survival in stressed environments. These strategies include arsenic oxidation, reduction, intracellular bioaccumulation and methylation. These strategies can be used in mitigation of the environmental arsenic from contaminated sites. In bacteria, the uptake of As(III) is mediated by GlpF whereas the A(V) uptake is facilitated by Pst and Pit membrane proteins. The oxidation of arsenic occurs in the periplasm of the bacteria and is regulated by arsenite oxidase (AoxAB) enzyme. The arsenate As(V) reduction occurs either in cytoplasm or in periplasm of the bacteria by arsenate reductase, ArsC or by arrA and arrB,

G. K. Satyapal · N. Kumar (✉)
Department of Biotechnology, Central University of South Bihar, Gaya, Bihar, India
e-mail: nitish@cub.ac.in

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respectively. The bioremediation is a low-cost and eco-friendly technique for the treatment of arsenic contaminated sites.

Keywords

Arsenic · Arsenic distribution · Anthropogenic · Arsenic toxicity · Arsenite oxidation · Arsenate reduction · Bioremediation

6.1 Arsenic

Arsenic (atom. no. 33) is a poisonous semi-metallic element and is broadly distributed all around the world. In the earth's crust, arsenic was ranked 20th for its abundance (Bahar et al. 2012; Zhang et al. 2002). There are four oxidation states (−3, 0, +3 and + 5) of arsenic found in nature and most common forms are trivalent arsenite [+3, As(III)] and pentavalent arsenate [+5, As(V)] (Bahar et al. 2012; Mateos et al. 2006). The −3 species of arsenic, arsines and methylarsines, are generally unstable when present in air (Adriano 2001). As(III) is highly toxic in comparison with As(V) and has a high magnitude solubility which makes it difficult to remove from water (Bahar et al. 2012). More than 200 minerals occur in nature which contain arsenic, most of these minerals are in close association with metals such as Ni, Cu, Fe, Co, Ag, Cd and Pb. Most of the arsenic occur in minerals are sulphur conjugated for example, orpiment (As_2S_3), enargite (Cu_3AsS_4), realgar (As_4S_4) and arsenopyrite (FeAsS) (Drewniak and Sklodowska 2013). The anionic forms of arsenous acid and arsenic acid are the most common compounds of arsenite and arsenate, respectively. MMAs(V) (monomethylarsonic acid) and DMAs (V) (dimethylarsinic acid) are stable methylated form of inorganic arsenic in mammalian metabolites and are excreted in the urine. DMAs(V) and the sodium salts of MMAs(V) have been used as herbicides. For long time, DMAs(III) (dimethylarsinous acid) and MMAs(III) (monomethylarsonous acid) have been proposed intermediates in the arsenic metabolism (Hughes 2002).

6.2 Source of Arsenic

Arsenic is found everywhere in natural surroundings. It is a well-known toxic element for all forms of life (Banerjee et al. 2011; Tripathi et al. 2007; Villadangos et al. 2012). The main sources of arsenic in nature are anthropogenic and natural activities (Mandal and Suzuki 2002). Arsenic is released in the environment, primarily by natural activities like volcanic emission, weathering of minerals containing arsenic, etc. and due to anthropogenic activities such as burning of fossil fuels, smelting and mining (Bahar et al. 2012).

6.2.1 Natural

Arsenic is widely distributed in nature and is a rare crystal element. In rocks, the concentration of arsenic depends on the rock type, as higher concentration of arsenic is present in sedimentary rocks than igneous rocks (Mandal and Suzuki 2002). Generally, in sedimentary rocks, the range of mean value of arsenic concentrations is varied from 0.3 to 500 ppm and from 1.5 to 3.0 ppm in igneous rocks (Adriano 2001). The concentration of arsenic in rocks ranges from 0.5 to 2.5 mg kg^{-1} (Kabata-Pendias 2010); however, higher concentrations were present in phosphorites and finer-grained argillaceous sediments (Mandal and Suzuki 2002). More than 200 minerals occur in nature which contain arsenic (Drewniak and Sklodowska 2013), of which approximately 20% are sulphosalts and sulphides, 20% comprises silicates, arsenides, oxides and elemental arsenic and remaining 60% are arsenates (Mandal and Suzuki 2002). In soil, the arsenic concentration in various countries varies considerably among the geographic regions, and the range of arsenic concentration are 0.1–40 mg kg^{-1} and 1 to 50 mg kg^{-1} (Mandal and Suzuki 2002). In seawater, the arsenic concentration ordinarily found in the range of 0.001–0.008 mg l^{-1} (Johnson 1972). The high level of arsenic concentration was observed from an area nearby Alaska in well water samples after performing the arsenic speciation (Harrington et al. 1978), it shows inorganic As(III) comprises 3 to 39% and remaining were inorganic As(V) (Mandal and Suzuki 2002).

In unpolluted freshwater, arsenic concentrations range from 1 to 10 g l^{-1}; however, in the area of sulphide mineralization and mining it ranges from 100 to 5000 g l^{-1} (Smedley et al. 1996). In air, the concentration of arsenic ranges from 0.4 to 30 ng m^{-3}, thus human exposure to arsenic from air is generally very low (Mandal and Suzuki 2002).

6.2.2 Anthropogenic

Arsenic is released in the environment, primarily by natural activities like volcanic emission, weathering of minerals containing arsenic, etc. and due to anthropogenic activities such as burning of fossil fuels, smelting and mining (Bahar et al. 2012). Arsenic is extensively spread in water, land, and air through water run-off and wind-blown dust (Mateos et al. 2006). There are some more primary anthropogenic input derives from burning of fossil fuels in power plants based on oil- and coal-fire, discharge from metal smelters, combustion of solid waste from municipals and use of herbicides containing arsenic directly in agriculture and by industry (Zhang et al. 2002). Arsenic is naturally available in ores of copper, gold, lead and zinc and during the smelting process it can be released in the environment. The neighbouring ecosystem may become polluted by particulates and flue gases released from smelters (Adriano 2001).

The arsenic concentration in coal combustion residues and fly ash varies in the range from 100 to 1000 ppm (Adriano 2001). Therefore, generating power from combustion of coal and disposal of its fly ash may play a role in arsenic input in the

surroundings. Metal forms of arsenic are used in copper and lead alloys as an additive. Mainly compounds containing arsenic are being used in forestry and agriculture as silvicides, herbicides and pesticides. As(III) is a raw material for arsenical pesticides which includes sodium arsenite, calcium arsenate, lead arsenate, and organic arsenicals. These arsenicals are being used in the production of wood preservatives, algicides, fungicides, herbicides, insecticides and ship dips (Adriano 2001). For some animals, arsenic is an essential trace element and thus used as additive in the animal feed. Aluminium gallium arsenide or gallium arsenide crystals are used as a component of laser, light emitting diodes, semiconductors and in different types of transistors (Ratnaike 2003). The anthropogenic sources of arsenic are playing a crucial role for elevation of arsenic level in environment. The consequences occur by repeated use of arsenic in agricultural and industrial areas which results in increased levels of arsenic.

6.2.3 Source of Exposer to Arsenic

Humans can be exposed to arsenic by several ways. Probably, the most common way is ingestion of food or drinking water contaminated with arsenic (Ratnaike 2003; Zhang et al. 2002). The concentration of arsenic in worldwide aquifers ranges from <5 to 5000 μg/l and this leads it to become a human health concern globally due to its subsequent contamination in drinking water and food (Mandal and Suzuki 2002; Suttigarn and Wang 2005). According to the guidelines established by WHO, the permissible concentration of arsenic is 10 μg/l in drinking water but due to the economic reasons most of the developing countries accepted 50 μg/l, including Bangladesh (Bahar et al. 2012). Peoples are ingesting arsenic from contaminated water by agrochemical or industrial waste or from wells drilled in arsenic-rich geographic area (Adriano 2001). Arsenic contamination in fruit and vegetable crops occurs by uptake of arsenic from roots, soil or through spraying application. Seafood consumption from different sources may be another reason of arsenic intake by humans (Bishop and Chisholm 1966). Fish, algae and seafood are the sources of richest organic supplement (Edmonds and Francesconi 1987). Humans consuming seafood in their supplementary diet from different sources may be a reason for arsenic intake. The amount of arsenic in fish differs with their location and their species. The high level of arsenic is found in marine seafood products available commercially than terrestrial animals (Adriano 2001).

6.3 Arsenic Distribution

The arsenic level beyond permissible limits in drinking water around the world is the chief reason of arsenic toxicity. Such type of contamination was reported in India, Thailand, Mexico, Chile, Argentina, China, Taiwan, USA, Hungary and Bangladesh. In Nepal (2001), it came to notice that the groundwater of lower Plain area (Terai) is contaminated with arsenic (Chaurasia et al. 2012). In the Asian

countries, arsenic contamination was recorded from the Red River delta and from the Hanoi city. In addition, they reported high loads due to flooding and from delta plains of the Irrawaddy delta of Myanmar, in the Indus basin and Mekong valley in Vietnam and Cambodia. This indicates that the arsenic groundwater contamination is prone in lower flood plains and delta regions of south-eastern Asia (Saha 2009). The chronic mass toxicity of arsenic contamination in groundwater is a reason of large scale thread and there are more than 20 countries in the midst of it, including India (Chaurasia et al. 2012). However, due to drinking of arsenic contamination groundwater, the largest population affected by chronic arsenic toxicity in the world belongs to China, Bangladesh and India (Chaurasia et al. 2012; Saha 2009). In 1983, the first arsenic groundwater contamination was reported in West Bengal (Chakraborti et al. 2003; Ghosh and Singh 2009). In India, contamination of arsenic was first identified in Punjab, Haryana, Uttar Pradesh and Himachal Pradesh (Chaurasia et al. 2012). The groundwater contamination of arsenic and its effects on health were noticed in 1999 in Rajnandgaon district (Chhattisgarh, India). In 2002, in the western part of Bihar (India), the two villages of Bhojpur districts, Semaria Ojha Patti and Brisban, were reported for exceeding permissible level of 50 μg/l arsenic contamination in groundwater (Chaurasia et al. 2012; Ghosh and Singh 2009; Nath et al. 2015). States of India, like Jharkhand, Uttar Pradesh, Bihar, West Bengal come under the flood plain of River Ganga; Manipur and Assam come under the flood plains of rivers Imphal and Brahmaputra, are reported above 50 μg/l of arsenic contamination level in groundwater (Ghosh and Singh 2009). The availability of arsenic in India and Bangladesh depends geologically on nature. The sediment deposition took place 25,000 to 80,000 years ago, i.e., the Quaternary Period, in the arsenic affected areas. These sediments almost cover entire region of the river Ganga and it contains arsenic-rich pyrite (Adriano 2001).

6.4 Arsenic Toxicity

Arsenic is well-recognized to cause cancer in humans (Hughes 2002; Shi et al. 2004). The species of arsenic are toxic and bioactive (Zhang et al. 2002). Arsenic toxicity largely depends on its physical state and chemical form of the arsenic compound. Inorganic As(III) is highly toxic in comparison with the inorganic As (V), however inorganic As(V) is more toxic than the methylated form of arsenic (Adriano 2001). The exposure to arsenic in drinking water even in low concentrations can result in many types of cancer like prostate, bladder, lung and skin. The ingestion of arsenic in low levels can also result in non-cancerous effects such as diabetes, anaemia and developmental, cardiovascular, reproductive, neurological and immunological. The exposure to high dose of arsenic for short-term may result in many adverse health problems (Zhang et al. 2002). The arsenic toxicity also leads to skin lesions, rhagades, and damage to digestive, circulatory, respiratory and mucous membrane (Rehman et al. 2010). The most prevalent form of arsenic in oxic condition is As(V) and its toxicity depends on its tetrahedral oxyanion structure which resembles phosphate, thus As(V) is involved in uncoupling the intermediary

metabolic conversions, for example in oxidative phosphorylation (Kruger et al. 2013; Villadangos et al. 2014). As(V) may interfere in the methylation state or repair system of DNA, oxidative stress, promotion of cell proliferation, telomerase activities and inhibition of p53 inhibit activation of transcription factors by interfering with signal transduction pathways (Butt and Rehman 2011; Shakoori et al. 2010). As(III) is highly toxic in comparison with As(V), as it can react with free thiols which results in disturbing the redox homeostasis. Additionally, As(III) stimulates the production of reactive oxygen species (ROS), subsequently ROS damages the DNA as well as proteins (Villadangos et al. 2014). The presence of arsenic during DNA replication shown to induce sister chromatid exchanges and chromosomal aberrations, and arsenic is mutagenic according to the results of genotoxicity studies (Shakoori et al. 2010). 200 enzymes can be inactivated by arsenic toxicity, mostly the enzymes that are involved in cellular energy pathways. It generates ROS which in turn exerts its toxicity causing DNA damage and lipid peroxidation (Ratnaike 2003). Arsenic also exerts its toxicity on plants involving in their metabolisms. Plants can easily take up As(III) and As(V) by their root cells. The roots tissue of plants is the first one to interact with arsenic, which in turn results in inhibition of root proliferation and extension. After taken up from the roots, the arsenic is translocated to the shoots, where it arrests or slows down the biomass accumulation and expansion by inhibiting the plant growth. Arsenic also leads plants to compromise in their reproductive capacity by losing fruit production, yield as well as plant fertility (Garg and Singla 2011). Both, As(III) and As(V), play role in disruption of plant metabolism by distinct mechanism of action. As(V) is structurally resembles phosphate, it can disrupt phosphate dependent metabolisms. It competes with phosphate uptake in plants leading to imbalance of phosphate supply. As (V) forms unstable and short-lived adducts by competing with phosphate in phosphorylation reactions. The enzymes that contain closely spaced dithiol co-factors or cysteine residues are inactivated by As(III) as it binds with the thiols group of the enzymes, as As(III) is a dithiol reactive compound (Finnegan and Chen 2012).

6.5 Bioremediation of Arsenic

Bioremediation is the process of eliminating toxic waste from environment by exploiting biological agents (Ahemad 2012). The metals present in industrial effluents can be removed by conventional methods like chemical reduction or oxidation, chemical precipitation, ion exchange, filtration, evaporation recovery, membrane technologies, electrochemical treatment and reverse osmosis (Ahluwalia and Goyal 2007). When the concentration of metals in solutions is 1–100 mg/l then these conventional methods are ineffective or extremely expensive. So, there is an urgent need to develop an eco-friendly, cost-effective and innovative technique for elimination of the metals from contaminated water (Rehman et al. 2010). The microorganisms can transform the oxidation state of arsenic having different solubility properties, thus performing an important role in biochemical cycle of arsenic (Silver and Phung 2005). In metal-stressed environment, the bacteria have

developed several mechanisms for their survival to reduce the uptake of heavy metals (Nies 1999). Bioremediation of arsenic by microorganisms involves their intracellular bioaccumulation, methylation, reduction and oxidation (Satyapal et al. 2016). The arsenic can be utilized in metabolism of bacterial strains which are arsenic resistant for producing energy by chemoautotrophic As(III) oxidation (Santini et al. 2000). In aerobic respiration, bacteria can utilize As(V) as terminal electron acceptor (Ahmann et al. 1994; Stolz and Oremland 1999).

6.5.1 Arsenic Uptake and Extrusion System in Bacteria

Numerous mechanisms have been adopted by bacteria to survive in metal stress, to tolerate the heavy metal uptake and to protect themselves from cell homeostasis caused by heavy metals. These mechanisms include the efflux of metal ions, reduction of heavy metals and metal ion complexation and accumulation inside the cell (Ahemad 2012). In prokaryotes, the uptake of arsenic is due to its molecular similarity with the substrates of membrane transporter proteins. In aqueous solutions, at optimum pH, As(III) is structurally similar to glycerol and exists as $As(OH)_3$. However, As(V) is taken up by phosphate transporter proteins of membrane as it is a structural analogue of phosphate (Maciaszczyk-Dziubinska et al. 2012). The GlpF, an aquaglyceroprotein, involves in the transport of As(III) across the cell membrane. Pst and Pit are phosphate transporter proteins facilitating AsV uptake in bacteria (Kruger et al. 2013). In bacteria, arsenic extrusion is done by an arsenite-translocating ATPase. The three gene operon, *arsRBC*, present in bacteria encoding ArsB, involve in arsenite extrusion. Majority of the bacteria use ArsB alone to extrude arsenite. Some bacteria have the five gene operon, *arsRDABC*, encoding for ArsA and ArsB as components of ArsAB ATPase complex (Rosen 2002; Satyapal et al. 2016). The arsenite permease Acr3, an arsenic resistance transporter, is a member of the bile/arsenite/riboflavin transporter (BART) superfamily. BART includes members of archaea, fungi, and bacteria. Acr3 are more widely available than ArsB and are small-sized proteins (Villadangos et al. 2012).

6.5.2 Bacterial Arsenite Oxidation

The As(III) can be oxidized by bacteria into As(V), a less toxic form of arsenic. The *Centibacterium arsenoxidans* contains *aoxABCD* operons consisting four adjoining genes encodes for arsenite oxidase, which is involve in arsenite oxidation (Satyapal et al. 2016). The larger subunit of arsenite oxidase is also known as aoxB/asoA/aioA and the small subunits are called as aoxA/asoB/aioB (Silver and Phung 2005; Van Lis et al. 2013). In *H. arsenoxidans*, *aox* operon is regulated by *aoxR* gene product and *aoxS* gene product is a sensor kinase, both are involved in quorum sensing (Koechler et al. 2010). The expression of *aox* operon leads to the synthesis of arsenate oxidase, AoxAB complex, which is then exported to the periplasm of the bacteria by a Tat (Twin-Arginine Translocation) protein. In periplasm of the bacteria

the AoxAB complex involves in oxidation of As(III) to As(V) (Silver and Phung 2005).

6.5.3 Bacterial Arsenate Reduction

The *ars* operon is involved in the reduction of As(V) to As(III). The *arsRBC*, a three gene operon, is present in *E. coli* genome, whereas a five gene operon, *arsRDABC*, is reported in *S. aureus* (Rosen 2002). The transcriptional regulator (arsR) is encoded by *arsR*, whereas *arsA* and *arsB* encode arsA and arsB, respectively. These are components of ArsAB, ATPase, an arsenite efflux pump and *arsC* encodes for an arsenate reductase (arsC) (Arsène-Ploetze et al. 2010). The ArsD encoded by *ArsD* acts as arsenic chaperone. The *ars* operons, *arsRBC* and *arsRDABC*, may present in a single strain, as observed in *T. arsenitoxidans* 3As (Anderson and Cook 2004). The arsenate reduction in prokaryotes is of two types: periplasmic and cytoplasmic arsenate reduction. Pst and Pit are membrane transporter proteins involve in the uptake of As(V). The As(V) is then reduced to As(III) by ArsC, arsenate reductase (Kruger et al. 2013). The As(III) is then transferred by arsenic chaperon, ArsD, from the glutathione-bound complex to the small subunit, ArsA, of the ArsAB complex which in turn activates the ArsAB pump. The As(III) is then extruded out through the ArsAB pump (Satyapal et al. 2016). The As(V) reduction in periplasm of bacteria is mediated by the components of respiratory arsenate reductase, i.e., arrA and arrB encoded by the *arr* operon (Kruger et al. 2013).

6.5.4 Arsenic Methylation in Bacteria

Arsenic methylation is very less known in bacterial system; however, it was considered as a detoxification process. In methylation process, the intermediate compounds or methylated products are more toxic for the eukaryotic cell lines in comparison with the inorganic forms of arsenic (Kruger et al. 2013; Stolz et al. 2006). In methylation process, the methylated arsenicals are more toxic because of increase in their volatility (Kruger et al. 2013). The bacteria can perform animatic activity for the methylation of arsenic by involving a *S*-adenosylmethionine (SAM) and methyltransferase enzyme. The methyltransferase, ArsM/AS3MT, is an *arsM* gene product which methylates As(III) into a MMAs(III) (monomethyl arsenite/MMA^{3+}) (Obinaju 2009; Satyapal et al. 2016). This MMAs(III) is then methylated to form DMAs(III) (dimethyl arsenite/DMA^{3+}) followed by a final product as TMAs(III) (trimethyl arsine). These arsenicals can be extruded out from the cell through the process of diffusion (Hughes 2002). Though, the demethylation mechanism of arsenic in prokaryotes is not well understood. The demethylation of arsenic compounds (mono and dimethyl) is observed in some microorganisms, e.g., *Alcaligenes*, *Pseudomonas* and *Mycobacterium* species (Stolz et al. 2006).

6.6 Conclusion

Arsenic is found worldwide and is one of the most toxic pollutants found in nature. It is naturally found and distributed in rocks, rivers, soils, sea, air and water. The anthropogenic activities are the big reason in distribution of arsenic at large scale. Nevertheless, there are some bacterial systems that involve in detoxification of toxic arsenic in present nature. The bacteria have developed tolerance against arsenic by different mechanisms. These mechanisms of oxidation, reduction and methylation may play a great role in bioremediation of arsenic. The genes regulating these mechanisms may play a great role in developing a cheap and cost-effective model for arsenic bioremediation.

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Assessment of Arsenic Contamination in Groundwater and Affected Population of Bihar

7

Arun Kumar and Ashok Kumar Ghosh

Abstract

Arsenic poisoning has become a global problem in the recent times. It is estimated that >300 million population are exposed to arsenic worldwide. Bihar is the state in India, which is in the vicinity of river Ganges where seven major tributaries from Great Himalayas through Nepal meet river Ganges. This entire Gangetic plain area is highly fertile land, with very high population density. In this state an estimated 10 million people are exposed to arsenic contaminated drinking water as well as irrigation water. Groundwater is the primary source of arsenic poisoning which has caused serious health hazards to the exposed population. The exposed population are exhibiting typical symptoms of arsenicosis such as hyperkeratosis, melanosis, pigmentations and other skin manifestations. Apart from this they are also exhibiting other symptoms such as disorders of liver, kidney, nervous system, cardiovascular, hormonal, etc. The prolonged arsenic exposure also leads to different types of cancer. The cancer among the exposed population is of skin, liver kidney, gall bladder, bladder, breast, colorectal, etc. Hence, it is very important to evaluate the health problems exhibited in the exposed population. The present study highlights the health problems of the exposed population of different parts of Bihar with confirm presence of elevated arsenic concentration in groundwater (>10 μg/L). Apart from this the study also examined the mitigation strategies undertaken by the state Government for the exposed population.

Keywords

Arsenic poisoning · Health hazards · Districts of Bihar · Mitigation strategies

A. Kumar (✉) · A. K. Ghosh
Mahavir Cancer Sansthan and Research Centre, Patna, Bihar, India

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7.1 Introduction

Arsenic menace in the recent times has caused serious health hazards in the population worldwide. Drinking water is the major source where contamination of arsenic is significant. In a recent study, it has been estimated that >300 million population are exposed to arsenic worldwide (Hassan 2018; Naujokas et al. 2013; Murcott 2012; Straif et al. 2009; ATSDR 2005; IARC 2004). In Asia alone an estimated >200 million are affected with arsenic poisoning which includes countries such as Bangladesh, India, Myanmar, Cambodia, China, Iran, Japan, Nepal, Pakistan, Taiwan, Thailand, Turkey and Vietnam. In India and Bangladesh together >150 million people are exposed to arsenic poisoning (Chakraborti et al. 2003, 2004, 2008, 2009, 2015, 2016a, 2017; Mukherjee et al. 2006; Nickson et al. 2007; Hassan 2005; Rosenboom 2004). Apart from this, in other continents, such as in north America an estimated population of 2 million, in south America about 2.5 million, in Europe about 1.2 million, in Africa about 0.5 million, respectively, are exposed to arsenic poisoning (Hassan 2018). Arsenic exposure has caused serious health hazards in the exposed population such as skin manifestations, gastrointestinal tract disorders, neurological disorders, respiratory disorders, cardiovascular disorders, hormonal disorders, etc. and non-communicable diseases like cancer (Sinha and Prasad 2020; Marshall et al. 2007; Argos et al. 2011; Kumar et al. 2020; Powers et al. 2018; Ersbøll et al. 2018; Profili et al. 2018; Wang et al. 2016; Kumar et al. 2015; Susko et al. 2017; Weidemann et al. 2015; Engström et al. 2015; Yang et al. 2013; Roh et al. 2017; UNICEF 1998).

7.2 Arsenic Problem in Indian Subcontinent

In Indian subcontinent, arsenic has caused severe health hazards in the population residing in the Ganga–Meghna–Brahmaputra (GMB) plains. This arsenic poisoning in Indian subcontinent is a geogenic problem. As far as the magnitude of arsenic poisoning due to geogenic activity in groundwater in India is concerned, following states have severe arsenic problem: West Bengal, Assam, Bihar, Uttar Pradesh, Uttarakhand and Punjab (Kumar et al. 2015, 2016a; Chakraborti et al. 2003, 2016b, c; Ahamed et al. 2006; Shankar and Shanker 2014; Goswami et al. 2020; Bhowmick et al. 2018; Richards et al. 2020; Roychowdhury 2010; Mondal and Chattopadhyay 2020). However, in few states in India like Chhattisgarh, Jharkhand, Karnataka, Madhya Pradesh, there has been reporting of arsenic poisoning in groundwater due to anthropogenic activities (Manju et al. 2017; Acharyya et al. 2005; Chakraborti et al. 1999). Unfortunately, in Ganga–Meghna–Brahmaputra plains the health-related issues in the exposed population have increased many folds in the recent years. The major rivers like holy Ganga and Brahmaputra cater the major river plain region of this subcontinent. Through many studies it has been confirmed that the arsenic in the form of arsenopyrite is carried out through the river streams from the great Himalayas and are being deposited in the river banks where the meandering of the river is very high. In due course of time, after 1980, when

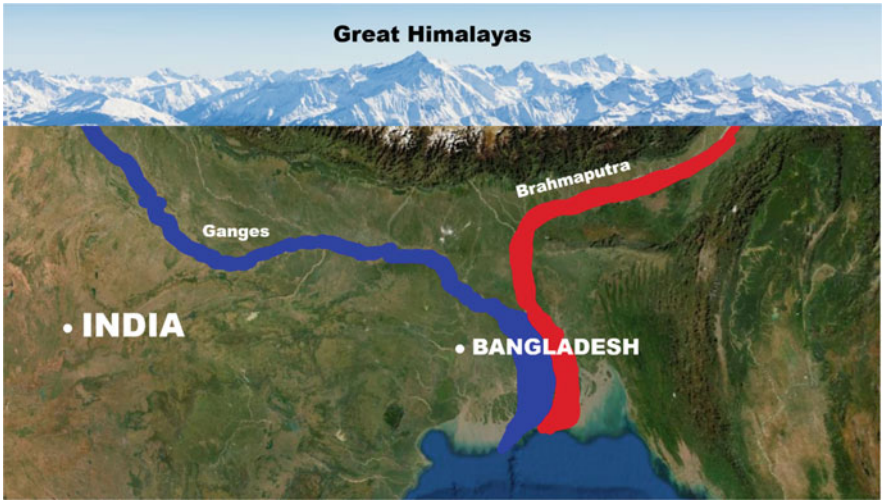

Fig. 7.1 Showing Ganga—Meghna—Brahmaputra plains affected with arsenic poisoning in Indian subcontinent

millions of handpumps were drilled in India led to over-exploitation of groundwater. It changed the chemistry of aquifer leading to arsenic poisoning through groundwater with more than WHO permissible limit of 10 µg/L (Guillot and Charlet 2007; Saha and Sahu 2016; Acharyya and Shah 2007; Chakraborty et al. 2015; Edmunds et al. 2015; Mukherjee et al. 2019) (Fig. 7.1).

7.3 Arsenic Problem in State of Bihar

Bihar is located in the eastern region of India between latitude 24°-20′-10″N ~ 27°-31′-15″ N and longitude 83°-19′-50″E ~ 88°-17′-40″ E. It is an entirely land-locked state, in a subtropical region of the temperature zone. It is bounded in east by West Bengal, in west by Uttar Pradesh, in north by Nepal and in south by Jharkhand. The Bihar plain is divided into two unequal halves North Bihar and South Bihar by the river Ganges. The major river of the state is river Ganges which flows from west to east in a stretch of 405 km. There are seven major tributaries of the Ganges which flows from the Great Himalayas through Nepal to Bihar catering the river course through the entire districts of the north Bihar. Unfortunately, the arsenic poisoning in the groundwater in the state is also reported from the districts of the north Bihar including the districts near the river Ganges. In Bihar, the river Ganges flows through the following districts—Buxar, Bhojpur, Saran, Vaishali, Samastipur, Begusarai, Luckeesarai, Munger, Khagaria and Bhagalpur. In the recent times,. the seven major rivers which have their origin from the great Himalayas are Gandak, Burhi Gandak, Bagmati, Kamla, Kosi and Mahananda. However, there are other rivers as well

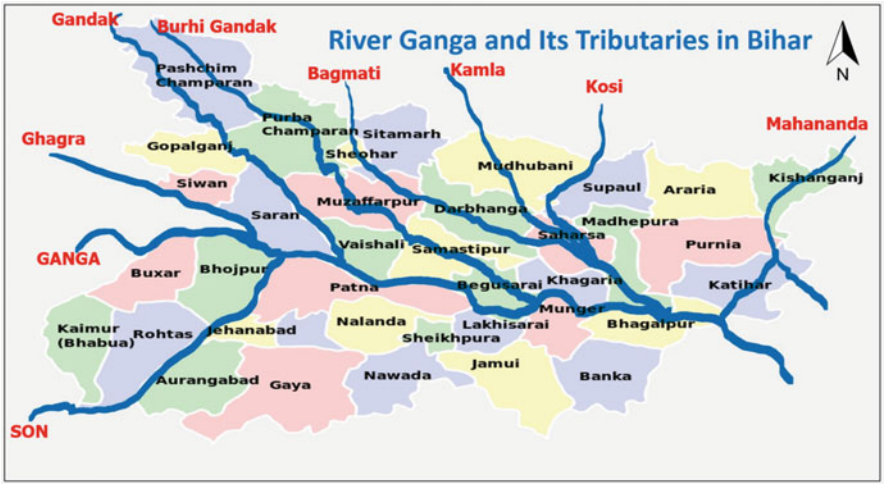

Fig. 7.2 Tributaries of river Ganges

which are the tributaries of river Ganges coming from the southern region of the state such as Son, Punpun, Phalgu, Kiul, Chandan, etc. (Fig. 7.2).

7.4 Assessment of Arsenic Poisoning in Districts of Bihar

The Gangetic plain region of the state and the north Bihar river plain regions have become the hotspot areas of arsenic poisoning. It is quite apparent that in due course of time, the arsenopyrite load coming from great Himalayas through these rivers could have deposited in the sediment in past. The geogenic and anthropogenic activities led to arsenic poisoning in this area. Consumption of these arsenic contaminated water (>10 μg/L) has caused serious health hazards in the population inhabiting in these regions. Out of 38 districts of the state, 18 districts are affected from arsenic poisoning (Singh 2017; Kumar et al. 2015; Chakraborti et al. 2016a; Rahman et al. 2019). Unfortunately, the arsenic poisoning is very common in the river basins of north Bihar. These north Bihar arsenic affected river basin districts are West Champaran, Saran, Muzaffarpur, Vaishali, Samastipur, Madhubani, Supaul, Darbhanga, Begusarai, Khagaria, Kishanganj, Purnia and Katihar (Fig. 7.3).

Arsenic poisoning in Bihar has caused health-related problems in the exposed population. Till date the studies carried out are in the pockets as the reporting are in scattered form. Our team have assayed the maximum affected districts along with the public health surveys in the state.

1. *Patna District*: In Patna district, we have surveyed the flood plain regions of river Ganges in one of the villages named Gyaspur Mahaji of Bakhtiyarpur Block (N25°30′02.3″E085°27′14.2″). The village is in the vicinity of river Ganges

Fig. 7.3 Arsenic map of Bihar

Fig. 7.4 Aerial view of the arsenic exposed village Gyaspur Mahaji along with inset river Ganga

Table 7.1 Showing Arsenic caused common disease symptoms and their percentage in the village population

Symptoms	Problems present in the population	No problems observed	Total cases	*P*-value
Hyperkeratosis in palm and sole	16 (2.76%)	564 (97.24%)	580	<0.001
Melanosis in palm and trunk	44 (7.59%)	536 (92.41%)	580	<0.001
Other skin problems	339 (58.45%)	241 (41.55%)	580	<0.001
Anaemia	156 (26.90%)	424 (73.10%)	580	<0.001
General body weakness	410 (70.69%)	170 (29.31%)	580	<0.001
Gastritis and flatulence	438 (75.52%)	142 (24.48%)	580	<0.001
Constipation	424 (73.10%)	156 (26.90%)	580	<0.001
Loss of appetite	276 (47.59%)	304 (52.41%)	580	<0.001
Breathlessness	248 (42.76%)	332 (57.24%)	580	<0.001
Mental disability	11 (1.90%)	569 (98.10%)	580	<0.001
Lump in the body	18 (3.10%)	562 (96.90%)	580	<0.001
Cancer	06 (1.00%)	574 (98.90%)	580	<0.001

between the two streams of river called as Diara land (island in two streams of the Ganga river) (Fig. 7.4). The village had severe arsenic contamination in the handpumps with highest level as 826.2 μg/L, and in human blood 64.98 μg/L in one of the individuals. We carried out extensive health assessment in the village along with the groundwater assessment. Population of this village exhibited typical symptoms of arsenicosis such as hyperkeratosis in sole and palm and hyperpigmentation in palm was prominently observed. We interviewed $n = 580$ individuals of the village and they arsenic related health issues apart from the skin manifestations. The most unfortunate part of the study was the increasing incidences of cancer among the village population. During our study we observed 06 cancer cases in the village (Table 7.1). The subjects were still drinking arsenic contaminated water (Fig. 7.5).

2. *Buxar District*: In Buxar district, we surveyed the flood plain region of river Ganges in one of the villages named Tilak Rai Ka Hatta of Simri block ($25^0 41' 36'' N$, $84^0 07' 51'' E$). The village too is in the vicinity of river Ganga (Fig. 7.6).

The village had maximum arsenic concentration in one of the handpumps up to 1908 μg/L, while blood arsenic concentration in one of the individuals was up to 664.7 μg/L. We carried out extensive public health assessment and found that the subjects had typical symptoms of arsenicosis along with arsenic related disease. The disease burden in this particular village in percentage was highest among the study carried out by our team (Fig. 7.7).

In this village the subjects had the highest disease burden ever explored in the arsenic exposed population of Bihar. The female disease burden was higher in the

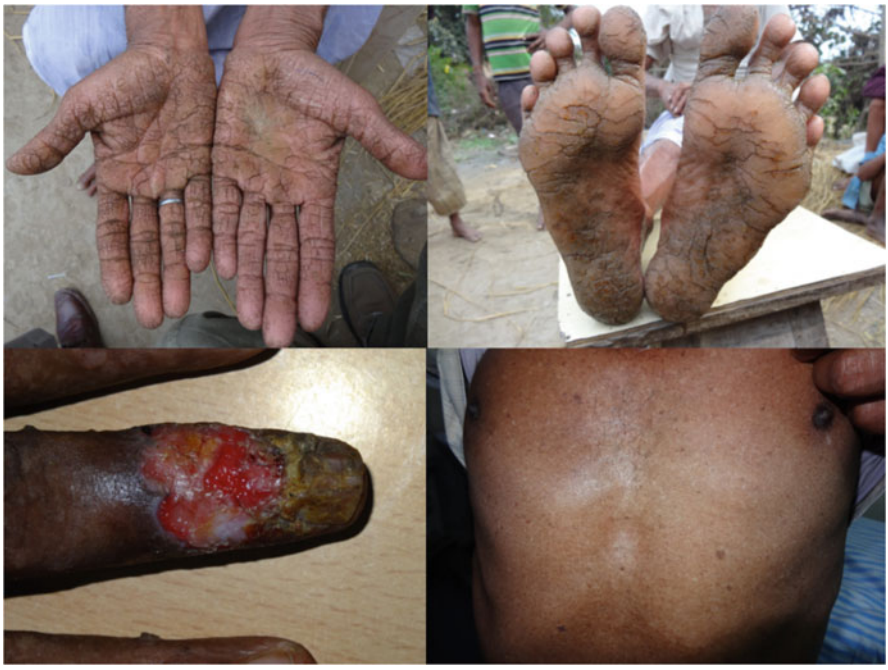

Fig. 7.5 Arsenic exposed individuals showing skin manifestations along with skin cancer (confirmed squamous cell carcinoma) in the index finger

Fig. 7.6 Aerial view of the arsenic exposed village Tilak Rai Ka Hatta along with inset river Ganga

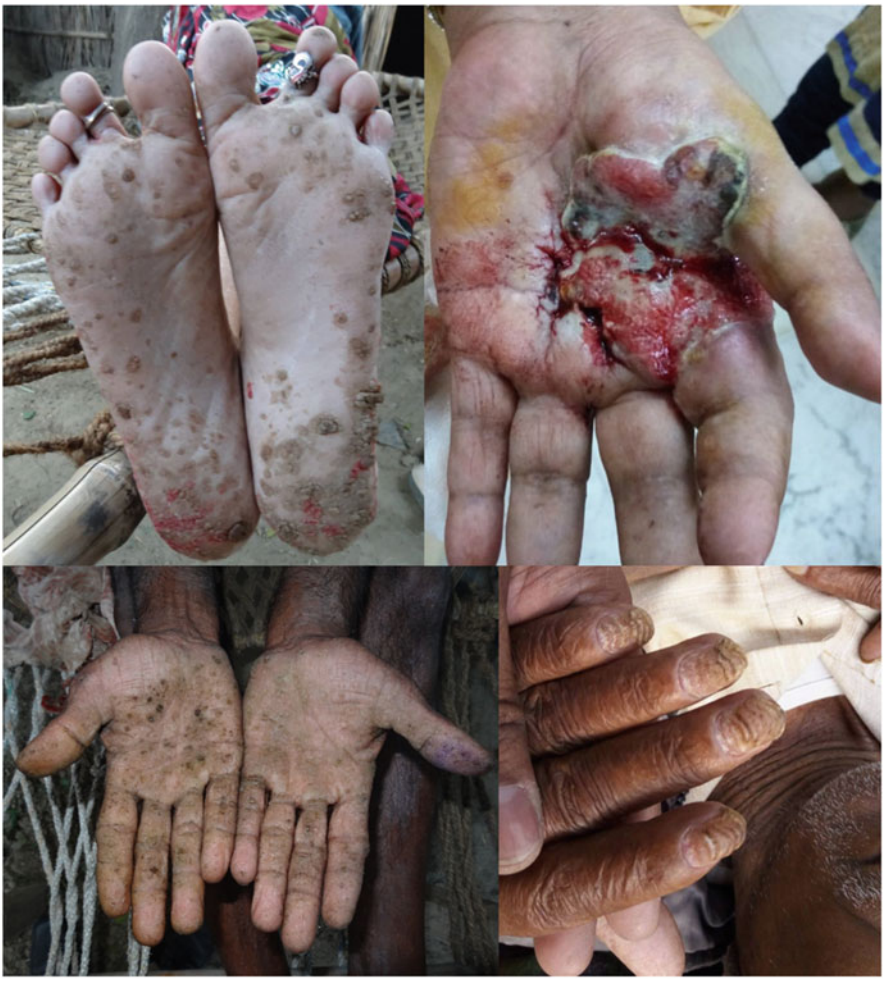

Fig. 7.7 Arsenic exposed individuals showing skin manifestations along with skin cancer (confirmed squamous cell carcinoma) in the entire palm. One individual who is exhibiting typical Mees lines (very rarely observed)

exposed population than the male population. The incidences of infertility were also reported from the village along with severe skin manifestations (Table 7.2).

3. *Saran District*: In Saran district, we surveyed the flood plain region of river Ganges and river Gandak in one of the villages named Sabalpur of Sonepur block (25°40′37.4″N 85°10′48.0″E). The village is in the confluence of river Ganga and river Gandak (Fig. 7.8).

Table 7.2 Showing Arsenic caused common disease symptoms and their percentage in the village population (Kumar et al. 2015)

Symptoms	Problems present in the population	No problems observed	Total cases	*P*-value
Hyperkeratosis in palm and sole	428 (28%)	1102 (72%)	1530	<0.0001
Melanosis in palm and trunk	473 (31%)	1057 (69%)	1530	<0.0001
Other skin problem—irritation	351 (23%)	1179 (77%)	1530	<0.0001
Anaemia	872 (57%)	658 (43%)	1530	<0.0001
Gastritis	1315 (86%)	215 (14%)	1530	<0.0001
Liver problem	887 (58%)	643 (42%)	1530	<0.0001
Constipation	596 (39%)	934 (61%)	1530	<0.0001
Loss of appetite	979 (64%)	551 (36%)	1530	<0.0001
Infertility in male and female	15 (1%)	1515 (99%)	1530	<0.0001
Irregular menstrual cycle	137 (9%)	1397 (91%)	1530	<0.0001
Asthma or bronchitis	45 (3%)	1485 (97%)	1530	<0.0001
Cancer cases	12 (0.4%)	1518 (99.21%)	1530	<0.0001

Fig. 7.8 Aerial view of the arsenic exposed village Sabalpur along with inset river Ganga and river Gandak

In this village, the maximum arsenic concentration in handpump water was 172.6 µg/L, while blood arsenic concentration in one of the individuals was up to 245.6 µg/L. The subjects exhibited typical severe symptoms of arsenicosis such as

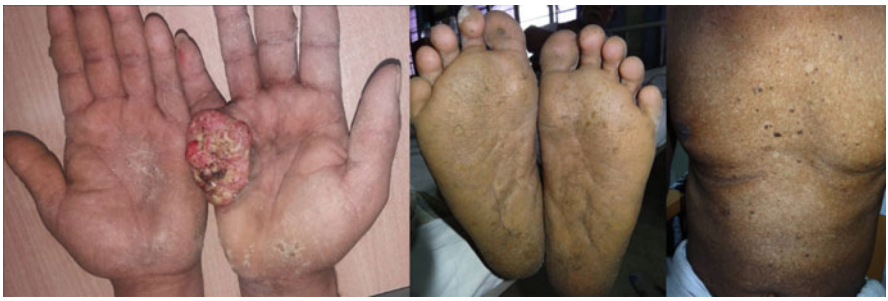

Fig. 7.9 Arsenic exposed individuals showing skin manifestations along with skin cancer (cauliflower shaper squamous cell carcinoma) in his right palm

Table 7.3 Showing arsenic caused common disease symptoms and their percentage in the village population

Symptoms	Problems present in the population	No problems observed	Total cases	*P*-value
Arsenicosis symptoms in palm and sole	7 (0.01%)	630 (99.99%)	637	<0.001
Melanosis in palm and trunk	7 (0.01%)	630 (99.99%)	637	<0.001
Other skin problems	91 (14.29%)	546 (85.71%)	637	<0.001
Anaemia	153 (24.01%)	484 (75.99%)	637	<0.001
General body weakness	114 (17.89%)	523 (82.11%)	637	<0.001
BP problem	96 (15.07%)	541 (84.93%)	637	<0.001
Diabetes	54 (8.477%)	583 (91.53%)	637	<0.001
Breathlessness	88 (13.81%)	553 (86.19%)	637	<0.001
Mental disability	19 (2.99%)	618 (97.01%)	637	<0.001
Lump in the body	113 (17.74%)	524 (82.26%)	637	<0.001
Cancer	6 (0.94%)	631 (99.05%)	637	<0.001
Other health problem	184 (28.88%)	453 (71.12%)	637	<0.001

hyperkeratosis in sole and palm along with the rain drop pigmentation. One subject had cauliflower shaped tumour (squamous cell carcinoma) in his palm and had the treatment of cancer in our institute (Fig. 7.9).

The village population had arsenic related diseases along with the arsenicosis symptoms. We interviewed 637 individuals of the village who shared their health-related problem with our team (Table 7.3).

4. *Samastipur District*: In Samastipur district, we surveyed the flood plain region of river Ganges and river Bagmati. The village Hansopur is situated in the vicinity of river Bagmati (25°52′41.9″N 85°57′56.4″E) (Fig. 7.10)

Hansopur Village In this village, the maximum arsenic concentration in handpump water was 114.8 μg/L, while blood arsenic concentration in one of the individuals

Fig. 7.10 Aerial view of the arsenic exposed village Hansopur in the vicinity of river Bagmati in Samastipur district

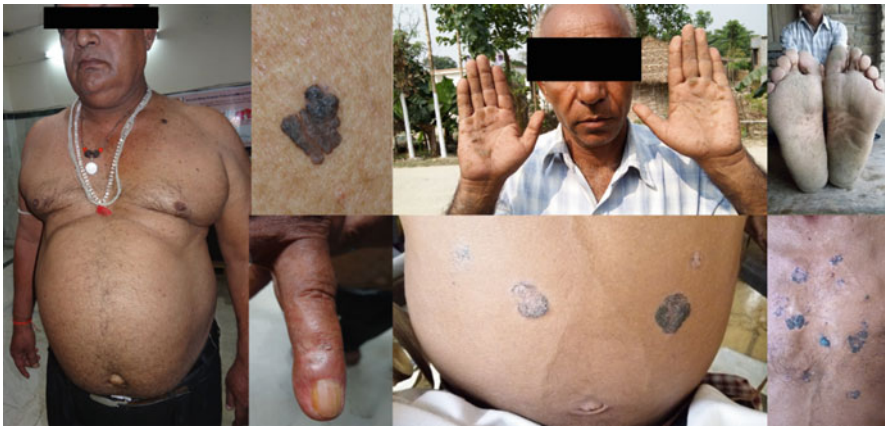

Fig. 7.11 Arsenic exposed individuals showing skin manifestations along with cancer diseases—squamous cell carcinoma, Bowen's disease and skin melanoma

was up to 173 μg/L. The subjects exhibited typical severe symptoms of arsenicosis such as hyperkeratosis in sole and palm along with the rain drop pigmentation. One subject had cancer of two types skin cancer in finger (squamous cell carcinoma) and suspected skin melanoma in his back and was having the treatment of cancer in our institute. Two other subjects exhibited Bowen's disease (Fig. 7.11).

Table 7.4 Showing arsenic caused common disease symptoms and their percentage in the village population

Symptoms	Problems present in the population	No problems observed	Total cases	*P*-value
Arsenicosis symptoms in palm and sole	28 (6.02%)	437 (93.98%)	465	<0.001
Melanosis in palm and trunk	8 (1.72%)	457 (98.28%)	465	<0.001
Other skin problems	212 (45.59%)	253 (54.41%)	465	<0.001
Anaemia	108 (23.22%)	357 (76.78%)	465	<0.001
General body weakness	378 (103.56%)	87 (18.71%)	465	<0.001
BP problem	29 (6.23%)	411 (93.77%)	465	<0.001
Diabetes	16 (3.44%)	449 (96.56%)	465	<0.001
Breathlessness	102 (21.93%)	353 (78.07%)	465	<0.001
Mental disability	02 (0.430%)	463 (99.57%)	465	<0.001
Lump in the body	04 (0.86%)	461 (99.14%)	465	<0.001
Cancer	05 (1.07%)	460 (98.93%)	465	<0.001
Other health problem	126 (27.09%)	339 (72.91%)	465	<0.001

Fig. 7.12 Aerial view of the arsenic exposed village Chapar (in box) in the vicinity of river Ganga (inset) in Samastipur district

The entire village population is about 5200 while the survey was carried out in one of the habitations named Babhantoli which comprised 2030 population while there were 120 households in this habitation. We interviewed 465 individuals of the village who shared their health-related problem with our team (Table 7.4).

Chapar Village The village Chapar is situated in the vicinity of river Ganga (25°32′56.4″N 85°39′58.8″E) (Fig. 7.12).

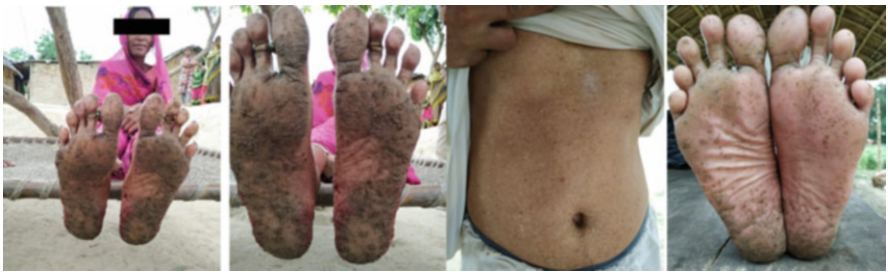

Fig. 7.13 Arsenic exposed individuals showing skin manifestations

Table 7.5 Showing Arsenic caused common disease symptoms and their percentage in the village population

Symptoms	Problems present in the population	No problems observed	Total cases	P-value
Arsenicosis symptoms in palm and sole	44 (13.66%)	278 (86.34%)	322	<0.001
Melanosis in palm and trunk	26 (8.07%)	296 (91.93%)	322	<0.001
Other skin problems	186 (57.76%)	136 (42.24%)	322	<0.001
Anaemia	54 (16.77%)	268 (83.23%)	322	<0.001
General body weakness	178 (55.27%)	144 (44.73%)	322	<0.0001
BP problem	47 (14.59%)	275 (85.41%)	322	<0.001
Diabetes	21 (6.52%)	301 (93.48%)	322	<0.001
Breathlessness	62 (19.25%)	260 (80.75%)	322	<0.001
Mental disability	04 (1.24%)	318 (98.76%)	322	<0.0001
Lump in the body	05 (1.55%)	317 (98.45%)	322	<0.001
Cancer	07 (2.17%)	315 (97.83%)	322	<0.001
Other health problem	83 (25.77%)	239 (74.23%)	322	<0.001

In this village, the maximum arsenic concentration in handpump water was 655 μg/L, while blood arsenic concentration in one of the individuals was up to 88.3 μg/L. The subjects exhibited typical severe symptoms of arsenicosis such as hyperkeratosis in sole and palm along with the rain drop pigmentation (Fig. 7.13).

The entire village population is about 3600 while the survey was carried out in one of the habitations which comprised 1800 village population while there were 60 households in this habitation. We interviewed 322 individuals of the village who shared their health-related problem with our team (Table 7.5).

5. *Bhagalpur District*: In Bhagalpur district, we surveyed the flood plain region of river Ganges. The village Kali Prasad is situated in the vicinity of river Ganga (25°20′45.9″N 87°23′40.1″E) (Fig. 7.14).

Fig. 7.14 Aerial view of the arsenic exposed village Kali Prasad (in box) in the vicinity of river Ganga (inset) in Bhagalpur district

In this village, the maximum arsenic concentration in handpump water was 340.3 μg/L, while blood arsenic concentration in one of the individuals was up to 78.2 μg/L. The subjects exhibited typical severe symptoms of arsenicosis such as hyperkeratosis in sole and palm along with the rain drop pigmentation. One subject had skin melanoma cancer in his back (Fig. 7.15).

The entire village population is about 2400 while the survey was carried out in one of the habitations which comprised 1000 village population while there were 210 households in this habitation. We interviewed 234 individuals of the village who shared their health-related problem with our team (Table 7.6).

6. *Begusarai District*: In Begusarai district, we surveyed the flood plain region of river Ganges. The village Gyantoli is situated in the vicinity of river Ganga (25°22′60.0″N 86°23′08.4″E) (Fig. 7.16).
   In this village, the maximum arsenic concentration in handpump water was 535.7 μg/L, while blood arsenic concentration in one of the individuals was up to 58.4 μg/L. The subjects exhibited typical severe symptoms of arsenicosis such as hyperkeratosis in sole and palm, palmoplantar keratosis along with the rain drop pigmentation (Fig. 7.17).

The entire village population is about 1300 while the survey was carried out in one of the habitations which comprised 800 population while there were 55 households in this habitation. We interviewed 186 individuals of the village who shared their health-related problem with our team. The village was near the banks of the river Ganga with cancer incidences. There were many subjects who died

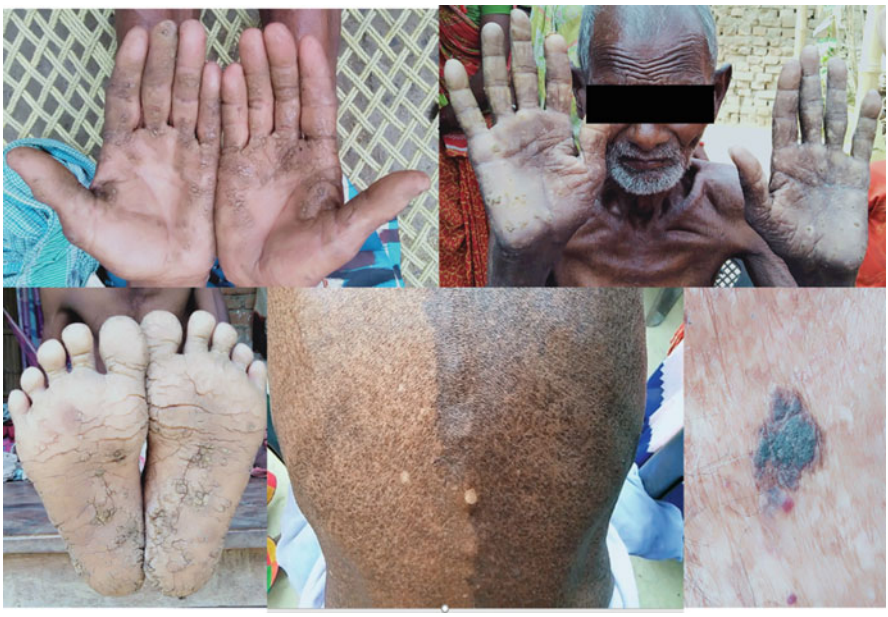

Fig. 7.15 Arsenic exposed individuals showing skin manifestations along with cancer disease skin melanoma

Table 7.6 Showing Arsenic caused common disease symptoms and their percentage in the village population

Symptoms	Problems present in the population	No problems observed	Total cases	*P*-value
Arsenicosis symptoms in palm and sole	82 (35.04%)	152 (64.96%)	234	<0.001
Melanosis in palm and trunk	32 (13.6%)	202 (86.4%)	234	<0.001
Other skin problems	144 (61.53%)	90 (38.47%)	234	<0.001
Anaemia	24 (10.25%)	210 (89.75%)	234	<0.001
General body weakness	18 (7.69%)	216 (92.31%)	234	<0.001
BP problem	28 (11.96%)	206 (88.04%)	234	<0.001
Diabetes	37 (15.81%)	197 (84.19%)	234	<0.001
Breathlessness	29 (12.39%)	205 (87.61%)	234	<0.001
Mental disability	02 (0.85%)	232 (99.15%)	234	<0.001
Lump in the body	04 (1.70%)	230 (98.30%)	234	<0.001
Cancer	03 (1.28%)	231 (98.72%)	234	<0.001
Other health problem	65 (27.77%)	169 (72.33%)	234	<0.001

Fig. 7.16 Aerial view of the arsenic exposed village Gyantoli (in box) in the vicinity of river Ganga (inset) in Begusarai district

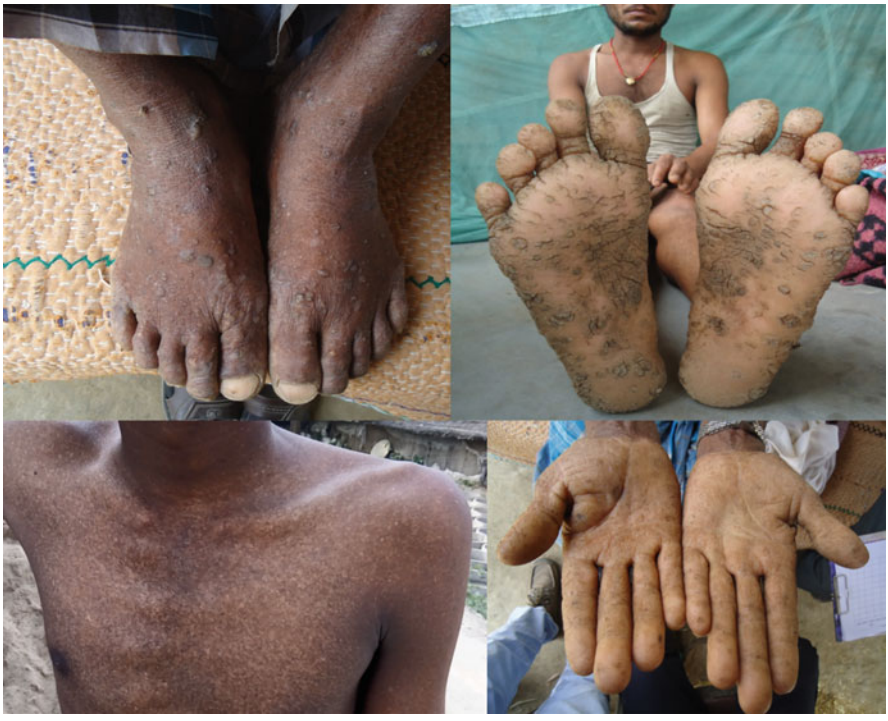

Fig. 7.17 Arsenic exposed individuals showing skin manifestations

Table 7.7 Showing Arsenic caused common disease symptoms and their percentage in the village population

Symptoms	Problems present in the population	No problems observed	Total cases	*P*-value
Arsenicosis symptoms in palm and sole	47 (25.26%)	139 (74.74%)	186	<0.001
Melanosis in palm and trunk	18 (9.67%)	168 (90.33%)	186	<0.001
Other skin problems	87 (46.77%)	99 (53.23%)	186	<0.001
Anaemia	12 (6.45%)	174 (93.55%)	186	<0.001
General body weakness	53 (28.49%)	133 (71.51%)	186	<0.001
BP problem	11 (5.91%)	175 (94.09%)	186	<0.001
Diabetes	14 (7.5%)	172 (92.5%)	186	<0.001
Breathlessness	36 (19.35%)	150 (80.65%)	186	<0.001
Mental disability	01 (0.53%)	185 (99.47%)	186	<0.001
Lump in the body	02 (1.07%)	184 (98.93%)	186	<0.001
Cancer	08 (4.30%)	178 (95.70%)	186	<0.001
Other health problem	38 (20.43%)	148 (79.57%)	186	<0.001

with cancer in this village habitation with gallbladder and liver cancer. The disease burden in this village habitation was very high in comparison to the other arsenic exposed area in Begusarai district (Table 7.7).

7.5 Disease Burden

The arsenic poisoning with time is increasing many folds in the exposed population of the state. Our team carried out extensive study in the arsenic exposed area of the state and observed that the village population are getting more or less with some disease. The arsenicosis symptoms are very common in the exposed population in the form of acute or chronic toxicity such as keratoses, melanosis, rain drop pigmentation, leucomelanosis, anaemia, general body weakness, blood pressure disorder, diabetes disorder, breathlessness, lumps in the body, mental disability cases and finally cancer cases (Fig. 7.18).

This type of extensive health assessment has been rarely reported from the researchers. However, few studies have been carried out which correlates with the drinking arsenic contaminated water with disease burden (Chakraborti et al. 2016a; Clewell et al. 2016; Karagas et al. 2012; Kippler et al. 2016; Kumar et al. 2016b; Lin et al. 2013; Shankar and Shanker 2014; Quansah et al. 2015; WHO 2004). Moreover, the researchers have also reported the chronic arsenic exposure effect causing increased risk of wide array of diseases such as skin manifestations (Sarma 2016; Wei et al. 2017), lung cancer (Sherwood and Lantz 2016), bladder cancer (Medeiros and Gandolfi 2016), liver cancer (Lin et al. 2013), skin cancer (Karagas et al. 2001), kidney cancer (Cheng et al. 2017), neurological disorders (Fee 2016; Kumar et al. 2019), diabetes (Kuo et al. 2015), and cardiovascular diseases (Barchowsky and

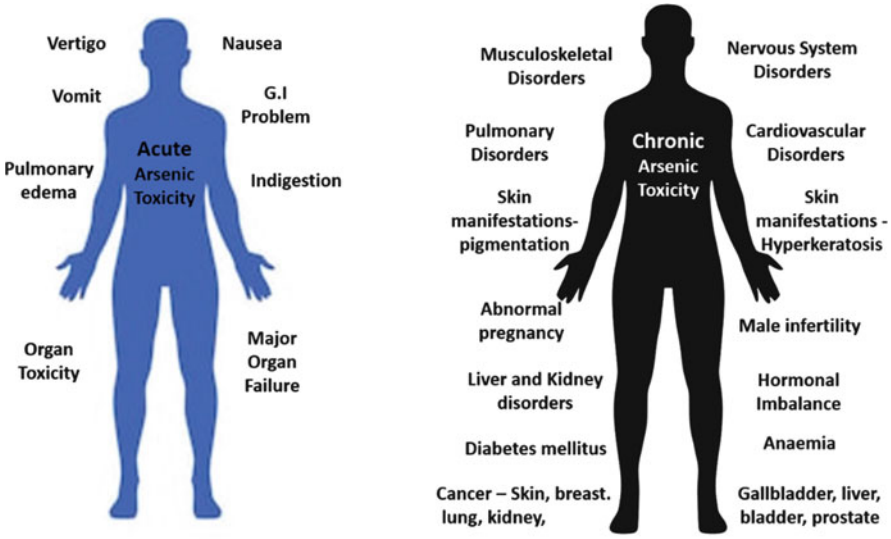

Fig. 7.18 Showing disease types in acute and chronic toxicity in arsenic exposed population

States 2016). Due to non-treatment of the acute toxicity disease, the disease burden leads to the disease of cancer in the arsenic exposed population (Arita and Costa 2009; Benbrahim-Tallaa and Waalkes 2008; Chervona et al. 2012; Peana et al. 2013; Zoroddu et al. 2019).

The mode of arsenic poisoning to human health mainly depends upon the chemical forms of arsenic such as As^{3+} or As^{5+} (Ratnaike 2003; Collotta et al. 2013; Pimparkar and Bhave 2010). Both the forms are highly toxic but especially the trivalent form causing major health hazard. The trivalent arsenic usually enters the human body through drinking water and is absorbed in to the blood and is transported to the vital organs of the body especially, the liver and kidney. The liver however reduces the toxicity by converting it furthermore to the less toxic compound dimethyl arsenic acid (DMA) and finally eliminating it by the kidney (Ameer et al. 2017; Bhattacharjee et al. 2013; Bustaffa et al. 2014; Hubaux et al. 2013; Lesseur et al. 2012; Van Breda et al. 2015). However, the DMA is also a carcinogen which if remains in the system, causes toxic effects to the vital organs (Rossman 2003; Jomova et al. 2011; Bjørklund et al. 2020; Hughes et al. 2011; Wei et al. 2017; Chen et al. 2009; IARC 1980, 2012; Bates et al. 1992; Kim et al. 2017). It furthermore also hampers the normal hormonal functioning as it disrupts the functions and acts as xenoestrogen. It influences the functions of the other hormones such as thyroid hormone function, PPAR receptor function, testosterone, progesterone and oestrogen receptor functions. Apart from this it also disrupts the functions of glucocorticoid, mineralocorticoid and retinoic acid receptor functions (Sengupta et al. 2015; Iavicoli et al. 2009; Wirth and Mijal 2010; Meeker 2010).

Altogether from the various studies it can be speculated that arsenic toxicity causes serious damage to the metabolic function of the body causing disease in the exposed population and if the toxicity is not controlled, then leads to cause disease of cancer. This can be correlated with studies which correlate with the increased disease burden in the arsenic exposed population (Adamson and Polya 2007; Argos et al. 2012; Vahter 2008; Smith et al. 2000; Khan et al. 2003, 2006).

7.6 Mitigation Strategies in Bihar

Arsenic poisoning was firstly reported in 2002 in Semaria Ojhapatti village in Bhojpur district of Bihar. After 10 years of the study, it was estimated that about 0.3 million population in the district were affected with the arsenic poisoning (Chakraborti et al. 2003, 2016b). Since, then the state Government has planned various plans to combat the arsenic problem in the exposed population. Following are the technologies on which are working in the arsenic exposed area of the state.

1. Surface water usage
   The surface water usage is the primary method for the arsenic mitigation but requires huge investment but its impact is on large exposed population. In Bihar, Moujampur plant in Bhojpur district is operational since 2014, catering about 0.3 million population residing in 48 villages of the district. The situation in these areas before was very serious as health-related issues were in pathetic condition. But, in the present times, the situation in these areas has relatively normalized as the exposed population is using this arsenic free water. In this Moujampur plant, the Ganges water is tapped, cleaned and is distributed to the 48 exposed villages through pipe water system. This has become hallmark of the state in providing arsenic free water to the exposed population of the state (Fig. 7.19).

Fig. 7.19 Moujampur plant in Bhojpur District utilizing Ganges water for arsenic exposed population

Fig. 7.20 Arsenic filters installed in Buxar and Saran districts of Bihar

2. Deep aquifer groundwater usage
   The state Government through *Har Ghar Nal Ka Jal* (meaning each house getting piped water) scheme is providing piped water supply in the arsenic exposed area. In this connection, the wells are bored between 200 and 300 m depths. The deep aquifer tapped was utilized for drinking purpose in the arsenic exposed area.
3. Arsenic filters
   Various media based arsenic filters have been installed in the arsenic exposed area of the state by the Government as well as by the private NGOs. This technology based arsenic filters usually contain different medias (adsorption based or ion exchange based or nano based) for the chelation of the arsenic from the arsenic contaminated water. The Government based filters due to lack of community participation have become defunct after 2 years of operation but few NGOs based installed filters are perfectly working due to involvement of the exposed population in the usage of arsenic filter. Mostly, 200–300 households are benefitted from these filters. Through our intervention, three arsenic filters have been installed in the two districts of the state Buxar and Saran. In Buxar, we have installed two arsenic filter one sponsored by Tagore Sengupta Foundation, Kolkata installed in 2017 village Tilak Rai Ka Hatta and the second by Central Glass and Ceramic Research Institute (CGCRI-CSIR), Kolkata installed in 2020 in Badka Rajpur village of the district. The third arsenic filter, same CGCRI-CSIR filter has been installed in 2020 in the village Sabalpur of Saran district. All of these three filters are popular and operational due to the involvement of the community, hence are successfully running (Fig. 7.20).
4. Open well usage
   Various villages in North Bihar especially in Samastipur and Khagaria district have now started reuse of open wells in the arsenic exposed villages. This technique has not been so much popular due to its validity related to clean water. However, in the exposed population, who are having no option of safe water (arsenic free water) are utilizing this water for drinking purpose.

5. Rain water harvesting
   Rain water harvesting is the best way to conserve the natural water and reuse for the drinking as well as for the other purpose. But, this has not been very much popular in the state of Bihar.

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Current Scenario of Groundwater Arsenic Contamination in West Bengal and Its Mitigation Approach

8

Ranjit Kumar, Sunil Kumar, and Ashok Ghosh

Abstract

Arsenic is found in minerals of earth crust in variable concentration throughout different geographical concentration. Leaching of arsenic from earth crust cause groundwater arsenic contamination. It was found in variable organic and inorganic form known as arsenate and arsenite compounds. Groundwater arsenic concentration were very high in Ganga-Meghna and Brahmaputra plain, it was very high in Bangladesh. In 1983 the first report on groundwater arsenic contamination was highlighted. After that many research scientists worked there, but research findings of Dr. Dipankar Chakraborti and Dr. Guha Majumdar have significant contribution in awareness and detection of groundwater arsenic contamination in West Bengal. They have even highlighted effect of groundwater contamination on Public health of West Bengal. West Bengal is severely affected with arsenic contamination and now reports on crop contamination are alarming. According to 2006 reports only 6 districts are arsenic contaminated out of total 18 districts. While according to 2016 reports 9 districts were reported with high level of arsenic contamination in Bengal. Still it was found in new areas. Severe arsenic contaminated districts are Malda, Murshidabad, Nadia, Howrah, Bardhaman, Hoogley, North and South 24 Pargana. Severe health hazards were reported in these districts including skin pigmentation, arsenicosis, peripheral vascular disease, blackfoot disease, skin lesions, and cancer. Many types of mitigation approaches were practiced from last three decades in West Bengal including traditional methods of rainwater harvesting, dug well, deep tube well,

R. Kumar (✉) · S. Kumar
School of Life Sciences, Department of Animal Sciences (Zoology), Central University of Himachal Pradesh, Dharamshala, Kangra, Himachal Pradesh, India

A. Ghosh
Mahavir Cancer Institute and Research Centre, Patna, Bihar, India

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and surface water use, but all have limitations and not found very much suitable for rural household uses. Government of West Bengal supplies treated Ganga water in many villages as arsenic remedial measures. Government also puts some deep tube well below 150 m in many villages for providing safe drinking water to rural people at community level. These techniques are very costly and not feasible at household level. Many technologies were tried including oxidation method, coagulation-flocculation method, and adsorption techniques for removal of arsenic from groundwater but they also have some limitations. In current scenario adsorption techniques using oxy hydroxides and iron hydroxides dominate the current market in West Bengal. Use of biological arsenic removal techniques through microbes is advancing scope in development of future arsenic mitigation techniques.

Keywords

Dug well · Adsorption techniques · Coagulation–flocculation method · Leaching

8.1 Background on Arsenic

Arsenic (As) is common constituents in the earth's crust and it was found in variable concentration. Leaching of arsenic from rocks caused ground water arsenic contamination. Still definitive cause of increased level of arsenic in ground water is not well known. Arsenic is not very essential element required for human beings. Due to variable reactive state, living organism is more vulnerable to arsenic induced toxicity through groundwater and food. Now many research showed that arsenic contamination in agriculture products like pulses, cereals and vegetables. World Health Organization fixed 10 ppb as safe level of arsenic in drinking water, while safe level in human blood is less than 1 ppb. Arsenic toxicity is widely dependent on its different chemical form found in environment. Two major forms of arsenic are found in groundwater which include arsenate and arsenite. Arsenite is more toxic for organism in comparison to arsenate. In groundwater various forms of arsenic are found which include H_2AsO_3, H_3AsO_3, H_3AsO_4, $HAsO_3$, $HAsO_4$, and H_2AsO_4. The groundwater arsenic concentration varies in different geographical locations and confined to particular aquifer. Ore of arsenic like $HAsO_4$ and H_2AsO_4 are dominantly found in Korea and the USA, while H_3AsO_3, is more prominently found in several regions of Bangladesh and few districts of West Bengal in India (Saxena et al. 2004).

8.1.1 Chemistry of Arsenic Found in Ground Water

Arsenic are found in deprotonated or protonated oxyanions in groundwater known as arsenites (As^{III}) or arsenate (As^{V}) form. Arsenic compound exhibit variable level of toxicity, which depends on its different oxidative sate present in environment. Redox

state of arsenic and pH are very crucial in determination of arsenic toxicity. Toxicity of different organic combinations is also exhibiting variability. Since arsenite a trivalent form are most toxic form of arsenic, organo-arsine compounds are less toxic than arsine, while arsenate and its oxides are less toxic than organo-arsine compounds and arsenates are less toxic than arsenites. Arsonium metals and native arsenic metal are least toxic in nature (Sanyal et al. 2015). In aquatic conditions arsenites are very toxic, mobile, and soluble than arsenate. In oxidized environment at pH 6–8 both $H_2As^VO_4^-$ and $HAs^VO_4^{2-}$ ions are found in significant proportions, while under reduced conditions the arsenous acid, $H_3As^{III}O_3$, are found predominant in aquatic system (Sadiq 1997). Mobilization of arsenic in aquatic system causes reduction of compounds of arsenate into arsenite.

The organic forms of arsenic found in soil are cacodylic acid or dimethylarsinic acid (DMA), which are converted into trimethyl arsines on reduction in soil. Monomethylarsonic acids (MMA) are found in groundwater and soil. In aerobic oxidized environment at pH 6, arsenic acid and arsenate oxy-anions are mostly found in aquatic systems, while under reducing conditions like in flooded paddy soil the $H_3As^{III}O_3$, arsenous acid and arsenite oxyanion are predominant species. Soil with neutral pH contains more prevalent arsenic species in West Bengal and Bangladesh, which is due to the fact that trivalent arsenic exists in neutral conditions, it has uncharged molecule known as, arsenous acid and $H_3As^{III}O_3^0$, which are predominantly found in most natural groundwater and neutral soils according to the equation of Henderson's (Sanyal et al. 2015), it shows least retention capacity on charged surfaces of minerals in sediments and soils.

It would also known that soil or groundwater are facing affluxes, influxes and circulation due to excess withdrawal of ground water it would make an open thermodynamic system.

At high pH, the hydroxyl ion concentration increases leading to displacement of trivalent and pentavalent form of arsenic, which can bind with competitive ligand binding receptors. The natures of soil colloidal fraction are directly responsible for arsenic sorption through pH of the particular sorption medium. Increase in pH of media causes decreased arsenate adsorption and decrease in pH of media facilitates arsenic adsorption in groundwater and soil. Arsenic showed different gradient of electrostatic potential as well as variable-charge on soil colloidal media with increased solubility, pH, and arsenic salt buffering action (Majumdar and Sanyal 2003).

8.2 Groundwater Arsenic Contamination a Serious Issue Worldwide

Groundwater arsenic contamination due to natural or anthropogenic activities shows several social impact as well as health hazards in many countries of the world. Several millions of people residing in many countries are forced to take arsenic contaminated water because there is no alternate safe water source in these areas of world. Arsenic is mobilized in aquifers and groundwater leading to arsenic

contamination in water system due to hydraulic fracturing of arsenopyrite. Hence, groundwater arsenic contamination affects large number of people in different countries of world (Murcott 2012). Groundwater arsenic contamination are found in more than 70 countries in different concentrations which range from 0.5 to 5000 ppb based on finding of different research groups (Ravenscorft et al. 2009). In Bangladesh many severe cases of groundwater arsenic contamination were observed with severe health manifestations. Where provisional guidelines of WHO for arsenic in groundwater 10 ppb is changed to 50 ppb due to severe contamination in maximum areas. Since the groundwater arsenic contamination is widespread global phenomenon and few countries even set higher permissible limit due to existence of higher arsenic level than the set guideline value. The people using arsenic contaminated water for very long periods showed many types of health hazards in different parts of the world.

8.3 Groundwater Arsenic Contamination Scenario in India

Leaching of soil and agriculture runoff introduces arsenic in soil and groundwaters, weathering of rocks are also adding it. It would also be added in ground water through anthropogenic activities. Many factors like redox potential, precipitation, arsenic speciation, adsorption, pH, desorption, dissolution, and bio-transformation can control arsenic transport in groundwater. The arsenic speciation, pH, solid-phase dissolutions, adsorption and desorption reactions can vary in different aquifer, it depends on geo-chemical and geoenvironment condition of particular aquifer. Due to which there is need of detailed geochemical investigation of aquifer for revealing geochemistry of arsenic under different geo-environmental and hydro geological conditions of aquifers. The detailed investigation may be required to understand the problem and development of sustainable solution. In 1983 first case of arsenic contamination in groundwater were reported from West Bengal, then it were found in different states like Bihar, Jharkhand, Ganga river flood plain of Utter Pradesh; Manipur in river bed of Brahamaputra, Imphal, Assam and Chhattisgarh has explored as severe arsenic contaminated areas. People residing in these areas are exposed chronically to arsenic through consuming arsenic contaminated water from, bore well, tube well and hand pumps above 10 μg/L of permissible limit. Many regions of North Eastern States in flood area of different rivers has also considered with high groundwater arsenic contamination. After studies on every new arsenic-affected area, it would be reported that more villages and many more people are affected with arsenic related health hazards. Major arsenic-affected areas of India were covered by rivers originated from the great Himalayan region. In recent decades the problem of groundwater contamination with arsenic becomes complicated, and spreads to larger number of district where previously it was not reported, concentration of arsenic contamination are also increased in groundwater in India in the last few years. Groundwater arsenic does not only affects human being through drinking but it also enters into food through irrigated water, which caused different types of health hazards and affects socioeconomic dissolution in society.

8.3.1 Arsenic Contamination in Groundwater in Delta Basin of River Ganga

In the Indo-Gangetic plains arsenic level in groundwater was reported from 50 ppb to 1600 ppb in many areas of Bihar, Utter Pradesh, Assam, and West Bengal while many alluvial aquifers of Punjab are showing arsenic contamination from 4 ppb to 688 ppb in general. At many places arsenic level is found higher than Indian Standard for permissible arsenic limit of 50 ppb, which are considered Maximum Acceptable Limit (MAL) in Bangladesh, India, and several other countries (Sanyal et al. 2015) in contrast to WHO maximum permissible limit of 10 ppb in drinking water.

Guha Mazumdar in 1998 has well documented health effect of arsenic in adult who are regularly exposed to inorganic form of arsenic through water. The main focus was indented to find arsenic contamination in drinking water exclusively derived from groundwater. While in Ganga basin groundwater are exclusively used for crop irrigation, more than 90% of agriculture were found with elevated level of arsenic in agronomic food product. Several researches has illustrated arsenic uptake mechanism of agriculture crop which are grown in arsenic containing irrigated water and contaminated soil, it shows presence of arsenic in agriculture product (Sanyal et al. 2015). Such findings alerts us because maximum research group were focused on groundwater arsenic contamination, food contamination through agriculture crop is very challenging new area in arsenic toxicity on human being.

8.3.2 Current Scenario of Groundwater Arsenic Contamination in West Bengal

West Bengal was the first state in India reported with groundwater arsenic contamination in 1983 (Garai et al. 1984). Many states were also reported with high arsenic contamination after Bengal finding. Chakraborti et al. (2008) reported that not only West Bengal but other states of India are also chronically affected with arsenic contamination. Ganges-Brahmaputra-Meghna plain is currently most arsenic contaminated site in the world with concentration ranges up to >4000 μg/L (Rahman et al. 2006). During 1980s only few cased with arsenical dermatitis, arsenicosis and raindrop pigmentation were observed in two districts from the West Bengal (Chakraborti et al. 2008). West Bengal was the first arsenic endemic state in India, out of total 18 districts 9 districts were reported with high level of arsenic contaminated in groundwater. Arsenic detected in these 9 districts were very higher than the WHO's maximum permissible limit of 10 ppb (Mukherjee et al. 2003). In India the Ganga-Brahmaputra plains cover 7 states and the Padma-Meghna plains in west Bengal and Bangladesh together were the world's most widespread arsenic-affected area (Ghosh and Singh 2015). Groundwater is used as the primary drinking water source in rural area of West Bengal. Inorganic arsenic is not only reported in drinking water but it was found in raw rice as 93.8% as well as cooked rice as 88.1%

in the state (Halder et al. 2014). A epidemiological study done by Indian Institute of Hygiene and Public Health and School of Tropical Medicine in 1980s has described that arsenicosis is a major health crisis for public health around the whole world (GWB PHED 2014). The West Bengal State Government has currently estimated that almost 79 blocks in different districts of state are severely affected with arsenic contamination, which causing threat to 26 million people in state across 2600 villages (Paul et al. 2013).

The West Bengal has divided its arsenic contaminated districts into three zones, which are, respectively, severe zone, mild zone, and safe zone. There is overall 88,750 km^2 area which were identified as arsenic contaminated zone in West Bengal, out of which 38,861 km^2 areas were severely contaminated zones, which include North 24 parganas, South 24 parganas, Nadia, Murshidabad, and Kolkata (Chakraborti et al. 2009). Mobilizations of arsenic compound under natural conditions are responsible for hydrological arsenic contamination in environmental. Bhattacharya et al. (2007) reported that morphology of land, hydrology, geology and its land use pattern gives us better idea about arsenic contamination in particular area. Different types of geological and biological factors are guiding arsenic compounds release from soil sediment to groundwater. Irrigation of crops with arsenic contaminated groundwater causes high amount of food grain and agriculture product arsenic contaminated. In West Bengal majority of the agriculture products shows arsenic contamination due to irrigation of crop with contaminated waters (Christopher and Haque 2012). The arsenic uptake mechanism in different plants varies widely. Many plants easily uptake large quantities of arsenic as well as translocate the absorbed arsenic in plant tissues are known as hyperaccumulator. Many other plants showed low level of translocation known as excluders because it has developed restricted mechanism of arsenic translocations from roots hairs to shoots. Rice is an ideal example of arsenic translocation as can efficiently uptake the arsenic and accumulates more arsenic than wheat, barley, and cereals crop (Bhattacharya et al. 2009, 2012). In West Bengal majority of crop and vegetables can accumulate arsenic from irrigated water or soil and enters into human food chain leading to many health hazards in them.

West Bengal State Government has identified need for community-based piped water supply schemes development in different arsenic contaminated villages with single-point arsenic treatment facilities (PC GOI 2007). The WHO also supports comprehensive action plan for water testing, treatment, awareness-building campaigns in villages and development of arsenic mitigation options through the use of alternative water sources, which are microbiologically safe river, pond or surface water, and development of advanced arsenic removal technologies for these areas.

Planning Commission in 2007 has made a Task force, which has submitted their report on "Formulation of action plan for arsenic contamination removal in West Bengal", it identifies the use of alternate source of surface water and arsenic-free shallow dug wells as the best possible long-term remedies, with simultaneous contamination source identification and permanent sealing of these source for preventing future use. It was also found that only 2–3 arsenic removal plants are

functional out of the 12 arsenic removal units were installed and started in 2006 in Technology Park of Baruipur in West Bengal. The committee overwhelmingly recommended for adopting the household-level arsenic removal technology at the place where there is no alternative water supply system. While harvesting of rainwater were recommended as a very much viable and eco-friendly alternative at the places which are receiving abundant rainfall, artificial groundwater recharge is also a very novel approach for people of West Bengal. The report has given extra emphasis on generation of awareness and avoiding use of these contaminated drinking water for both drinking and cooking purposes.

Household-level awareness and educational interventions through the local media have been proven very much effective in community-based motivation for undertaking fee based testing of their water source for identifying alternative safe drinking water sources (George et al. 2013). Habitual use of arsenic-safe water use depends upon self-efficacy, instrumental attitude to find safe water options, attitude to find contaminated tube wells and vulnerability (Inauen et al. 2013). Thus, behaviour change is base for development of sustainable long-term intervention. Many research studies have identified that cooking rice in very low-arsenic-containing water (<10 μg/L) is a best way for risk-reduction strategy (Halder et al. 2014). Aerobic-flooded cultivation was found very effective in reduction of arsenic contamination risk of rice (Sun et al. 2014). These findings give us way to prepare new strategic plan to develop arsenic mitigation technology for risk reduction in West Bengal.

8.4 Health Effect of Arsenic Toxicity in Human

Arsenic contamination through food and groundwater leads to serious health hazards in many regions of world. It were very well established that trivalent arsenic is highly toxic than pentavalent arsenic, while inorganic arsenic shows high toxicity than organic forms of arsenic on health. However, different organic forms of arsenic species exhibit variable degrees of toxicity. The organic metabolic form like monomethylarsonic acid (MMAV) as well as dimethylarsinic acid (DMAV) are very least toxic than inorganic form, while monomethylarsonous acid (MMAIII) and dimethylarsinous acid (DMAIII) exhibit high toxicity level in comparison to inorganic arsenic. The toxic level of arsenic metabolite in increasing toxicity order are as follows; nitrate, MMAV, DMAV, Arsenite, MMAIII and DMAIII (Petrick et al. 2000) (Fig. 8.1).

8.4.1 Arsenic Uptake and Metabolism

Terrestrial environmental condition contains arsenic in inorganic form in pentavalent condition in aerobic and trivalent form under anaerobic environmental condition. Trivalent arsenic is found generally in neutral aqueous condition at neutral pH. The mode of toxicity expression of trivalent and pentavalent arsenic is different (Gailer

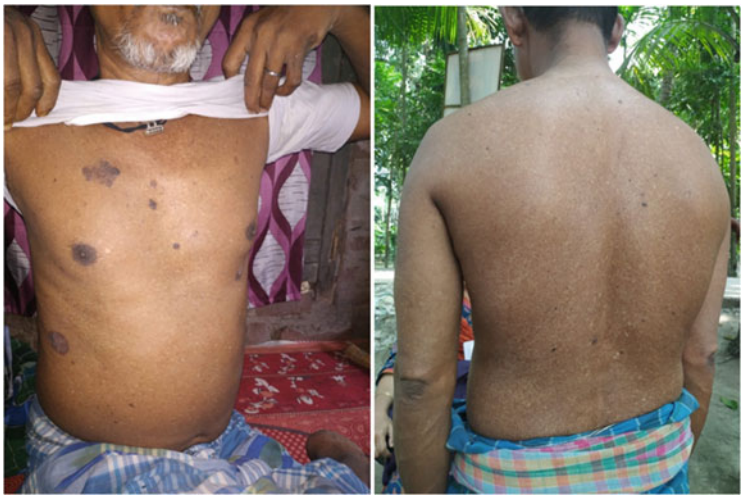

Fig. 8.1 Showing raindrop pigmentation and arsenicosis in back and front side of people residing in Deganga Block, North 24 Pargana, West Bengal

2007). Trivalent arsenic is transported into cells through aquaglyceroporins, because it possesses structural similarity to glycerol. Aquaglyceroporins is a pore protein responsible for transportation of small compounds like glycerol and urea (Liu et al. 2002). While pentavalent arsenic follows different pathways to express its toxicity in animals and human cells. Pentavalent arsenic was found as oxy anions in water like phosphate, they can use phosphate transporters for entry into cells (Huang and Lee 1996). After entry into the cells, pentavalent arsenic is suddenly reduced to trivalent arsenic. Therefore, trivalent arsenic undergoes multi-steps transformation through arsenite methyltransferase enzyme in cells and uses Sadenosylmethionine (SAM) as the methyl donor motifs, it results in formation of methylated arsenic compounds like MMAIII, MMAV, DMAIII, and DMAV (Kojima et al. 2009). A pathway of Arsenic methylation is first given by Challenger (1945). According to him methylation of arsenic involves many oxidation and reduction steps. Zakharyan and Aposhian (1999) observed that trivalent arsenic may be methylated without any enzyme in the presence of glutathione (GSH) and methylcobalamin. Many research studies described the role of different enzymes in methylation mechanism of arsenic.

Since DMAIII is an unstable compound, it directly oxidized to DMAV compound, pentavalent DMA is major metabolite of arsenic excreted from cells (Rehman and Naranmandura 2012). Naranmandura et al. (2006) described a unique arsenic metabolism pathway through formation of intermediate hepatic and renal metabolites, after experimentation on rats, which are intravenously administered with trivalent arsenic compound. They found that trivalent arsenic binds to proteins is metabolized by of step wise reductive methylation in presence of GSH and SAM and this metabolite is excreted outward. On chronic exposure of arsenic trivalent and

pentavalent organic compound, inorganic arsenic compound was observed in urine samples of exposed people (Devesa et al. 2004).

8.4.2 Toxicity of Arsenic

Arsenic toxicity in living organism like humans and animals were well documented in many research papers. Arsenic is also considered as a potent carcinogen, leading to many cancers including liver, lung, gall bladder, and skin (Yoshida et al. 2004; Tapio and Grosche 2006). Arsenic causes induction of epidemiological toxicity. Arsenic exposure caused the formation of excess ROS, which leads to degenerative changes in organisms (Wang et al. 2001; Shi et al. 2004a, b). Cytotoxicity (Zhang et al. 2003; Suzuki et al. 2007) and genotoxicity (Gentry et al. 2010; Benbrahim-Tallaa et al. 2005) was reported after prolonged arsenic exposure. Chronic exposure to arsenic compound through ingestion or inhalation can lead to skin pigmentation, arsenicosis, peripheral vascular disease, blackfoot disease, skin lesions, and cancers. While, many studies support that arsenicosis occurs due to prolonged exposure to elevated arsenic content (Sharma et al. 2006) (Figs. 8.2, 8.3, and 8.4).

8.4.3 Epidemiology

Now on the basis of different study it was observed that arsenic is potent carcinogen which induces carcinogenesis mechanism in many tissues especially skin and lung in human. Evidences suggest that arsenic causes hindrance in multiple gene proliferation processes of cell cycle, DNA damage, DNA repair, and differentiation process. Arsenic also distorts pathways of signal transduction through Nrf2-mediated

Fig. 8.2 Showing arsenicosis in palm of people residing in Deganga block, North 24 Pargana, West Bengal

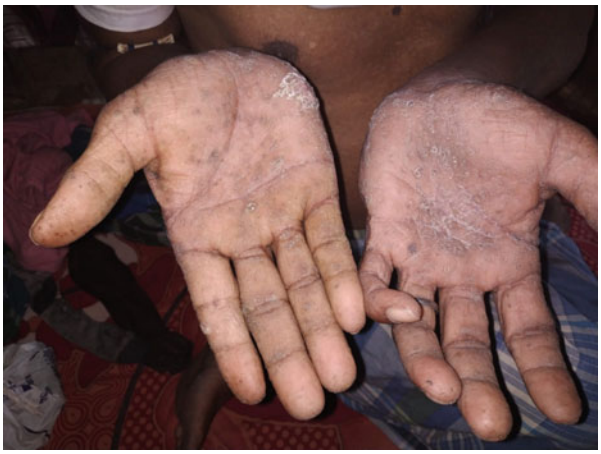

Fig. 8.3 Showing arsenicosis in both palm of people residing in Deganga block, North 24 Pargana, West Bengal

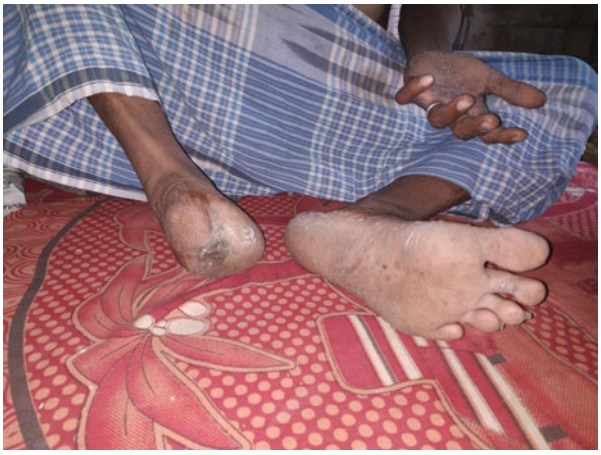

Fig. 8.4 Showing amputation of right leg due to arsenicosis related issues in people residing in Deganga block, North 24 Pargana, West Bengal

pathway, MAPK pathway, and protein signaling pathway (Wang et al. 2012; Sinha et al. 2013). Reactive oxygen species formation caused by arsenic may leads to cancer in human (Shi et al. 2004a). Many investigations suggests that methylation in arsenic metabolite are significant initiator of carcinogens. Wei et al. (2002) observed that DMA leads to urinary bladder cancer in animal model. It was known carcinogen, it exhibit many noncancerous multisystemic diseases, which includes hypertension, cardiovascular disease, dermal disease, and diabetes (Sharma et al. 2014; Centeno et al. 2002). Many research studies reported that trivalent arsenic like MMAIII, AsIII, and DMAIII would cause diabetes through glucose metabolism pathway distortion caused due to malfunctioning of pancreatic beta cells of mice (Douillet et al. 2013; Paul et al. 2007). Arsenic caused inhibition of α-ketoglutarate dehydrogenases and pyruvate is the principal cause of diabetes induction (Navas-Acien et al. 2006). Hypertension is always associated with many types of cardiovascular disease. There are many pathways which explain mechanism of arsenic-

induced hypertension. It also includes inflammatory activity promotion, endothelial cells dysfunction and blood vascular system alteration, which finally leads to malfunctioning of kidney (Abhyankar et al. 2012). Many research groups worked on detailed pathway of activation of reactive oxygen species and its role in arsenic-induced noncarcinogenic effects (Nesnow et al. 2002; Halliwell 2007). Arsenic-induced Reactive oxygen species are always associated with alteration in normal cell signaling pathways, increased cytokine production, apoptosis, and inflammation, it finally results in production of more Reactive oxygen species leading to mutagenesis, it is the key pathways in arsenic pathogenesis leading to different diseases (Eblin et al. 2006).

8.4.4 Cytotoxicity

Cytotoxicity is development of cellular anomalies due to toxic contaminants exposure. The mechanisms of arsenic-induced cytotoxicity in human cells through different pathways were studied by many researchers (Selvaraj et al. 2013; McKenzie et al. 2002). Arsenic causes Generation of reactive oxygen species which induces cellular cytotoxicity (Sies et al. 1992). Reactive oxygen species levels increase exponentially into cells when it is induced with arsenic toxicity. Arsenic causes Reactive oxygen species generation through activation of NADPH oxidase enzyme (Chou et al. 2004). Increased amount of Reactive oxygen species causes damage in proteins and lipids which adversely affect mitochondrial functions (Kim et al. 2002; Eun et al. 2007). Shen et al. (2001) observed that Reactive oxygen species causes oxidative stress in mitochondria which reduces apoptosis. It were also studied that Reactive oxygen species induces cytotoxic effects by causing activation in c-Jun N-terminal kinases activity (JNK), which is a member of mitogen-activated protein kinase, it directly controls many functions of cells including cell differentiation, apoptosis and cell proliferation (Shen and Liu 2006). Reactive oxygen species may act as modulator in signal transduction pathways; it finally affects different cellular processes includes cell adhesion, apoptosis, cell growth and HIV activation (Suzuki et al. 1997; Apel and Hert 2004). Arsenic causes suppression of tumor suppressor protein leading to cytotoxicity (Yih et al. 2000; Huang et al. 1999). Protein controls different cellular functions through controlling, regulations and controlling cell growth, cell cycle, DNA synthesis, cellular differentiation, DNA repair, and apoptosis (Ryan et al. 2001; Amundson et al. 1998). Yih and Lee (2000) observed that arsenic leads to accumulation of protein in fibroblasts cells of human, which leads to apoptosis by promoting translocation of Bax gene from cytosol to mitochondria, it also releases cytochrome c and activates caspase-9 through apoptosome and Apaf-1 (Kircelli et al. 2007; Bargonetti and Manfredi 2002). In addition, arsenic causes cell cycle arrest at G2 stage of interphase through activating the inhibitor of cyclin-dependent kinases (Vogelstein et al. 2000; Akay et al. 2004), and it leads to autophagy through damage-regulated autophagy modulator system (DRAM) (Crighton et al. 2006).

8.4.5 Genotoxicity

When any toxic exposure causes damage to nucleotide inside the cell is known as genotoxicity it finally caused mutation. Several research studies were conducted on genotoxic effect of arsenic (Valdiglesias et al. 2010; Lu et al. 1995). Arsenic also induces genotoxicity by generating Reactive oxygen species like observed in cytotoxicity (Hei et al. 2004). Reactive oxygen species when present in excess in cell, it reacts inside cellular machinery leading to genotoxicity. Genotoxicity were observed due to reaction of ROS with deoxyribose and bases of DNA, it leads to base pair lesions and DNA double strand breaks. Reactive oxygen species also caused alteration in mechanism of DNA repair, oxidation of DNA, gene stability, and gene regulation pathway (Ramana et al. 1998). Arsenic interacts with DNA zinc finger motifs proteins, which are crucial for proper transcription mechanism, DNA repair mechanism and it also facilitates protein–protein and DNA–protein ligand formation (Hartwig 2001). Zhou (2011) has observed that trivalent arsenic affects zinc fingers motifs which binds with PARP-1, which finally leads to DNA strand breaks and DNA damage (Ho 2004).

8.5 Current Mitigation Measures Used for Arsenic Mitigation in West Bengal

8.5.1 Deep Groundwater

It was studied through many studies that more arsenic contamination were found in the shallow groundwater, while deeper aquifers are free from arsenic contamination. According to British Geological survey data only 5% deep tube well below depth 150 m had more than 10 ppb and only 1% aquifer exceeds 50 ppb of arsenic concentrations (BGS 2001). Water supplied from deep tube wells would be the safe and best source. While the depth of these aquifer varies with geographical locations. The deep water extraction unit installation is very costly, due to which common people could not afford this; it may be applicability only on community basis. The common drawback of this mitigation option is availability of the arsenic-free aquifer in that region (Hoque et al. 2012).

8.5.2 Shallow Groundwater (Well Switching)

In shallow groundwater arsenic contamination varied widely. It may be persisting in different strips of villages many non contaminated area were seen in same village. The British Geological Survey (2001) in Bangladesh as well as Chakraborti et al. (2004) found that arsenic contamination proportion of tube well varies from 20% to 50% in Ganga-Meghna-Brahmaputra plain. It were most probable to find non-contaminated hand pump in adjacent nearby areas around contaminated source, well switching to non-contaminated shallow tube well is best option at that place.

Well switching to shallow hand pump was preferred method in West Bengal; it was practiced by almost 29% populations (Ahmed et al. 2006). The major drawback of this method is degree of the temporal and spatial variation in groundwater arsenic contamination in the same area. This makes it very difficult and nonpredictable for its long turn reliably. Many studies find that there is change in arsenic level in the tube wells with time, and it was found very high in monsoon season in comparison to winter season (Rahman et al. 2003; Rahman and Ishiga 2003). Due to which regular monitoring and persistent analysis is required to ensure that the hand pump would remain free from arsenic for longer time.

8.5.3 Dug Well Water

The open deep wells are known as dug well which contains arsenic free drinking water; it may also obtain water through shallow aquifers. Dug wells are preferred for getting safe drinking water and it was most used alternative water supply sources in West Bengal in early 1990 before deep tube well installation (Ahmed and Rahman 2003). Several researches showed that level of arsenic were very limited in dug wells and it was extremely lower than WHO limit (Warner et al. 2008; Bennett et al. 2010) due to oxidative environment and mineral precipitation as well as regular ground water recharge through rainwater (Hira-Smith et al. 2007). It was suggested for local people of West Bengal in 1990 to 2000 and it was preferred alternatives of safe drinking water due to less operational cost involvement and least maintenance cost (DPHE 2004). The dug well performance was evaluated in Bengal and found it suitable for implementation in society (Joya et al. 2006). But long tern observation suggests that tube wells were preferred than dug wells due to easily availability of water at house hold level by tube well (Milton et al. 2007). The dug wells become not very popular due to obnoxious taste, smell, turbidity, microbial contamination and distance as well as limitations for water fetches in particular time (Hoque et al. 2004). Microbial contamination were very commonly found in dug wells water. Drinking water must be treated before use, without appropriate treatment this causes many diseases including typhoid, cholera, dysentery, diarrhea, and hepatitis. Very high frequency of coliform contamination was found in dug wells, it was contaminated up to 94% in different season and were maximum in monsoon (Ahmed et al. 2005).

8.5.4 Surface Water

Rivers, lakes, pond generally contains very low arsenic, due to which water supply from these source would provide safe drinking water. Water from river Ganga is treated for microbial contamination and supplied in major arsenic contaminated area of West Bengal. Major arsenic-affected areas were found in close vicinity of different rivers, this river water can be served in nearby village population as mitigation approach for very long run over decades. The bacteriological

contamination adds major health risk associated with use of river, lakes and ponds water, microbial treatment plant must be needed at the point of water supply. This was main limiting factor due to which groundwater is not replaced by surface water. Introduction of surface water for drinking require proper treatment of microbe and sand filters were used as disinfectants source (Yokota et al. 2001) or complex treatment unit for surface water treatment. In West Bengal river Ganga water is treated and supplied in different districts near river Ganga. The sand filter use is also supported by National Policy for arsenic Mitigation in Bengal (DPHE 2004). More than 95% pond sand filters would found contaminated with microbes in monsoon season in comparison to summer season (Ahmed et al. 2005).

8.5.5 Rainwater Harvesting

Rainwater harvesting was used since historical time; it was widely applied method in whole world. It is very old method which utilizes rainwater for domestic use and drinking purpose (WHO 2011). It was widely used in water scars area at household and community level worldwide. It was also community accepted method for getting safe water. The rainwater harvesting method is safe method if water is stored hygienically; it is practical in areas where average rainfall exceeds 1600 mm per year (DPHE 2008). It is main drinking water source in coastal areas because water found in shallow and deep tube wells is containing high salinity there. Rainwater was stored there in very large tanks or pond (Islam et al. 2011) this practice may be feasible to arsenic contaminated regions. The major limitations of this method is high cost in building very large storage tank and roof for rainwater collection due to uneven precipitation of rainwater throughout year. Microbial contamination were also found in storage tank if not maintained properly is also a limiting factor (Karim 2010).

8.6 Advanced Arsenic Mitigation Approach Applied in West Bengal

Arsenic removal highly depends on chemical diversity and composition of arsenic in contaminated water. Arsenic was found in trivalent form in maximum reported cases, while oxidation of trivalent arsenic to pentavalent form is essential to obtain arsenic removals satisfactorily.

8.6.1 Oxidation

It converts soluble arsenite to arsenate, which is responsible for precipitation of arsenate. It was found in anoxic groundwater. Arsenite is the most common form found at neutral pH (Masscheleyn et al. 1991). Arsenate adsorbs very effectively on solid surfaces in comparison to arsenite. The process of oxidation and adsorption is

required for effective arsenic removal (Leupin and Hug 2005). Several external oxidants may be used for the oxidation process. The first order reaction kinetics were shown by H2O2, NH2Cl, O3, Cl2, and ferrate, in both arsenite and their oxidants. The arsenite concentrations and their oxidant level were the limiting factor for monitoring effectiveness of arsenic removal from aqueous solution. This was very rapid reaction for chlorine, ozone, and permanganate in comparison to chloramine and H_2O_2 which were utilized for the oxidation of arsenite to arsenate (Dodd et al. 2006). According to Bajpai and Chaudhuri (1999) ozone causes complete oxidation of arsenite to arsenate while pure air oxygen can oxidize it up to 54–57% in contaminated groundwater.

8.6.2 Coagulation-Flocculation

The introduction of coagulant and the floc formation is very effective method applied for groundwater arsenic removal. During coagulation process positively charged cationic coagulants decrease negatively charged colloids, results in formation of large particles due to particle aggregation (Choong et al. 2007). Due to polymeric bridge formation between particles the flocs are formed through the process of flocculation. Further agglomerate process were utilized for larger clustered particle formation. Soluble arsenic easily precipitated from flock and eliminated from water. Removal of arsenic from this type of flock requires iron and aluminum based coagulants (McNeill and Edwards 1995).

While large amount of sludge formation with arsenic is critical limitation factor in this process. Management of this contaminated sludge with arsenic is important for preventing secondary pollution of environment, due to which this method is not frequently applied in field.

8.6.3 Adsorption

Arsenic removal by adsorption is very popular method, it uses activated or coated surfaces and its operation system is very simple and sludge free. This technology may use many adsorbents, and it would be reused and regenerated, which makes this technology very common in present scenario (Mohan and Pittman 2007). Arsenic removal depends on pH and the arsenic speciation through adsorption techniques. It removes arsenate in better way as in comparison to arsenite at lower pH than neutral (Kanematsu et al. 2013). Grains of ferric hydroxide, ferrihydrite, and hydrated ferric oxide was more commonly used iron hydroxides and oxides used for removal of both arsenite and arsenate compound (Guan et al. 2008) (Figs. 8.5 and 8.6).

Groundwater contains high iron content caused major problems with aforesaid adsorption technology as it clogged to the filter membrane and reduces filter efficiency and lifetime (Bamwsp et al. 2001). Zero valent iron was used for removal of arsenic in field (Klas and Kirk 2013) and laboratory (Khan et al. 2000). Hussam and Munir (2007) observed that more than 350,000 zero valent iron filters are still

Fig. 8.5 Showing community level water filtration unit in Deganga, block, North 24 Pargana, West Bengal

functional in India, Nepal, Pakistan, Bangladesh and Egypt. Many studies showing effective removal of arsenic in field (Neumann et al. 2013). These filters require proper maintenance at regular intervals to prevent clogged on surface.

8.6.4 Latest Advancements in Arsenic Removal Through Adsorption Technology in West Bengal

Large numbers of materials were tested for their adsorption potential to arsenic but oxy hydroxides and iron oxides were the most reliable in present scenario, its

Fig. 8.6 Showing community level Arsenic removal unit by adsorption techniques in Deganga, block, North 24 Pargana, West Bengal

commercial products already in use for removal of arsenic and these are preferred over other technology. Iron oxy hydroxides were used in water treatment plant to prepare fixed bed pressure columns for providing mechanical resistant. Iron oxy hydroxides are cheap and easily produced, due to which it was popularly used in water treatment plant. .

The amorphous hydroxides structure provides its high affinity, high surface area values and high selective binding with the arsenate in groundwater at natural pH. Tresintsi et al. (2012) prepared many iron oxy hydroxides at pH 3–12 with the help of very low cost common salts of iron like $FeCl_2 \cdot H_2O$ and $FeSO_4 \cdot H_2O$. It serves as adsorbents of arsenic in high oxidative condition. Iron oxy hydroxides at acidic pH 4.0 are very effective arsenic adsorbent in oxidizing condition.

8.6.5 Biological Arsenic Removal Through Microbes

Arsenic geochemical cycling was highly dependent on bacterial activities through oxidation, reduction reactions, it also used in determination of its mobility and speciation (Smedley and Kinniburgh 2002). Reduction of arsenate compound and oxidation of arsenite are main mechanisms of detoxification induced by microorganism (Silver and Phung 2005). Microbe causing conversion of organic arsenic through anaerobic oxidation and changed it to arsenates. These are called arsenate respiring bacteria (ARD) or dissimilatory arsenate reducing bacteria such as *Geospirillum barnesi*, *Geospirillum arsenophilus*, *Bacillus arsenicoselenatis, Crysiogenes arsenatis*, and *Desulfotomaculum auripigmentum* (Oremland and Stolz 2005). These bacteria use pentavalent arsenic as acceptor of electron in respiratory chain process. Oxidation of trivalent arsenic is performed through many chemical such as H_2O_2, chlorine, potassium permanganate, ozone (Jekel 1994). Many chemical reagents used in treatment of groundwater are not supported

due to formation of undesirable end products like trihalomethanes (THMs) (Katsoyiannis et al. 2004).

Leptothrix ochracea and *Gallionella ferruginea* cause biological oxidation of iron, it would be very effective technology for selective removal of groundwater arsenic contamination. This enquires iron oxide coating on filter material with introduction of microorganisms. It provides favorable environment for adsorption and removal of arsenic from groundwater. Under optimum bacterial conditions, this trivalent arsenic was oxidized by bacteria leading to 95% arsenic removal even if arsenic level were more than 200 mg/L (Katsoyiannis and Zouboulis 2004). Arsenate was also removed by the same process leading to residual concentrations below 10 ppb. This technology was efficiently removing arsenic from groundwater and it has many advantages over classical physicochemical process of water treatment. Use of this technology avoids the chemical reagent use for removal of trivalent arsenic through oxidation; hence, it is an eco-friendly and economical method.

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Low-Cost Nanoparticles for Remediation of Arsenic Contaminated Water and Soils

9

Elsayed Elkhatib, Mohamed Moharem, Hala Hamadeen, and Mohamed Mesalem

Abstract

Arsenic is considered a threat to human and ecosystem due to its serious impacts on soil and water. Nanotechnology is a promising approach that offers significant opportunities to develop green, sturdy, and economic approaches for remediation of arsenic contaminated water and soil. Because nanomaterials possess high specific surface area and reactivity, its use in water treatment applications has shown great success in overcoming the restrictions of conventional treatment technology. The current chapter deals with the green, low-cost, and easily accessible nanosorbents that are used for arsenic removal from contaminated water such as green cellulose nanocrystals, iron oxides/hydroxide nanoparticles, green magnetic nanoparticles, biochar magnetic nanocomposites, and nanoparticles derived from industrial and agricultural wastes. Adsorption mechanisms responsible for arsenic removal by waste-based adsorbents have been discussed. The green synthesis of nanosorbents using natural and abundant bio-materials as well as surface modification and functionalization to overcome constraints associated with sorbents derived from waste materials is also discussed with respect to its potential for water remediation.

Keywords

Water pollution · Nanotechnology · Green nanomaterials · Industrial and agricultural wastes

E. Elkhatib (✉) · H. Hamadeen · M. Mesalem
Department of Soil and Water Sciences, Alexandria University, Alexandria, Egypt

M. Moharem
Regional Center for Food and Feed, Agricultural Research Center, Alexandria, Egypt

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9.1 Introduction

Arsenic, the 20th toxic element on earth, originates naturally and from anthropogenic activities as arsenate ($HAsO_4^{2-}$–As(V)) and arsenite (H_3AsO^3 –As(III)) species. Arsenic is classified as one of the seven heavy metals strongly diffusing through environment (USEPA 2001) that endangers ecosystem and human health due to its serious impacts on plant, soil, and water (Ng et al. 2003). The predominant As (V) species exist in soils and water under oxidized conditions as oxyanions of arsenic acid (H_3AsO_4, H_2AsO^{4-}, $HAsO_4^{2-}$ and AsO_4^{3-}) and have multiple practical applications, such as agricultural pesticides, wood preservatives, and semiconductor industries. Under saturated soil conditions or organic matter rich soils, arsenite exists in the form of arsenious acid (H_3AsO_3, H_2AsO^{3-}, $HAsO_3^{2-}$). Inorganic species like arsenate and arsenite undergo a series of methylation steps to form tri and pentavalent methylated metabolites of methylarsonite (MMA^{III}), methylarsonate (MMA^{V}), dimethylarsinite (DMA^{III}), and dimethylarsinate (DMA^{V}) (Table 9.1) (WHO 2001). In general, organic arsenic species are 100 times less toxic than inorganic arsenic species whereas As(III) is 60 times more toxic than As(V) (Jain and Ali 2000). Also, arsenite is more mobile than As (V) which refers to the difference in pK_a values for arsenic acid (H_3AsO_4) (2.3) and arsenous acid (H_3AsO_3) (9.3) (Yaghi and Hartikainen 2018).

Arsenic is introduced in the surface water and soils through natural and anthropogenic sources. It exists naturally in more than 200 mineral species and the most abundant is arsenopyrite (FeAsS). Arsenic is released into sediments and groundwater by natural weathering of arsenopyrite according to the following reaction (Jones 2007; Muloin and Dudas 2005):

$$4FeAsS(s) + 14O_2 + 16H_2O \rightarrow {}_4H_3AsO_4\,(aq) + 4Fe(OH)_3(s) + 8H^+ + 4SO_4^{2-}.$$

The main natural process responsible for arsenic distribution in environments are minerals dissolution, microbial activity, natural organic complexation, geothermal activities, wind-blown dust, and forest fires (Fang et al. 2018), whereas water and

Table 9.1 Some identified arsenic species in water[a]

Name	Abbreviation	Chemical formula	Molecular weight
Arsenic, trivalent			
Arsenous acid (arsenite)	As^{III}	$As(OH)_3$	125.94 g/mol
Monomethyl arsonous acid	MMA^{III}	$CH3As(OH)_2$	123.97 g/mol
Dimethylarsinous acid	DMA^{III}	$(CH3)_2AsOH$	122 g/mol
Arsenic, pentavalent			
Arsenic acid (arsenate)	As^{V}	$AsO(OH)_3$	141.94 g/mol
Monomethyl arsonic acid	MMA^{V}	$CH_3AsO(OH)_2$	139.97 g/mol
Dimethyl arsinic acid	DMA^{V}	$(CH3)_2AsO(OH)$	137.99 g/mol

[a]National Research Council (1999), Francesconi and Kuehnelt (2002)

arsenic contamination with As can result from human activities such as mining, metal industries, crop desiccation, and use of agricultural pesticides. These uses introduced a large cumulative quantity of anthropogenic derived arsenic causing a potentially hazardous environment and severe health problems for human (Hering et al. 2017; Bissen and Frimmel 2003; Smedley and Kinniburgh 2002; Pott et al. 2001). Sarkar and Paul (2016) reported that the annual quantity of As emission into the environment exceeds 60,000 tons (Fig. 9.1).

The contaminated drinking water and groundwater with arsenic are causing serious health problems to more than 150 million people worldwide such as cancer, hypertension, cardiovascular diseases, diabetes, blood vessels and nervous system diseases (Tondel et al. 1999; Abdul et al. 2015; Mohan and Pittman 2007). Diseases related to As contamination are causing great concern in many countries worldwide. Arsenic concentrations in surface and groundwater in the range from 50 to 3000 ppb are commonly found in Bangladesh, West Bengal, India, Pakistan, Argentina, Mexico, Chile, Nepal, Vietnam, and Taiwan and recently China (Bibi et al. 2015; Baig et al. 2009; Fatmi et al. 2009; Chowdhury et al. 2000). Around 50 million people in Bangladesh and India are still consuming arsenic contaminated water (Chakraborti et al. 2003, 2017; Chen et al. 2009).

The United States Environmental Protection Agency (USEPA 2001) and the public health service (Mohan and Pittman 2007) have developed series of standards to control As concentration in drinking water. The maximum concentration level (MCL) of As in drinking water allowed in the USA is 10 μg/L, and in Australia the MCL of As in drinking water is 7 μg/L (Smith and Smith 2004). Throughout the world, drinking water containing more than MCL of 10 μg As/L represents 3.6% whereas drinking water containing more than 20As μg As/L represents 5% (Samadder 2011). Lowering MCL of As in drinking water will force water suppliers to comply with the drinking water standard. Therefore arsenic contamination has become an issue of concern worldwide and that necessitates developing cost-effective yet efficient remediation technology (Qu et al. 2013; Shwe et al. 2012).

Recently, the use of nanomaterials in water remediation has shown great potential due to their high surface area-to-volume ratio, which greatly enhances their removal capability of As contaminant (Shak et al. 2018) as compared to bulk materials. Environmental Scientists demonstrated the successful and effective removal of different types of contaminants and bacteria (Elkhatib et al. 2015a, 2018; Leshuk et al. 2018; Song et al. 2018) with different kinds of nanomaterials derived from natural products and waste by-products. The nanomaterials mostly used as sorbents for water and soil remediation are based mainly on metals and metal oxides, cellulose, chitosan, active carbon and agricultural and industrial wastes. Therefore, this review article highlights the performance and the sorption behavior of such nanosorbents for the purpose of developing green and low-cost technologies for remediation of As contaminated water and soils.

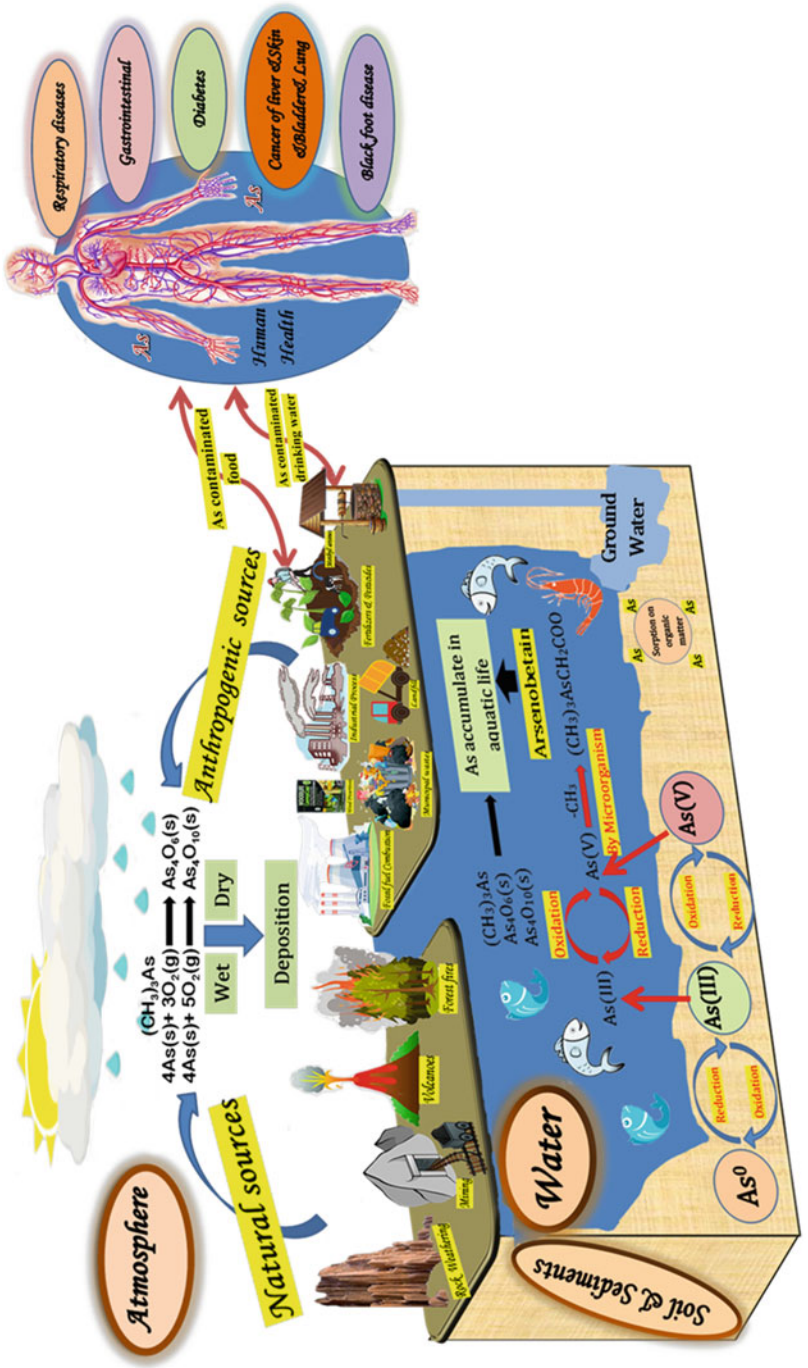


Fig. 9.1 Arsenic biogeochemical cycle in nature

9.2 The Adsorption Process

Contaminated environment with heavy metals is considered a major concern worldwide, since it has bad impacts on human health and can damage the ecosystem. Increasing industrial and agricultural activity causes heavy metals concentration to increase in various environmental elements such as soils and water (Wang et al. 2017a, b). High concentration of heavy metals including As in soil may cause these metals to reach growing plants and thus enter food chain (Caussy 2003; Liphadzi and Kirkham 2006). With respect to contaminated water, discharging of effluents carrying high concentration of As without sufficient treatment into water streams could deliver these toxic metals to humans through aquatic organisms intake (Ventura-Lima et al. 2011). Thus, it is imperious to employ suitable approaches to remediate As contaminated soils and wastewater.

The major technologies developed and commonly used for the treatment of As contaminated water and soil include oxidization, coagulation–flocculation (Bilici Baskan and Pala 2010; Mólgora et al. 2013; Yusoff et al. 2018, Khalid et al. 2017), membrane separation (Yoo 2018; Pal et al. 2014), ion exchange (Tresintsi et al. 2012), chemical extraction, electro-kinetics, phytoremediation (Wu et al. 2015; Li et al. 2019; Yang et al. 2019), and adsorption (Elkhatib et al. 2015b; Chammui et al. 2014) (Fig. 9.2). Among these techniques, adsorption process is considered the best and the most widely used technique for contaminants removal from water based on its safety, simplicity, easy to modify, easy to operate, reusability, low toxic sludge generation, and economic feasibility (Duru et al. 2016; Xiang et al. 2017; Li et al. 2018). Remediation technologies based on the use of natural materials derived from locally available waste by-products are considered ecofriendly, more accessible, and cost effective (Fig. 9.3). Therefore, low-cost, environment-friendly, and efficient green sorbents should be utilized for remediation of contaminated wastewater and soils (Moharem et al. 2019; Elkhatib et al. 2019). Adsorption process is defined as the movement of adsorbate from the solution towards the adsorbent surface and hereafter the surface-active site is gradually occupied by the adsorbate (Stumm 1992). Adsorption is occurred through physical and chemical bonds. Physical bonds involve van der Waals forces and outer sphere complexes while chemical bonds involve inner-sphere complexation, covalent/ionic bonding, and chelation reaction (Caporale and Violante 2016). The sorption process—in general—is influenced by multiple conditions such as sorbent capacity, sorbate concentration, pH, time, and temperature (Elkhatib et al. 2019; Scheckel and Sparks 2001). Recently, researches concerning the application of high adsorptive capacity materials in arsenic contaminated soils and water have become a magnificent attention. For instance, biochar magnetic nanocomposites (Tian et al. 2017), titanium dioxide nanoparticles (Qu et al. 2013), nanostructured waste derived from by-products of drinking water industry (Elkhatib et al. 2015b; Moharem et al. 2019), iron oxides-hydroxide (Fe_3O_4, hematite: α-Fe_2O_3 and maghemite γ-Fe_2O_3) nanoparticles (Feng et al. 2012; Wong et al. 2017), and nanoscale cellulose−cysteine fibers (Chen et al. (2019) have been examined. These materials, in general, can immobilize arsenic in soil by reducing metal mobility and

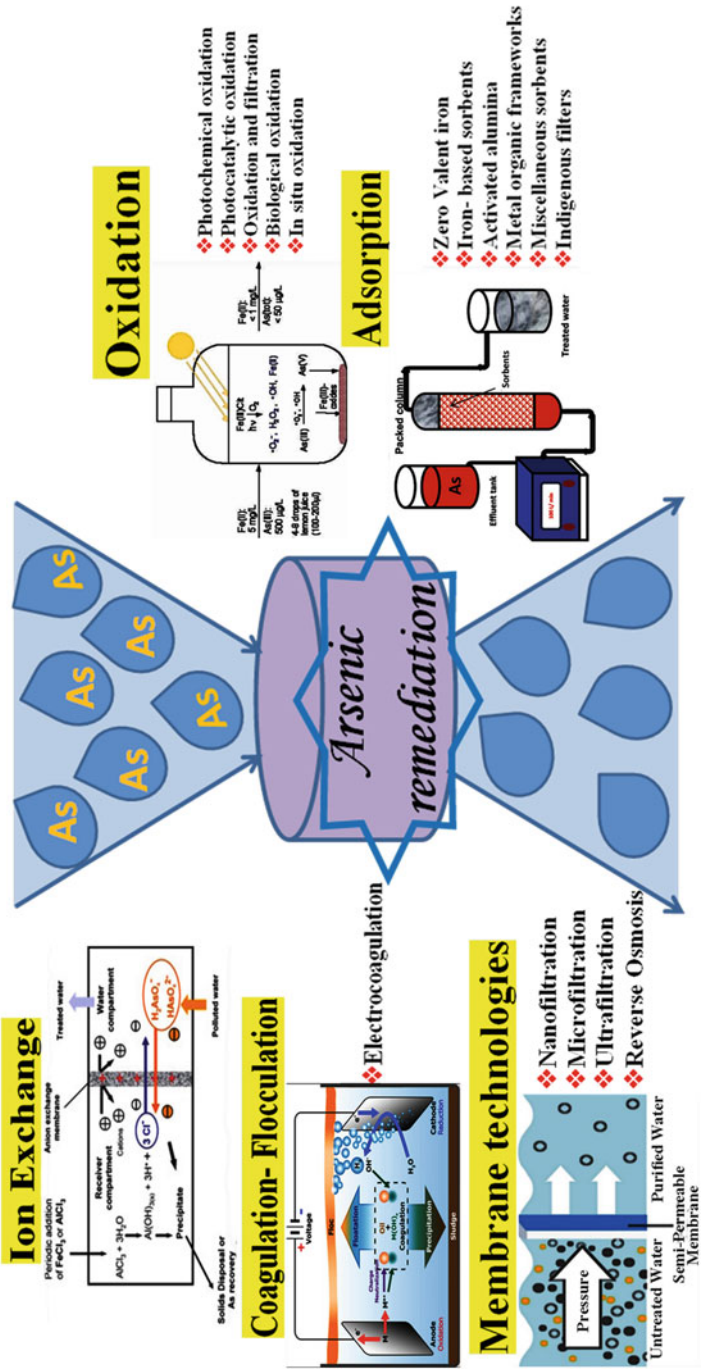


Fig. 9.2 The used technology for remediation of As contaminated soil and water

Fig. 9.3 Selection criteria of arsenic remediation technology

bioavailability due to binding of the metal with sorbents-functional groups (Basta et al. 2005). Similarly, sorbent materials can scavenge arsenic into aqueous solution and hence efficiently remove the toxic metal from wastewater (Almomani et al. 2020; Es-sahbany et al. 2019).

9.3 Low-Cost Nanomaterials for Environmental Remediation

9.3.1 Nanocellulose

Cellulose is a biodegradable, renewable, non-toxic, and the most abundant organic compound in nature and easily obtained in great quantities at low cost. Around 33% of annual plants, 50% of wood and 90% of cotton are cellulose which is composed of 44–45% carbon, 6–6.5% hydrogen, and 50% oxygen (Klemm et al. 2005; Tian et al. 2011). Recently researchers have produced nanosized cellulosic materials using different chemical and mechanical methods. These materials are classified into cellulose nanocrystals (CNCs) and cellulose nanofibers (CNFs) (Barbash and Yashchenko 2020). The CNCs look like short needles with nanoscale diameter and length in 100–500 nm range, whereas CNFs are long nanofibers having micro dimension length and nano-dimension diameter (Fig. 9.4). CNFs can be

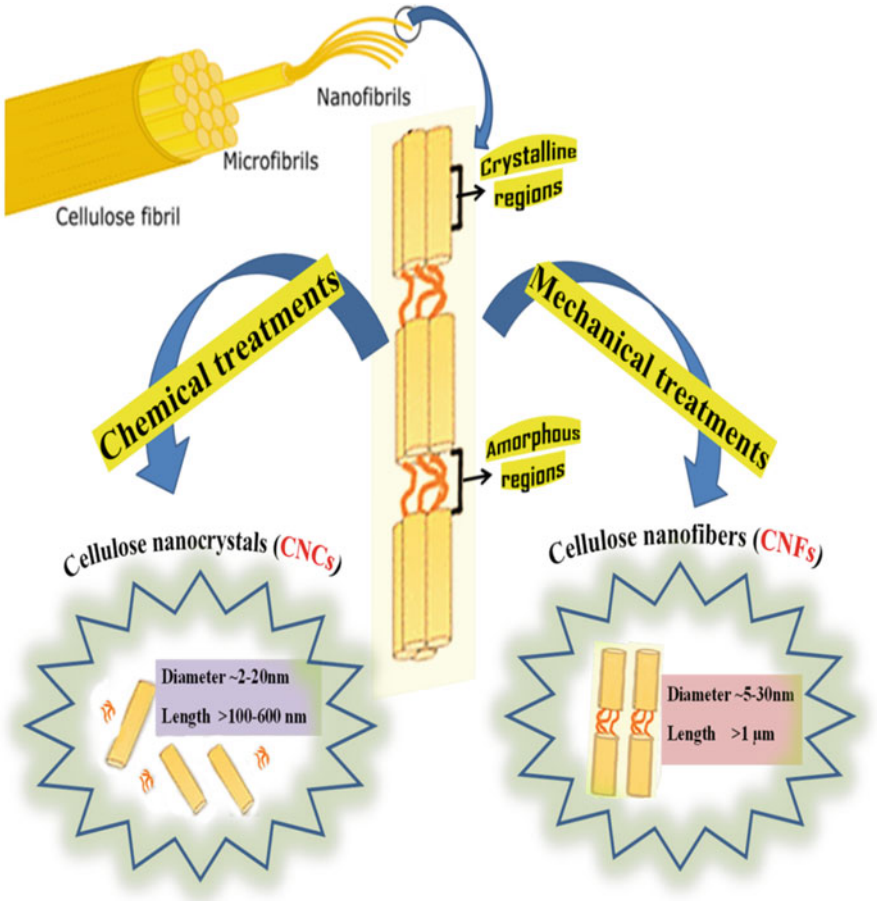


Fig. 9.4 Morphological structure and production of cellulose nanocrystals and cellulose nanofibers

manufactured by various processes like grinding, homogenization, steam explosion, whereas CNCs can be formulated by using strong acid like sulfuric acid to destroy all the amorphous portion and lead to the nanocrystal structure. The cellulose source and extraction conditions generally determine the CNCs dimensions and crystallinity (Abdul Khalil et al. 2014; Nechyporchuk et al. 2016).

9.3.1.1 Green Technology for Production of Cellulose Nanocrystals (CNCs) and Nanofibers

High energy ball milling is a green and efficient technique that can be used to manufacture nanocellulose through mechano-chemical process. Generally, CNCs are produced from natural fibers and require the following: (1) reduction of size using ball milling; (2) chemical treatment (acid hydrolysis) to release CNCs; and (3) ultrasound treatment (Gorrasi and Sorrentino 2015). Application of ball milling

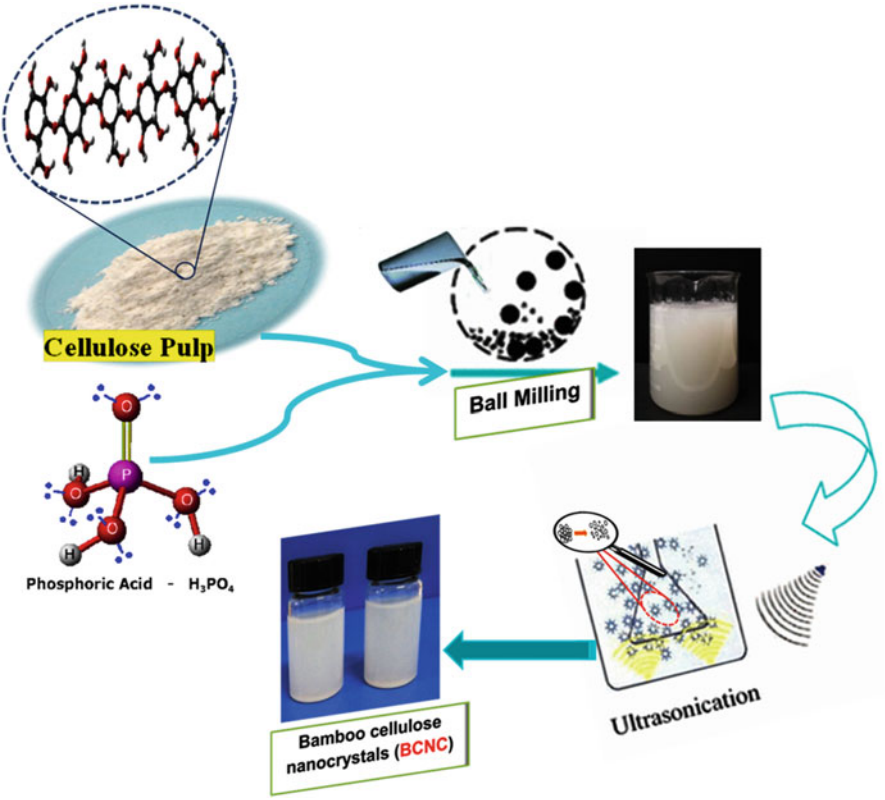


Fig. 9.5 Production of bamboo cellulose nanocrystals using ball milling

for the production of CNCs is an easy-to-use, economic, and ecofriendly technique which allows avoiding organic solvents (Lu et al. 2015, 2016). It has been used efficiently to produce bamboo cellulose nanocrystals (BCNC) with the dissolving effect of phosphoric acid. The resulting BCNC are rod-shaped particles with 100–200 nm length and 15–30 nm width (Fig. 9.5). Similarly, sphere-shaped CNCs were also produced from cotton linters using precision milling for 24 h at 1000 rpm, freeze drying and then hydrolyzed by using sulfuric acid or hydrochloric acid (Yang et al. 2013).

Zhang et al. (2010) have employed the green mechano-chemical technique to produce NFCs from wood pulp. They first pretreated the dried wood pulp with water and phosphoric acid to loosen the fibers, then the resulting fibers were milled in aqueous medium for 2 h and the average diameter of NFCs produced was 32 nm. Acid- and alkaline-assisted ball milling pretreatments of raw materials were also described by many investigators (Harini et al. 2018; Rajinipriya et al. 2018; Huang et al. 2016). Nowadays, nanocellulose materials are gaining exceptional attraction from biomedical engineering and surface chemistry owing to its renewable nature,

excellent mechanical and thermal properties, tailorable surface chemistry, high aspect ratio, bio-degradability, and biocompatibility. On ground of these superior material properties, huge market for nanocellulose as a renewable and sustainable material for broad applications in our daily life is anticipated.

9.3.1.2 Nanocellulose-Based Adsorbents

The use of nanocellulose as a new nanosorbent derived from natural and abundant resources for environmental remediation has attracted much attention lately. Nanocellulose is considered an excellent natural adsorbent for wastewater treatment due to its large surface area, high reactivity and availability of several functional groups (Nath et al. 2016). Mishra et al. (2018) reported that the adsorption capacity of nanocellulose-based adsorbents could be improved through surface functionalization to enhance removal of specific contaminants. In addition, the broad availability of nanocelluloses in low cost along with their capability for physical and chemically modification makes CNCs excellent candidates to form polymer-based nanocomposites. Pretreatments and functional modifications have proven to enhance the adsorption capacity of the cellulose biopolymer.

More research is needed to devise means of employing cellulose-based materials for large-scale removal of various contaminants including As from wastewater. Chen et al. (2019) produced nanostructured dialdehyde cellulose−cysteine fibers, have been prepared from wood pulp and determined its As(III) removal efficiencies and mechanism. The maximum adsorption capacity of the nanostructured dialdehyde based cellulose fiber for As(III) was estimated using Langmuir model and found to be 357.14 mg/g. The X-ray diffraction and thermogravimetric analysis revealed that thiol group on cysteine was responsible for the adsorption process.

9.3.2 Iron Oxides/Hydroxides Nanoparticle

Iron oxides-hydroxide (i.e., magnetite; Fe_3O_4, hematite:α-Fe_2O_3, maghemite;-γ-Fe_2O_3 and FeOOH) nanoparticles are efficient sorbents for As removal due to its high reactivity, surface charge, non-toxic nature, together with stability and low cost (Feng et al. 2012; Wong et al. 2016). Iron oxide minerals are considered low-cost sorbent for household water treatment. In addition, magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) nanoparticles are easy to handle and to recover in water systems due to their magnetic character.

Prathna et al. (2018) determined the maximum sorption capacity of the iron oxide nanoparticles for As(III) and As(V) at pH 7 using Langmuir model and found to be 909 and 3333 μg/g, respectively, which indicated that the synthesized iron oxide nanoparticles could be used efficiently for As removal in small-scale water systems. Feng et al. (2012) tested the nanosized superparamagnetic ascorbic acid-coated Fe_3O_4 as adsorbent for As removal from wastewater. The adsorption data were well fitted to Langmuir model and the maximum adsorption capacities of the sorbent were 16.56 mg/g and 46.06 mg/g for As(V) and As (III), respectively. The efficiency of oleic acid-coated Fe_3O_4 nanoparticles for As removal was examined for various

Table 9.2 Arsenic adsorption capacity of magnetic nanoparticles and magnetic nanoparticles modified

Adsorbent	Adsorption capacity (mgg^{-1})		Reference
	As (III)	As (V)	
Green nano iron particle—mint leaves	–	94.47	Prasad et al. (2014)
nZVIn	–	239	Li et al. (2014)
Magnetite nanoparticles	8.0	8.08	Roy et al. (2013)
Nanocrystalline magnetite	3.65	–	Bujnáková et al. (2013)
Magnetite particle size, at			
300 nm 20 nm 11.72 nm	1.56 29.5 114.9	1.08 11.4 46.72	Yean and Cong (2005)
γ-Fe_2O_3 nanoparticles	67.02	–	Dave and Chopda (2014)
Fe_3O_4 nanoparticles	46.06	16.56	Feng et al. (2012)
Fe_2O_3 nanoparticles	20.0	4.9	Luther et al. (2012)
Iron oxide/alumina nanocomposites	1.000	2.500	Prathna et al. (2018)
Chitosan modified iron oxide nanocomposite	267.2	–	Gerard et al. (2016)
magnetite-loaded amino modified nano/microcellulose composite NC-MA/L-MG	–	85.3	Taleb et al. (2019)
Ascorbic acid-coated Fe_3O_4 nanoparticle	–	16.56	Feng et al. (2012)
Fe-hydrotalcite supported magnetite nanoparticle	–	0.105	Türk and Alp (2014)
Iron oxide nanoparticles— *D. radiodurans* strains	–	131.5	Kim et al. (2019)

sizes in the range of 12–300 nm and the results ascertained increases in the adsorption capacities of the nanosorbents with decreasing nanoparticles dimensions due to the increase in specific surface area (Yavuz et al. 2006).

Various methods are used to produce magnetic nanoparticles including hydrothermal synthesis, sol-gel process, and co-precipitation (Tuutijärvi et al. 2009; Haw et al. 2010; Lin et al. 2012). However, these methods are energy consuming, use toxic chemicals, and generate hazardous by-products. Thus, a green, ecofriendly, low-cost, and efficient method has been introduced to synthesize magnetic nanoparticles in a one-step process using plant extracts (Nikic et al. 2019). The adsorption capacity of magnetite nanoparticles synthesized with a conventional chemical process was much lower than that of magnetite nanoparticles synthesized with the green approach using mint leaves extract (Table 9.2). The As adsorption

data clearly indicate that the green synthesis is an inexpensive, efficient, and a promising alternative for the treatment of arsenic contaminated water.

9.3.3 Green Synthesized Nanoparticles

9.3.3.1 Green Synthesized Magnetic Nanoparticles

Plant extracts contain natural sources of phytochemicals, proteins, enzymes, polysaccharides, and alcoholic compounds that can be used for synthesis of green nanoparticles to reduce sorbents production costs. Recently, green low-cost methods were developed to synthesize magnetic nanoparticles using onion peel (OP) extracts and corn silk (CS) for remediation of As contaminated wastewater (Fig. 9.6) (Niki et al. 2019). The specific surface areas of magnetic nanoparticles produced using OP and CS extracts exhibit much higher specific surfaces (243–261 m^2/g) than that produced using chemical method (72.1 m^2/g). The calculated maximum adsorption capacity (q_{max}) of magnetic nanoparticles produced using OP, Cs extracts, and chemical method are 1.86, 2.79, and 1.30 mg/g, respectively (Table 9.3). As we can see, the use of plant extracts to produce magnetic nanoparticles has proven to be

Fig. 9.6 Synthesis of green magnetic nanoparticles

Table 9.3 Maximum arsenic adsorption capacities of non-green and green magnetic nanoparticles synthesized with different extracts

Adsorbent	Adsorption capacity (mg g^{-1})		Reference
	As (III)	As (V)	
Magnetic nanoparticles—onion peel	1.86	–	Nikic et al. (2019)
Magnetic nanoparticles—corn silk	239	–	Nikic et al. (2019)
Non-green magnetic nanoparticles	1.30	–	Nikic et al. (2019)
nZVI—mulberry	1999	–	Poguberovic et al. (2016)
nZVI—oak	877	–	Poguberovic et al. (2016)
nZVI—cherry	1047	–	Poguberovic et al. (2016)
Fe_2O_3-nanoparticles Aloe vera	8.475	–	Mukherjee et al. (2016)
Magnetic Fe_3O_4 nanoparticle—tea waste	–	158.8	Lunge et al. (2014)
nZVI—blueberries	–	52.23	Manquian-Cerda et al. (2017)
Iron oxide nanoparticles on chitosan beads—eucalyptus	–	0.175	Martınez-Cabanas et al. (2016)
α-Fe_2O_3 nanoparticles—banana peel	–	2.715	Majumder et al. (2019)
Iron nano particles—Teucrium polium herb	61.7	–	Karimi et al. (2019)

cost-effective, ecofriendly, and sustainable (Pathan and Bose 2018; Nikic et al. 2019).

9.3.3.2 Green Synthesized Zero-Valent Iron Nanoparticles

Nanoparticles of zero-valent iron (nZVI) have great capabilities to adsorb various organic and inorganic aqueous contaminants due to their high adsorption capacity and reaction activity. However, nZVI produced via chemical synthesis, presents several limitations such as high cost and high tendency to agglomerate during the process (Chrysochoou et al. 2012; Kanel and Choi 2017). To avoid such limitations, use of natural product extracts having high antioxidant contents such as tree leaves, fruits, etc. is recommended (Chrysochoou et al. 2012; Abbassi et al. 2013; Weng et al. 2013; Machado et al. 2013). Green nZVI were successfully synthesized using the leaves of oak (OA), mulberry (ML), or cherry (CH) tress grown in gardens of Serbia. The leaves were collected, milled using a chopper, sieved to 2 mm and dried (50 °C for 48 h). The sieved dried leaves (3.7 g) were water extracted by shaking the mixture (sieved dried leaves and water) for 20 and 60 min at 80 °C for oak, cherry leaves and mulberry leaves, respectively, then filtered with Buchner funnel. A solution of 0.1 M Fe(III) was added to leaves extract in a 3:1 volume ratio to produce nZVI (Machado et al. 2013; Poguberovic et al. 2016). The adsorption capacity data for As(III) revealed that ML-nZVI is the highest in comparison with OA- nZVI and CH- nZVI sorbents (Table 9.3). The green method offers multiple advantages including the use of inexpensive, non-toxic, ecofriendly agents and valorization of natural products.

9.3.4 Titanium Dioxide Nanoparticles

Nanosized titanium dioxide (TiO_2) is widely used for the remediation of As contaminated water due to its high affinity to arsenic, low-cost, ecofriendly, strong oxidizing capability, and resistance to corrosion (Gupta et al. 2011; Mohammadi et al. 2011; Guan et al. 2012; Deedar and Aslam 2009). Macroscopic investigations on As(V) sorption have shown that amorphous TiO_2 nanoparticles have larger sorption capacities in comparison with the crystalline polymorphs due to the relatively larger surface area of nanoparticles. Jegadeesan et al. (2010) and Jing et al. (2009) reported that As (V) and As(III) formed binuclear bidentate inner-sphere complexes on the surface of amorphous TiO_2 at neutral pH. Experimental adsorption isotherm data for single and multi-metal adsorption by TiO_2 nanoparticles revealed that Langmuir model was the best model that fits the As sorption data very well which indicates a monolayer adsorption coverage on the surface of the TiO_2 nanoparticles with no interaction between sorbate molecules. The calculated maximum adsorption capacity of TiO_2 nanoparticles is much higher than that of TiO_2 bulk particles (Pena et al. 2006; Qu et al. 2013). The results of the aforementioned adsorption experiments suggest the potential of using Tio_2 nanoparticles as efficient sorbent for As removal from contaminated water due to its low-cost, high affinity for As, stability, and environmentally-friendly (Deedar and Aslam 2009). However, TiO_2 nanoparticles have some limitations as they tend to agglomerate into larger aggregates and that could be overcome through nanocomposites formation or metal oxides coating. Lee et al. (2015) employed Ti-loaded basic yttrium carbonate (Ti-loaded BYC) for arsenate removal from contaminated water. They reported the high adsorption capacity of Ti-loaded BYC for As(V) (Table 9.4) and suggested the applicability of Ti-BYC in As removal for long time adsorption process.

9.3.5 Nanosized Biochar

Biochar is the solid, carbon-rich material obtained by pyrolysis and it is considered a solution to the potential global problems such as greenhouse gas emission and environmental pollution (Creamer and Gao 2016; Xiong et al. 2019; Yoo et al. 2018; Yang et al. 2019). Because biochar is abundant, cheap, ecofriendly, and possesses large surface area and diverse function groups, it is potentially suggested to be largely used as a cheap sorbent to remove various contaminants from contaminated surface water and groundwater (Yang et al. 2018; Sun et al. 2019; Zhang et al. 2019a; Ahmed et al. 2018; Palansooriya et al. 2020; Xiang et al. 2020). However, insufficient porosity, moderate surface area, and catalytic performance may limit the biochar efficiency in water and soil remediation (Li et al. 2019). To overcome such limitations, using inexpensive and reproducible procedure such as ball milling could produce low-cost novel nanosized-biochar sorbents with enhanced functional characteristics for ecofriendly applications (Wang et al. 2019; Li et al. 2020; Fan et al. 2016). It has been proven the successful role of precision milling technology in particle size reduction, surface area improvement, functional groups

Table 9.4 Comparison of titanium dioxide nanoparticles; hybrid titania nanostructures and metal/metal oxide—titania nanocomposites for As removal

Adsorbent	Adsorption capacity (mg g^{-1})		Reference
	As (III)	As (V)	
Ti-loaded basic yttrium carbonate	–	348.5	Lee et al. (2015)
Titania nanotubes; Fe-TNTs	–	80.67	Wang et al. (2015)
Ce-Ti oxide (100–200 nm)	6.8	7.5	Deng et al. (2010)
Iron, titania/silica modified with zinc	7.0	–	Sadeghi et al. (2016)
Graphene oxide supported mesoporous Fe_2O_3/TiO_2 nanoparticles	7.0	6.0	Babu et al. (2016)
TiO_2 pillared montmorillonite	4.58	4.86	Li et al. (2012)
Protonated titanate nanotubes	7.0	3.0	Niu et al. (2009)
Titanium dioxide-coated carbon nanotube	1.8	1.13	Liu et al. (2014)
Zr-Ti oxide	28.6	–	Iven et al. (2016)
Hydrous titanium dioxide nanoparticles	83.0	–	Liu et al. (2012)

enrichment, and catalytic enhancement (Elkhatib et al. 2015a, 2019, 2020; Shan et al. 2016; Fan et al. 2016; Lyu et al. 2018, 2020; Naghdi et al. 2017; Wang et al. 2019; Li et al. 2020). Since nanostructured biochar is considered a better efficient sorbent than traditional biochar, carbon-based nanomaterials are currently used for arsenic and heavy metals removal from contaminated wastewater (Sadegh et al. 2016).

9.3.5.1 Biochar Magnetic Nanocomposites

Nanostructured iron materials exhibited higher removal efficiency of As from contaminated water attributable to the relatively larger surface area to volume ratio and multiple active sites compared with bulk iron materials (Saif et al. 2014; Tian et al. 2017). Therefore, a new high-efficient and low-cost biochar magnetic nanocomposite sorbent has been developed through pyrolysis process of impregnated palm waste with Fe^{+2}/Fe^{+3} for As removal from contaminated water and soil (Fig. 9.7) (Cui et al. 2019). The efficiency of biochar magnetic nanocomposite for As (III) removal from water was evaluated via adsorption isotherms (Cui et al. 2019). The adsorption data revealed the higher maximum adsorption capacity of biochar magnetic nanocomposite for As (III) (16.23 mg g^{-1}) at different pH values compared to the maximum adsorption capacity of raw biochar (2 mg g^{-1}). It is clear that incorporating iron nanoparticles into biochar has significantly promoted As (III) removal efficiency (Hu et al. 2015; Cui et al. 2019). Sun et al. (2019) investigated the impact of the Fe/Biochar mass ratio on the capability of biochar magnetic nanocomposites to remove As (V) from contaminated water. They indicated that the nanocomposites exhibited significantly

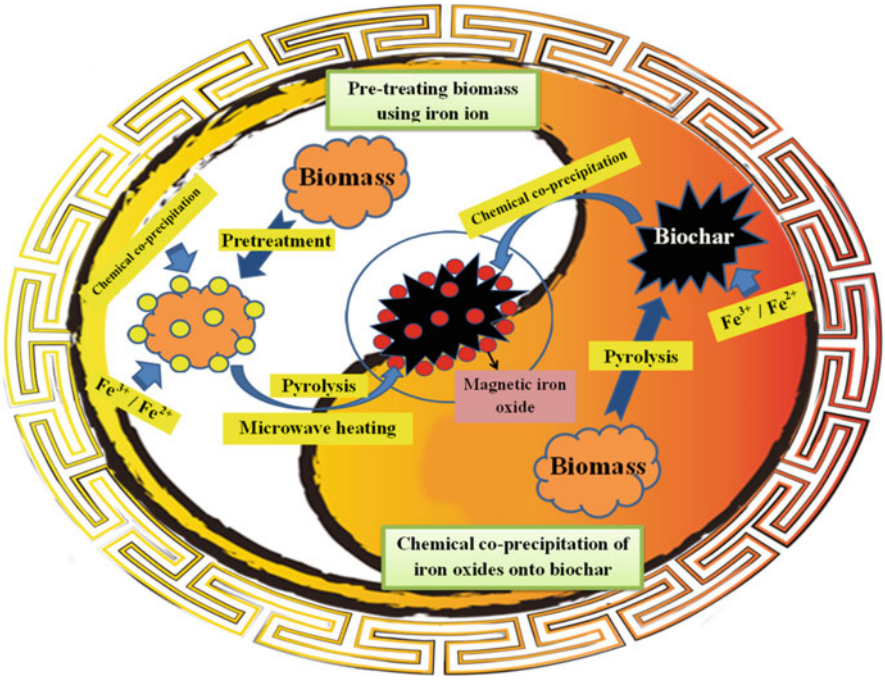


Fig. 9.7 Biochar magnetic nanocomposite

higher As (V) removal capability (65.9–77.7%) compared to raw biochar (55.6%) and increased with increasing of the Fe content.

A higher Fe impregnation ratio (1:1) promoted AsO_4^{3-} (44.4–52.6%) formation with a lower proportion of $HAsO4^{2-}$ (23.5–24.7%). Increasing Fe-biochar ratio (2:1) has caused $H_2AsO_4^-$ to completely develop into AsO_4^{3-} (80.7%) which suggested Fe–O–As(V) complex formation as the primary mechanism of As (V) adsorption (Bakshi et al. 2018; Zhang et al. 2019a).

Magnetization of biochar by Fe_3O_4 nanoparticles has proven to increase the biochar capabilities of remediating As contaminated water (Table 9.3) (Karunanayake et al. 2017, 2019). Alchouron et al. (2020) have assessed the As (V) removal efficiency of raw biochar (B), activated biochar (BA), raw biochar covered with Fe_3O_4nanoparticle (B-Fe), and BA covered with Fe_3O_4 nanoparticles (BA-Fe). The results revealed that sorption equilibrium for As was achieved within 2 h and biochar activation with KOH increased the surface area of B from 6.7 m^2/g to 1239.7 m^2/g (BA). The highest maximum adsorption capacity of the four sorbents studied were the sorbents covered with Fe_3O_4 nanoparticles (B-Fe = 90 mg/g and BA-Fe = 85 mg/g).

9.3.6 Nanoparticles of Industrial Waste

Several reports concerning arsenic and heavy metals immobilization/removal from contaminated water and soils using mining and industrial waste/by-product based adsorbents have been published. These adsorbents include steel manufacturing waste (Chakraborty et al. 2014; Oh et al. 2012), nitrogen fertilizer industry waste (Elkhatib et al. 2020), magnesia-loaded fly ash (Li et al. 2012), fly ash (Blissett and Rowson 2012), sulfuric acid Acidified Laterite (ALS), a by-product produced through ferric aluminum sulfate (FAS) production (Glocheux et al. 2013), akhtenskite (ε-MnO2), coated waste goethite (Shih et al. 2015), copper slag coated by silica gel (Li et al. 2020), plastic waste char (Miandad et al. 2017), and Fe-Mn dual oxide waste (McCann et al. 2018).

The environmental-friendly approach of using the abundant and cheap industrial by-product materials for removal of contaminants from water has become more popular in recent years due to its advantages, such as cost-effective, efficient, low maintenance, and waste valorization (Elkhatib et al. 2019).

Drinking Water Treatment Residual (WTRs), by-products of drinking water industry, has been studied as a promising sorbent for remediation of contaminated water and soil due to its amorphous nature and high sorption affinity toward heavy metals including arsenic. The potential use of bulk DWTRs as efficient cost-effective sorbent for As, Ni, Cu, Cd, and Pb has been reported by many researchers (Sarkar et al. 2007; Elkhatib et al. 2013, 2015b; Elkhatib and Moharem 2015). However, several studies reported that the specific surface area and reactivity of DWTRs are greatly influenced by the size of the particles, decreasing the particle size greatly increases the adsorption capacity and reactivity of DWTRs (Caporale et al. 2016; Elkhatib et al. 2015a). Recently, Elkhatib et al. (2015a) produced a novel nanosorbent derived from by-products of water industry for efficient remediation of contaminated soil and water using precision milling. Briefly, the bulk DWTR was collected from the DWT facilities that use aluminum sulfate for flocculation, air dried, crushed, and passed through 2 mm (m DWTR) and 51 μm (μDWTR) sieves. Subsamples of μDWTR (<51 μm) were milled using high energy ball mill (Fig. 9.8). The surface area of DWTR nanoparticles greatly increased (129 $m^2\ g^{-1}$) in comparison with the surface area of bulk DWTR (53.1 $m^2\ g^{-1}$).

To evaluate As(V) removal efficiency of nDWTRs from contaminated water, an adsorption equilibrium study was performed (Elkhatib et al. 2015b). The results revealed that As(V) sorption data best fitted to Langmuir model and the calculated maximum adsorption capacity (MAC) of nDWTR is 16 times higher than that of bulk DWTR**.** The high As(V) removal efficiency of nDWTRs from contaminated water and its comparatively greater adsorption capacity and stability of nDWTRs suggest its use as a promising low-cost and stable sorbent for As (V) removal from contaminated water and wastewater.

Similarly, Yenial et al. (2019) successfully produced magnetic $MnFe_2O_4$ nanoparticles from industrial wastes of Li-ion batteries and pyrite ash. The scanning electron microscope images ascertained that the average particle size of manganese ferrite particles produced was 24.3 nm. The manganese ferrite nanoparticles

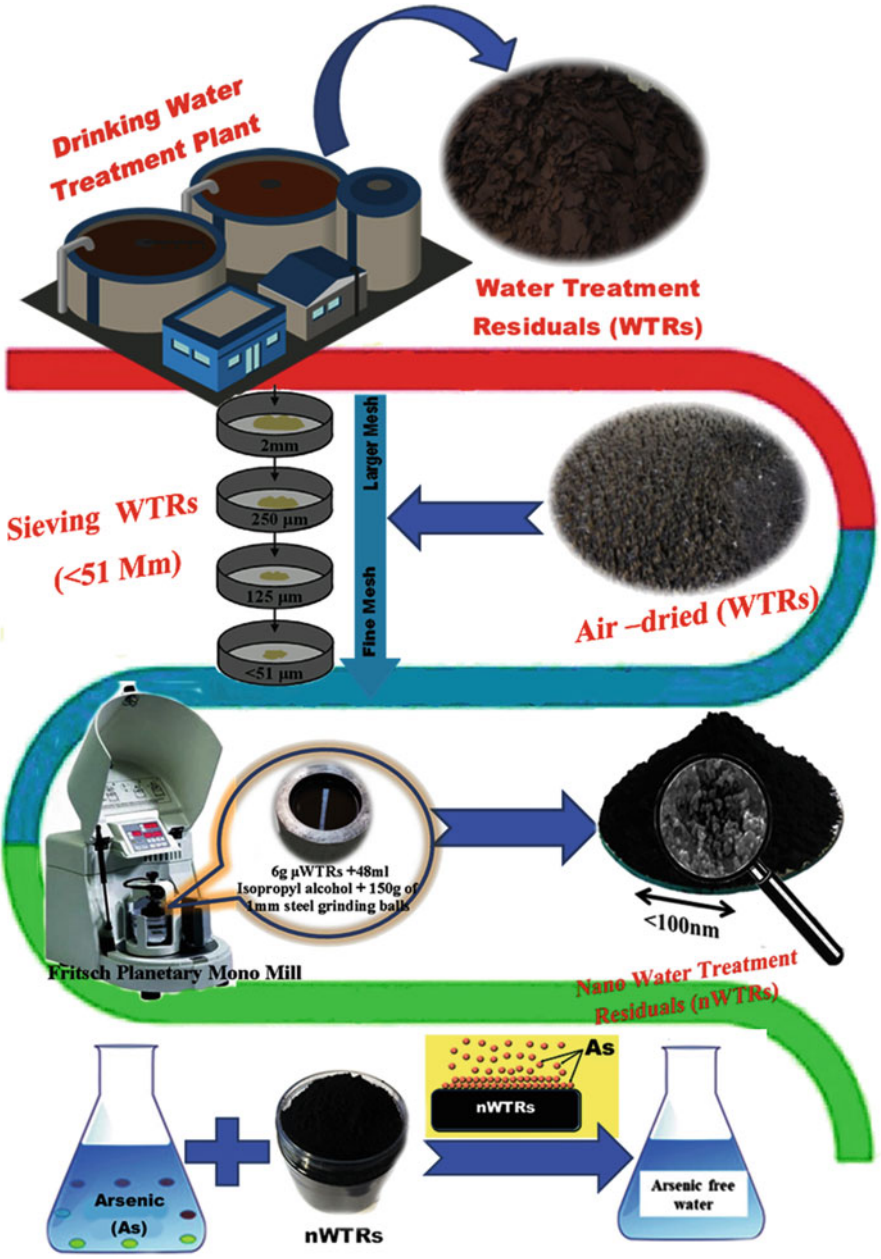


Fig. 9.8 Production of low-cost and ecofriendly drinking water treatment residuals nanoparticles (nDWTRs)

produced were tested for their As removal capabilities from contaminated solutions. The results indicated that the MAC of the manganese ferrite nanoparticles was found to be 101 ± 0.5 mg/g at acidic pH. The residual As concentration in the solution was found to be 0.78 mg/L, which is under the wastewater permissible limit (10 mg/L).

Utilizing industrial and agricultural wastes as cost-effective sorbents is attracting many researchers worldwide. However, sorbents derived from industrial and agricultural wastes may have other disadvantages such as low sorption capacity, low surface area, and low selectivity. To overcome such setbacks, research should focus on surface modification and functionalization to overcome constraints associated with cheap sorbents derived from waste materials.

9.3.7 Silica Based Nanoparticles

Nowadays, nanoparticles are commonly used to improve the sorption capacity of some sorbents since particles in nanoscale possess larger surface area, and permit rapid uptake and ultimately enhance the internal mass transport (Mohan and Pittman 2007). For this purpose, Hocaoglu et al. (2019) tested the capacity of micrometer-size silicate flakes and zirconium oxide nanoparticles or titanium oxide nanoparticles as composite for remediation of As (V) contaminated water. They found that the silicate flakes—zirconium oxide nanocomposites exhibit higher MAC (305 mg g^{-1}) and fast As removal (5 min.), whereas the MAC of the silicate flakes—titanium oxide nanocomposite was much lower (125 mg g^{-1}). Attinti et al. (2015) synthesized goethite/silica nanocomposite and tested it for aqueous As removal. They reported that the synthesized nanocomposite has shown MAC of 17.64 mg g^{-1} and high ability in removing As from aqueous media.

Barakan et al. (2020) studied arsenic removal from gold mine wastewater under alkaline conditions using modified bentonite with Al, Fe-columns and Al, Fe, Si-porous heterostructure framework. Adding Fe and Al has led to change the negative surface charge of bentonite to more positive surface charge which in turn favored the electrostatic attraction between the modified adsorbent and the As oxy-anion at high pH media. The role of silicate was creation of mesoporous structure due to the figuration of silica framework between montmorillonite layers. The authors proposed that the high MAC of the modified nano-bentonite was due to inner/outer sphere complexes formation at the surface, edge and interlayer. More recently, the fabrication of Fe_3O_4 quantum dots (QDs) graced silica micro–nano domain by a simplistic sol-gel method was achieved by Rakibuddin and Kim (2020). The functionalization between surface silica and Fe_3O_4 QDs was done by silica surface modification with APTES (amino-propyltriethoxy silane). The obtained composite (Fe_3O_4 quantum dot@ silica) was examined for remediation of As contaminated water. The results showed high efficient removal of As at various pH values which is attributed to surface area and pore volume improvements of the obtained composite due to the presence of Fe_3O_4 quantum dots (QDs) and mesoporous silica. Their final results indicate the promising tool of using nanocomposite in As contaminated water remediation field.

9.3.8 Nanoparticles from Agricultural Waste

Agricultural waste is defined as unwanted organic materials which produced by man through agricultural activities including plant waste, manure, agricultural products processing, and rural domestic wastes (Liu 2017). The agricultural waste materials mainly consist of lignin, cellulose, and hemicellulose (Salleh et al. 2011). Lignin involves carbonyl, hydroxyl, methyl, and other functional groups, whereas hemicellulose and cellulose involve carbonyl and hydroxyl groups and ether. These functional groups can scavenge heavy metals using various mechanisms such as chelation, ligand exchange, ion exchange, electrostatic forces, surface complexation (Zhou et al. 2015; Qian and Chen 2013; Qian et al. 2016). In addition, nanocellulosic biomass obtained from agricultural waste such as rice straw and cotton fiber can bind As (Table 9.5) (Kardam et al. 2012; Yu et al. 2013). Nanocellulose can be obtained from lignocellulose-rich plant residue and used in composites form with other nanomaterials to increase its stability and removal capacity towards heavy metals. Various nanocomposite sorbents have been tested for remediation of heavy metals contaminated wastewater such as cellulose/carbon nanotube (CNT) cellulose/graphene nanocomposites and cellulose/metal nanocomposites (Tshikovhi et al. 2020). A fast method for preparation of nanocellulose composite from residue of Kapok fiber (KF)—a natural plant fiber—was developed by Chai et al. (2020). The obtained nanocomposite (TEMPO-NC- PEI/GA) was tested for remediation of As (V) contaminated wastewater. The sorption data revealed fast and high As

Table 9.5 Maximum adsorption capacity of arsenic species on nanoparticles derived from agricultural waste

Adsorbent type	Adsorption capacity mgg^{-1}		Reference
	As(III)	As (V)	
Lanthanum and magnetite nanocomposite incorporated palm-shell waste based activated carbon	–	227.6	Jais et al. (2016)
Polysaccharide stabilized Fe–Mn oxide nanoparticles	**338.0**	**272.0**	Byungryul and Zhao (2012)
Magnetic Fe_3O_4 nanoparticles from tea waste	**189.0**	–	Lunge et al. (2014)
Rice husk iron oxide nanoparticles composite	**82.0**	–	Pillai et al. (2019)
Starch-bridged magnetite nanoparticles	–	**248.0**	An et al. (2011)
Green synthesized α-Fe2O3 nanoparticles	–	**38.47**	Mukherjee et al. (2016)
Zero-valent iron nanoparticles-produced leaf extracts of			
Oak Mulberry Cherry	**877.3** **1999.0** **1047.0**	–	Poguberovic et al. (2016)
FeNPs-produced shoots/leaves blueberry extract	–	**38.85**	Manquián-Cerda et al. (2017)

(V) removal efficiency of nanocellulose composite (TEMPO-NC- PEI/GA) at high As concentrations (Table 9.5). No significant reduction in As removal capacity of the nanocellulose composite was noticed after 8 generation cycles. Furthermore, Baruah et al. (2020) investigated the effect of rice husk (RH) and sugarcane bagasse (SB) waste-derived nanocellulose/iron oxide nano-biocomposites (SB and RH-NIONs) on remediation of As polluted groundwater. The adsorption isotherm and adsorption kinetic coupled with FTIR and XPS spectroscopy data were utilized to study As adsorption mechanisms on SB and RH-NIONs. The obtained data suggested formation of multi-dentate nuclear complexes with the involvement of covalent bonding between Fe_3O_4 and As. These findings reflect the high stability of adsorbed As on SB and RH-NIONs nanocomposite which could be successfully used for As removal from real groundwater.

9.4 Potential Nanoparticles Derived from Water Industry By-products for Arsenic Stabilization in Contaminated Soils

Agricultural soils can be contaminated with excess amount of arsenic (As) due to anthropogenic actions such as mining and industrial related activities and agricultural practices. Under alkaline conditions, i.e. alkaline soils, As solubility increases and causes widespread environmental contamination that poses a continuous threat to human health.

Water treatment residuals (DWTRs), drinking water sludge, are considered one of the most produced wastes rich in iron. These wastes are daily generated during the drinking water treatment process and have been used as an efficient and budget friendly approach for P, As, Ni, Cu, and Pb immobilization and stabilization in contaminated soils (Sarkar et al. 2007; Elkhatib et al. 2013, 2015a, b; Elkhatib and Moharem 2015). The unstable nature of arsenic species, mobility, and toxicity may change under different soil conditions and components such as clays, carbonaceous materials, and oxides of iron, aluminum, and manganese, may participate in adsorptive reactions with arsenic. Therefore, successful remediation of As contaminated soils necessitates understanding As chemistry in soils. Many investigators have tested the capability of DWTRs in remediating contaminated soils. Garau et al. (2014) investigated the influence of Fe DWTRs application at a rate of 3% on As immobilization in contaminated soil. They reported 27% reduction in specifically As sorbed. Nagar et al. (2015) examined the beneficial effect of Al and Fe DWTRs application on As bio-accessibility in As-spiked soils. They reported 50–80% decrease in bio-accessible As, compared to non-DWTRs treated soils.

Nowadays, the advance of nanosized materials enables the promotion of conventional macro-sized (DWTRs) to nanostructured water treatment residuals (nDWTR). Nano-DWTRs present exceptional characteristics like *large ratio* of *surface area to volume,* efficient adsorption, and stability. Such characteristics can be useful in soils decontamination. Since the conventional bulk WTRs have limited reactivity towards contaminates, Elkhatib et al. (2015a) have been a pioneer in employing Nano-

DWTRs for remediation of metal-contaminated soils. Sorption studies demonstrated that the MAC of nDWTRs were 50 mg As g^{-1}, 47 mg Cd g^{-1}, and 50 mg P g^{-1} compared to bulk DWTRs to 3 mg g^{-1}, 2.80 mg g^{-1}, and 1.67 mg $Pg^{-1}$for As, Cd, and P, respectively (Elkhatib and Moharem 2015; Elkhatib et al. 2016). Elkhatib et al. (2018) also ascertained that application of nWTRS at a rate of 0.3% by mass greatly reduced Pb and Cd mobility and phytoavailability (*Brassica napus* L.) by >99%. The use of nDWTRs as a low-cost efficient sorbent could eliminate the need for DWTR disposal in landfill and be more effective in contaminant remediation and cost feasibility.

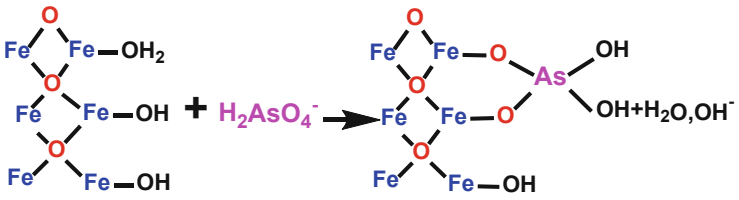
9.5 Mechanism of As Adsorption by Nanoparticles and Nanocomposites

Many investigators ascertained the high affinity of As towards Fe, Mn, Al, Cu, Co, Ti, and Si oxide/hydroxide surfaces (Mandal and Suzuki 2002; Navarathna et al. 2019; Zeng 2003; Zhang et al. 2019a, b. Goldberg and Johnston 2001; Sherman and Randall 2003). Furthermore, Fe oxides play a significant role in natural soil environments for As scavengers and hence reducing their mobility and bio-accessibility (Jain et al. 1999; Nickson et al. 2000; Stüben et al. 2003; Mench et al. 2006). Exclusively, iron oxide structured materials have a natural affinity for arsenic sorption and thus strongly react with As through inner-sphere complexion (Simeonova 2000; Aredes 2013; Goldberg and Johnston 2001; Sherman and Randall 2003).

Nowadays, utilization of nano-scaled materials derived from abundant natural and waste materials such as Fe_3O_4, TiO_2 nanoparticles, nanocellulose composite, DWTRs nanoparticles, aluminosilicate nanotube-iron oxide composite, iron-impregnated granular activated carbon, and green ZVI nanoparticles have been introduced as promising tools for treatment of metal-contaminated water and soils (Arancibia-Miranda et al. 2016; Stefaniuk et al. 2016; Elkhatib et al. 2017; Fang et al. 2018; Sepúlveda et al. 2018; Kalaruban et al. 2019). Elkhatib et al. (2015b) studied the adsorption reaction of As (V) on nDWTRs through adsorption equilibrium, fractionation, and kinetics experiments. The SEM-EDX and XRD study ascertained that the nDWTRs sorbent contained Fe and Al elements in appreciable amounts. Because of the high affinity of Fe and Al metals for As species and selectively, the subsequent As(V) adsorption mechanisms are suggested:

9.5.1 On Iron Sites

As(V) complexes with iron oxyhydroxide are formed either through ligand exchange mechanism, involving a hydroxyl groups from arsenate anion and iron oxyhydroxides or through stable 2 *C* bidentate complexes to adjacent iron surface sites. Fukushi and Sverjensky (2007) studied the surface complexation of As(V) and concluded that the bidentate complexes are the governing arsenate species on hematite at high surface coverage and low pH values.



9.5.2 On Aluminum Sites

As(V) and the coordinated hydroxyl group form inner-sphere complexes as follows:

$$\equiv \mathrm{Al} - \mathrm{OH} + \mathrm{H_2AsO4} - \longleftrightarrow \equiv \mathrm{AlH_2AsO4} - + \mathrm{OH} -$$

$$2 \equiv \mathrm{Al} - \mathrm{OH} + \mathrm{H_2AsO4} - \longleftrightarrow (\equiv \mathrm{Al})_2\ \mathrm{HAsO4} + \mathrm{H_2O} + \mathrm{OH}$$

Since arsenate is more strongly bound to Fe oxides compared to $Al(OH)_3$, it is suggested that the formation of inner-sphere complex could be the governing adsorption mechanism. Catalano et al. (2008) introduced an X-ray scattering evidence that supported the formation of inner- and outer-sphere complexes with As (V) on aluminol sites of corundum. In addition, the As fractionation results (Fig. 9.9)

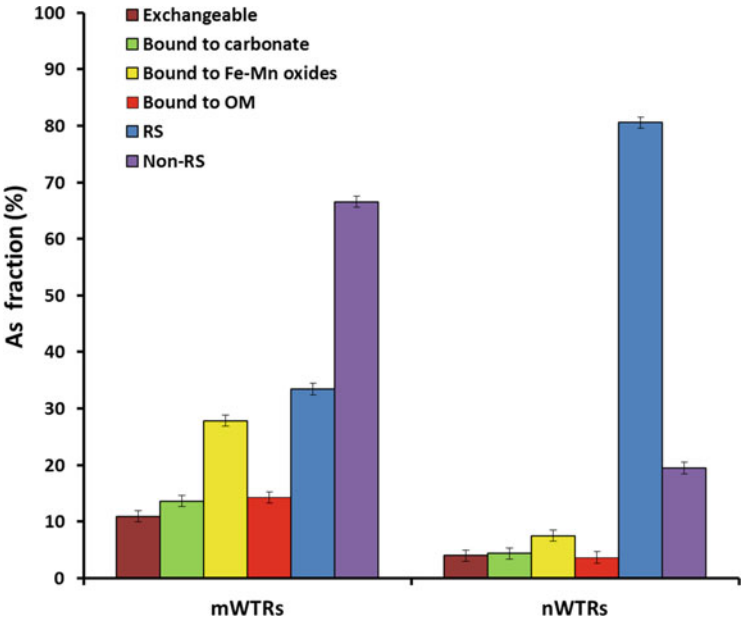


Fig. 9.9 Adsorbed As (V) on mWTRs and WTR nanoparticles (Elkhatib et al. 2015b)

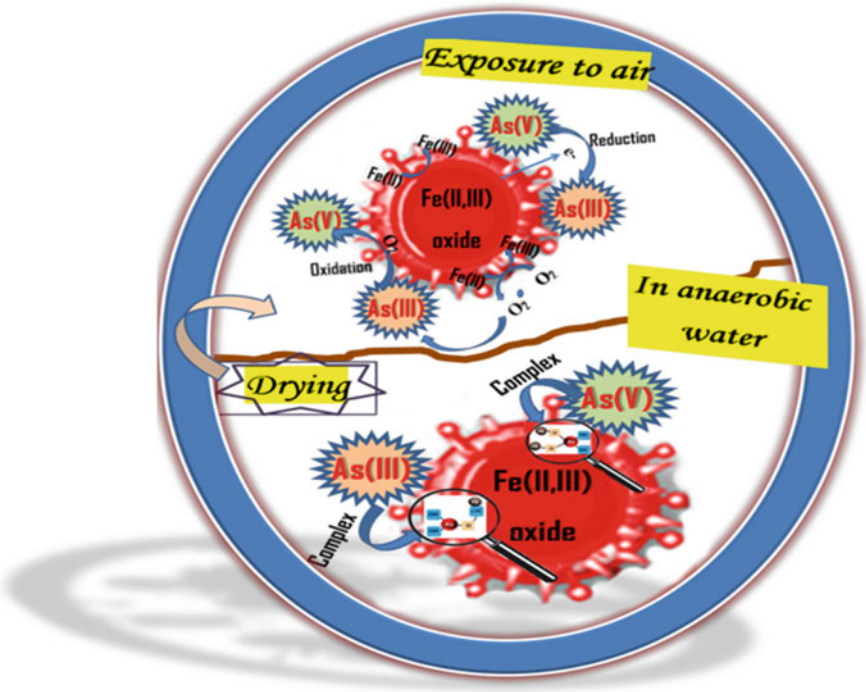


Fig. 9.10 Mechanism of arsenic adsorption on magnetite nanoparticles

showed that the association of 67% of adsorbed As(V) on bulk DWTRs was with the non-residual fraction (more mobile), whereas association of 80% of adsorbed As (V) on nano-DWTR nano was with the residual (the less mobile) fraction. These observations clearly indicate that application of DWTR nanoparticles has substantially decreased the more labile fractions and increased the immobilized (stable) fraction in soils.

Many researchers studied the mechanisms of As adsorption on nanoparticles and nanocomposites materials using different tools. Kong et al. (2014) studied the type of adsorption reaction of As(III) and As(V) on magnetic nanoscale Fe–Mn binary oxides loaded zeolite (MFM) through adsorption thermodynamic and kinetic experiments. They concluded that As(III) sorption on MFM is governed by both oxidation and adsorption processes while As(V) sorption took place through sorption process only. The incorporation mechanisms of As into Al-magnetite nanocrystals were examined using different microscopic and spectroscopic tools (Freitas et al. 2016). They noticed that the existence of Al enhances the formation and growth of the magnetite crystals leading to more As immobilization into the formed crystal. The authors interpreted stabilization of As on the mesocrystals to both As adsorption onto the newly formed nanoparticles (first) and As entrapment into the grown crystals (second). Micro-spectroscopic characterization using synchrotron radiation-based X-ray absorption spectroscopy (XAS) and X-ray

photoelectron spectroscopy (XPS) were conducted to understand in depth the geometries of adsorbed As(V) and As(III), on magnetic nanoparticles (MNPs) (Liu et al. 2015). EXAFS analysis proposed prevalent formation of bidentate binuclear complexes for arsenate and tridentate hexanuclear complexes for arsenite on MNP surfaces. Furthermore, XANES and XPS results demonstrated complex redox reactions of MNPs-adsorbed As exposed to air (Fig. 9.10). A new study also was conducted by Pranudta et al. (2020) to investigate the mechanisms of As adsorption onto hybrid anion exchange with Fe/Mn binary oxides nanoparticles (HA502P-Fe/Mn) using XANES to observe the change of oxidation state of the Mn oxides during As(III) removal. Because the bond distance between As-Fe and was larger (3.35A) than the distance between As-Mn(2.94A) of HA502PFe/Mn, the authors assumed that As(III) was first oxidized to As(V) and hereafter adsorbed on the surface of oxides nanoparticles through formation of inner-sphere complexes (Fig. 9.10).

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Biological Means of Arsenic Minimization with Special Reference to Siderophore

10

Pratika Singh, Azmi Khan, and Amrita Srivastava

Abstract

Arsenic (As), a p-block element, is a metalloid common on earth crust in various forms such as arsenopyrite and scorodite. It is known to be present in four oxidation states that are −3, 0, +3 and +5 of which pentavalent and trivalent forms are most toxic. Arsenic in its various forms proves hazardous to environment and all living beings including microbes, animals and plants. In animals, it affects almost all vital organs including liver, kidneys, heart and lungs. As is a known carcinogen too. In plants, As triggers production of reactive oxygen species hence deteriorate development and metabolism of plants. To mitigate these hazardous effects organisms have developed As detoxification mechanisms such as arsenic transforming enzymes, phytochelatins, etc. An emerging discovery in context of arsenic mitigation is utilization of siderophores. Siderophores are secondary metabolites of microorganisms, some plants as well as mammalian cells. These are low molecular weight peptides synthesized via ribosome independent process using non-ribosomal peptide synthetase enzymes. Major function of siderophore was believed to be chelation of iron to make it accessible for siderophore producers. However, studies proved that it can too binds with other heavy metals and metalloids and form thermodynamically stable complex. The complex formation between siderophores and different metals and metalloids including As depends on various physiochemical parameters. This chapter highlights different aspects of arsenic detoxification in organisms with special reference to siderophore utilization in arsenic mitigation.

P. Singh · A. Khan · A. Srivastava (✉)
Department of Life Science, School of Earth, Biological and Environmental Science, Central University of South Bihar, Gaya, India
e-mail: amritasrivastava@cub.ac.in

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Arsenic · Heavy metal · Siderophore · Detoxification · *ars* operon

10.1 Introduction

Heavy metals are well-defined as naturally occurring trace elements possessing density relatively five times higher than water (Duffus 2002; Li et al. 2017). It is a major threat in current scenario that has inflicted critical damage on environment and all life forms. The biological availability of these metals are affected by physical, chemical as well as biological factors that include temperature, sequestration, adsorption, solubility, thermodynamic stability, adaptation, characteristics of species, etc. (Hamelink et al. 1994). Being non-biodegradable in nature, most of them can enter food chain and thereby their bioaccumulation is detrimental to living organisms (Azeh Engwa et al. 2019). Sources of these metallic elements include industrialization, urbanization, domestic effluents, agricultural route and technological advancement (Florea et al. 2004). Some metals are utilized by organisms to perform biochemical and physiological functions if present in optimum concentration (WHO/FAO/IAEA 1996; Stern 2010; Tchounwou et al. 2012). However, metals/metalloids, namely silver (Ag), arsenic (As), aluminium (Al), lithium (Li), gold (Au), platinum (Pt), uranium (U), tin (Sn), etc. possess no biological role, rather affects body adversely if entered (Chang et al. 1996; Bhat et al. 2019). In biological systems, toxic metals disturb organelles such as endoplasmic reticulum, mitochondria, chloroplast, cell membrane and various enzymes associated with metabolic pathways, DNA damage repair system, cell cycle checkpoints (Wang and Shi 2001; Beyersmann and Hartwig 2008). These metals may compete metabolically with essential elements like iron, magnesium, etc. Toxic metals interact with nucleic acid leading to chromosomal aberrations and further cause conformational changes thereby inducing carcinogenesis or apoptosis (Yedjou and Tchounwou 2006, 2007). Systemic toxicants cause cardiovascular diseases, neurobehavioural and immunological disorder, produce reactive oxygen species, oxidative stress, multiple organ failure and are considered as carcinogens as stated by United States Environmental Protection Agency. Photosynthesis, fertility rate, metabolite and chlorophyll synthesis are severely hit by heavy metals. There is no any biological and chemical means for their degradation, thus can only be converted to less harmful form. Among biological non-vital elements, for example, Cd, Pb, As, Hg, Cr are ranked as priority elements owing to their high degree of noxiousness. The anthropogenic and geological/natural source has caused uncontrolled increase beyond permissible limit. Thus it affects riverine ecosystem, air quality, soil adversely as a function of its toxicity, bioaccumulation and persistence.

Arsenic is considered as 20th most abundant element and present in all environmental matrices. The increased amount of As in the environment is either due to natural process, viz. volcanic activities, weathering, etc. or via anthropogenic activities like mining, smelting, fertilizers, pesticides, etc. (Agency for Toxic

Substances and Disease Registry (ATSDR) 2000; Tripathi et al. 2012; Rahman et al. 2014; Singh et al. 2017). Industrialization and technological advancement leads to an accumulative problem on the surroundings by discharging huge amount of harmful waste and heavy metals (Carlin et al. 2016). Accumulation of arsenic (As) is imposing threat to human survival, affecting masses of people every year across the world. As causes severe epigenetic and biochemical alterations (Fig. 10.1).

Approximately millions of people are affected by As across the world. India, Bangladesh, Taiwan, Chile, Mexico are worst hit by As stress as their groundwater contain higher doses of As (Mukherjee et al. 2006; Brinkel et al. 2009). Nearly 40 million people belonging to various districts of West Bengal and Bihar (including middle Gangetic plains) are severely affected by As stress (Mandal et al. 2011). The present permitted limit for As in drinking water has been modified and is now 10 μg/L (WHO/FAO/IAEA 1996). Several cases of groundwater arsenic pollution have been informed across the world. Approximately four main events belonged to Asia: in Taiwan (Tseng et al. 1968), West Bengal, India (Das et al. 1994), Inner Mongolia, China (Xiao 1997) and Bangladesh (Biswas et al. 1998).

To combat As stress the utilization of plant growth promoting rhizobacteria were recently explored for their capacity to detoxify or mitigate As from contaminated regions. Various As-resistant microbes of genera, e.g., *Brevundimonas*, *Stenotrophomonas*, *Achromobacter*, *Comamonas*, *Microbacterium*, *Bacillus*, *Pseudomonas*, *Ensifer* and *Ochrobactrum* were considered to improve harmful effects of As thereby promote plant development through mobilization of As in vacuoles (Cavalca et al. 2010; Wang et al. 2011; Mesa et al. 2017; Mallick et al. 2018). Satyapal et al. (2018) isolated indigenous bacteria belonging to genes *Pseudomonas* from middle gangetic plain from Bihar, India that revealed toxic metals resistance against As, Cr (IV) Hg (II), Pb (II)Ag (I), Cd (II), Ni (II). Similarly, several plant species have been investigated that detoxify As stress. Strategies for metal detoxification in organisms include bioaccumulation, biotransformation, immobilization, use of different chelators like siderophore that have been employed for metal uptake, metal precipitation or metal detoxification. The chapter includes As minimization strategies adopted by plants, microbes and animals. Role of siderophore as effective, economic and eco-friendly measures for As mitigation has also been elaborated.

10.2 Biochemistry of Arsenic

Arsenic is considered as most toxic element and is placed under Group I carcinogen according to the US Environment Protection Agency (USEPA) (Rosas-Castor et al. 2014; Niazi et al. 2018). In natural environment, it occurs as sulfidic ores (metal arsenides), arsenates, arsenic trioxide and are found in rocks, soil, water, life forms ranging from parts per billion (ppb) to parts per million (ppm).

Albertus Magnus was the first to put forward the metallic property of As. The electronegative As has better oxidation potential thus increases cationic behaviour. Therefore, it shows +3 and +5 oxidation states and generally bonds to sulphur and

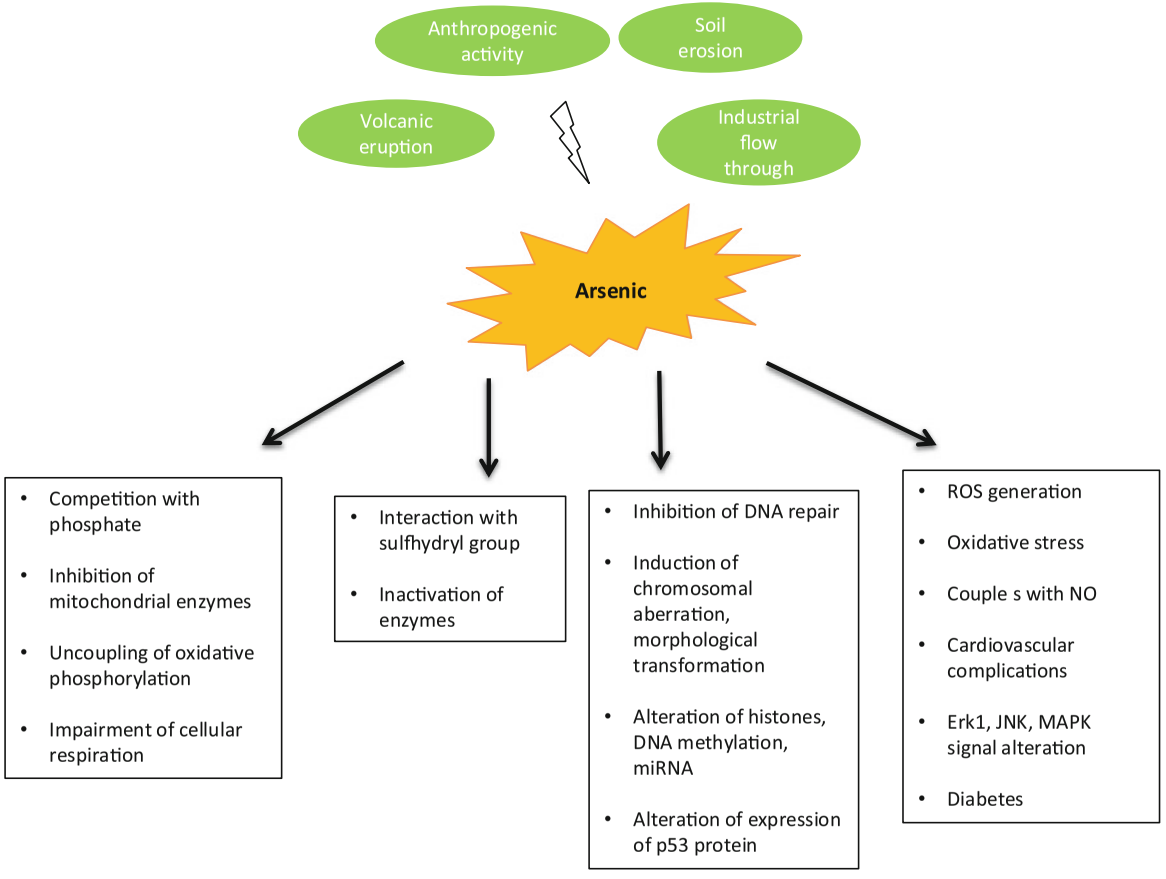


Fig. 10.1 Modes of arsenic toxicity

oxygen. Compared to As (V), As (III) is more toxic and mobile. It is due to the fact that As^{3+} binds with sulfhydryl groups very strongly and binds weakly to thiol groups (glutathione, cysteine and lipoic acid). The toxicity of As^{5+} occurs because it is able to compete with PO_4^{3-} for energetics and transport functions. It forms organic species by combining methyl groups like monomethyl arsenic acid (MMA) and dimethyl arsenic acid (DMA). MH_2AsO_3, M_2HAsO_3 and H_3AsO_3 (where M is a cation) are the known formulas for arsenites. Arsenates $(AsO_4)^{3-}$ co-ordinate in tetrahedral or octahedral manner with alkaline earth metal or transition metal with different anions like F^-, OH^-, Cl^- in order to balance the charge. It is noteworthy that As present in trivalent oxidation state because of its reactivity with sulphur is more poisonous than organic arsenicals and pentavalent oxidation state with the following toxicity level-

$$AsH_3\ (\text{arsine}) > \text{arsenite} > \text{arsenate} > RAs - X$$

Arsenic redox reaction depends upon pH and redox potential while the oxyanions' property depends upon pH condition (Masscheleyn et al. 1991; Valles-Aragón et al. 2013). H_2AsO^{4-} predominates at pH less than 7 while $HAsO^{4-}$ dominates at alkaline condition. Metabolism of inorganic As occur through biomethylation by two electron reduction of As (V) and oxidative methylation of As (III). The process involves reduction of pentavalent oxidation form of As to trivalent arsenicals by using arsenate reductase. As^{3+} methyltransferase (AS3MT) uses S-adenosylmethionine (SAM) and donates methyl group to form monomethylarsonic acid and then form dimethylarsenic acid by using MMA^{III} methyltransferase and glutathione as cofactor (Palmgren et al. 2017)

10.3 Arsenic Detoxification in Organisms

Arsenic is a persistent toxicant. Research on arsenic detoxification proves significant for controlling arsenic toxicity. Bio transformational mechanism of various organisms might prove to be the best tool for detoxification of arsenic. Various organisms can decrease toxicity of arsenic metalloid by incorporating metal restricting proteins. Almost all organisms have arsenic detoxification or mitigation process. Different mechanisms are described in case of plants, microbes and animals.

10.3.1 Arsenic Detoxification in Plants

Arsenic affects plant growth and productivity because of huge physiological and molecular alterations. The most crucial is biochemical change where reactive oxygen species generation occurs at subcellular level. The resulting superoxide molecules cause irreparable injury to plant primary metabolites as well as macromolecules (Srivastava et al. 2017; Talukdar 2017; Abbas et al. 2018). Various enzymatic and non-enzymatic antioxidants are responsible for detoxification of ROS under metal

stress (Ozturk et al. 2010; Pandey and Gupta 2015; Tripathi et al. 2017). Other mechanisms include binding of As with various ligands, viz. phytochelatins (PCs) and metallothioneins (MTs) so that to convert it into lesser/non-toxic forms. Transporting As-ligand bound complexation in vacuolar compartment is another strategy (Chandrakar et al. 2016; Dixit et al. 2016). The fundamental question about translocation of As from soil to plant and then its uptake and transport to different tissues have been comprehensively investigated and reviewed by different scientists (Abbas et al. 2018; Shri et al. 2019; Susan et al. 2019; Abedi and Mojiri 2020).

The availability of inorganic species of As (V/III) in soil is solely dependent on pH and also directly co-related to its bioavailability, mobility and toxicity (Shahid et al. 2012). At low pH (<5.5) As changed to inorganic As (III) which is considered as more soluble, mobile and toxic (Signes-Pastor et al. 2007; Adra et al. 2016). The initial defence process of plants to cope up with metallic stress is to minimize or inhibit the uptake of metal followed by gene regulation of metal associated transporters, receptors or chelators. Approximately 450 varieties of plants are reported to be hyperaccumulator of As (Sebastian and Prasad 2014). Apart from classic example of *Pteris vittata*, several other species like *Pteris umbrosa*, *Pteris cretica*, *Pteris longifolia* and other plants like *Silene vulgaris*, *Pityrogramma calomelanos* are considered as As accumulator (Zhao et al. 2002; Meharg 2002). The uptake of As depends on its chemical speciation thus As uptake mechanism varies in plants. As (V) and As (III) uses phosphate (Pi) channels and silicon (Si) transporters, respectively, because of being chemically analogous to phosphate and silicon (Wu et al. 2011). Various low and high affinity Pi transporter proteins (PHT) are involved in As uptake in plants. Since As and P compete for the same transporter, increasing the concentration of P might minimize As uptake. PHT1 proteins are considered to be high affinity transporters while low affinity transporters are not known yet (Nussaume et al. 2011; LeBlanc et al. 2013). After it enters, As (V) is transformed to As (III) by the help of arsenic reductase (ACR2) (Dhankher et al. 2006). Arsenite uptake occurs via bidirectional transporters called nodulin-26-like intrinsic protein (NIPs) and Si transporter (such as Lsi1 and Lsi2 located at epidermal and endodermal cells; Ma and Yamaji 2006; Bakhat et al. 2017). The thiol rich peptide is responsible for As detoxification or its storage in vacuoles, etc. thereby limiting its long distance travel in plant tissues (Liu 2010). Plants are responsible for generating several ligands in order to minimize and control metal stress like amino acids, organic non-ribosomal chelators, sulphur containing compounds, etc. Phytochelatins and metallothioneins are considered to be S-containing compounds that bind with metal in order to establish metal homeostasis and tolerance towards toxic metals.

Role of Phytochelatins

Glutathione (GSH) derived phytochelatins (PCs) are peptides that can bind with heavy metals. The detoxifying agent has an overall structure $(\Upsilon\text{-Glu-Cys})_n$–Gly (where $n = 2$–11). PC synthase is constitutively expressed and thus allows transpeptidation activity from Υ-glutamylcysteine dipeptides. Free metals are more toxic than immobilized metals thus the detoxification process may occur through

PCs (Zenk 1996). In O*ryza sativa*, two PCS homologues genes have been identified termed as OsPCS1 and OsPCS2 on chromosome number 5 and 6 (Table 10.1).

It was found that expression of OsPCS1 and OsPCS2 were upregulated in root and shoot, respectively, during As (III) stress (Yamazaki et al. 2018). The binding of PCs-As and later sequestering complex to vacuole is mediated through ATP binding cassettes (ABC) transporters, viz. AtABCC1 and AtABCC2 (Park et al. 2012).

Role of Metallothioneins

MTs are 4–8 kDa compounds belonging to a family of polypeptide rich in cysteine (Cys) with strong affinity towards different heavy metals. It was first discovered in renal cells of horse (Margoshes and Vallee 1957). These bind with different metal ions and protect plant from oxidative stress by scavenging ROS as well as regulate genes responsible for metal homeostasis. It consists of α (C-terminal domain) and β (N-terminal domain) that binds with metal ions through sulfhydryl cys residues thereby protecting plants (Sharma et al. 2016). These are classified on the basis of its numbers, arrangements, sequence similarities as well as phylogenetic relationships (Freisinger 2009). Plants MTs (pMTs) are classified as Type I (MT1) whose genes are predominantly expressed in root as well as leaves; Type 2 (MT2) group expresses genes during seed development, stems and leaves; Type 3 (MT3) expresses their genes majorly in fruits and leaves; and Type 4 (MT4) group genes gets expressed in tissues belonging to vegetation and reproduction (Waters et al. 2005; Leszczyszyn et al. 2013). Their function is not fully understood due to difficulty in isolation procedure. However, pMTs sequentially involve the following steps to promote metal homeostasis: metal binding with MTs, sequestration by forming complex with chelators and storage site followed by protection against oxidative stress (Saeed-ur-Rahman et al. 2020).

10.3.2 Arsenic Detoxification in Microbes

It is now clear that almost all bacteria and archaea possess arsenic resistance (*ars*) operon. This confirms the fact that As is ubiquitous toxic metalloid in environment. The biogeochemical cycle of As through microbial activity is ancient as well as ubiquitous process. Microbes have evolved over a period of time in order to resist or detoxify As. Genes associated with this function can be categorized into resistance or detoxification genes and metabolic genes. Interestingly, these are present even in those organisms that continue to live in low As concentration while absent in some, which is still unclear (Jackson et al. 2005; Zhu et al. 2017; Dunivin et al. 2018). The role of genes towards As biogeochemical cycle is still not fully understood and in experimental stage. Thus the preliminary question about its distribution, role and its impact on environment needs to be addressed. Dunivin et al. (2019) recently carry out global survey on As genes present in soil microbes. With the help of computational analysis on 922 soil genomes and 38 metagenomes, they observed that unlike common belief that all organisms possess As related genes, such was not observed

Table 10.1 *Oryza sativa* genes involved in As detoxification

S. No.	Gene symbol	Gene name	Chr. No.	Locus ID/RAP ID	Role
1.	OsLsi2	Low silicon rice 2	3	LOC_Os03g01700.1	Silicon efflux transmembrane transporter activity. As uptake
2.	OsLsi1	Low silicon rice 1	2	LOC_Os02g51110.1	Silicate transmembrane transporter activity. Arsenic upatke
3.	OsABCC1 OsABCC2	Multidrug resistance-associated protein 1	4	LOC_Os04g52900.1 LOC_Os04g52900.2	ABC transporter reduces arsenic accumulation
4.	OsNIP1	Nodulin26-like intrinsic protein 1	2	Os02t0232900-01	A member of the Nodulin26-like Intrinsic Protein (NIP) family, arsenite transporter
5.	OsPCS1	Phytochelatin synthase 1	5	Os05t0415200-01	Phytochelatin synthase, Heavy metal resistance
6.	OsPCS2b	Phytochelatin synthase 2b	6	Os06g0102300	Cadmium (Cd) and arsenic (As) tolerance
7.	OsACR2	Arsenate reductase 2, Sulfurtransferase 21	3	Os03g0108000	Arsenic metabolism
8	OsHAC1	Sulfurtransferase 5	2	Os02t0102300-01	Arsenate reductase, sulfurtransferase/rhodanese-like protein, Regulation of arsenic accumulation
9.	OsPT8	Phosphate transporter 8	10	Os10g0444700	Phosphate transporter, Pi homeostasis
10.	OsCLT1	CRT-like transporter 1	1	Os01g0955700	CRT-like transporter, glutathione homeostasis, arsenic tolerance
11.	OsGS2	Glutathione synthetase 2	12	Os12g0263000	Similar to Glutathione synthase
12.	OsHAC4	High As content 4, sulfurtransferase 8	2	Os02t0157600-01	Arsenate (As(V)) reductase, rhodanase-like protein, As (V) tolerance, control of arsenic (As) accumulation
13.	OsLsi3	Low silicon rice 3	10	Os10t0547500-01	Divalent ion symporter domain containing protein

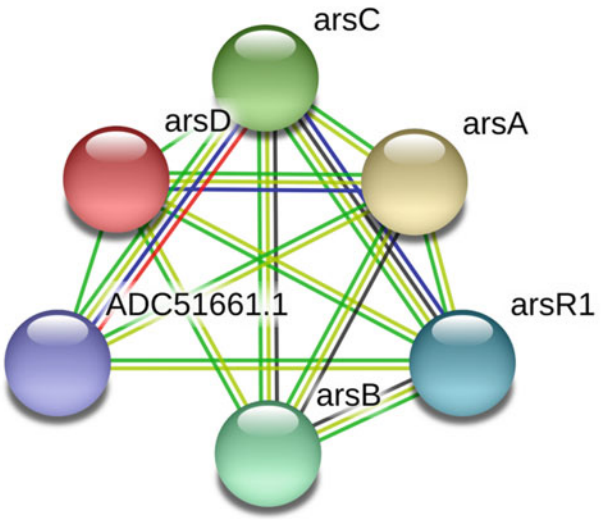
after analysis. The presence of genes encoding arsenic methylase (*arsM*) was predominant and this might play a pivotal function in As biogeochemical cycle.

Response of microbes for As minimization and detoxification involves the following processes—immobilization of cells, increasing the affinity of phosphate uptake thereby decreasing the amount of As entering inside cells, chelation through glutathione, PCs, MTs, siderophore followed by reduction, methylation and oxidation for detoxification (Silver and Phung 2005; Stolz et al. 2006; Paez-Espino et al. 2009; Yin et al. 2011a, b). Microorganisms sequester toxic metal ion in extracellular environment of cells and prevent it from entering the cytoplasm. This helps in inhibition of metal interaction with important cellular components. Even if As tends to enter, chelation by different peptides/proteins and ligands limits its accumulation. As (V) reduction mechanism involves two mechanisms where one is present in all microbes while other is restricted in some bacteria and archaea. This detoxification process is controlled by *ars* operon where *ars* genes encodes protein dedicated to reduce As (V) to As (III) and then removal through efflux pump occurs (Pandey et al. 2015; Brown et al. 2018).

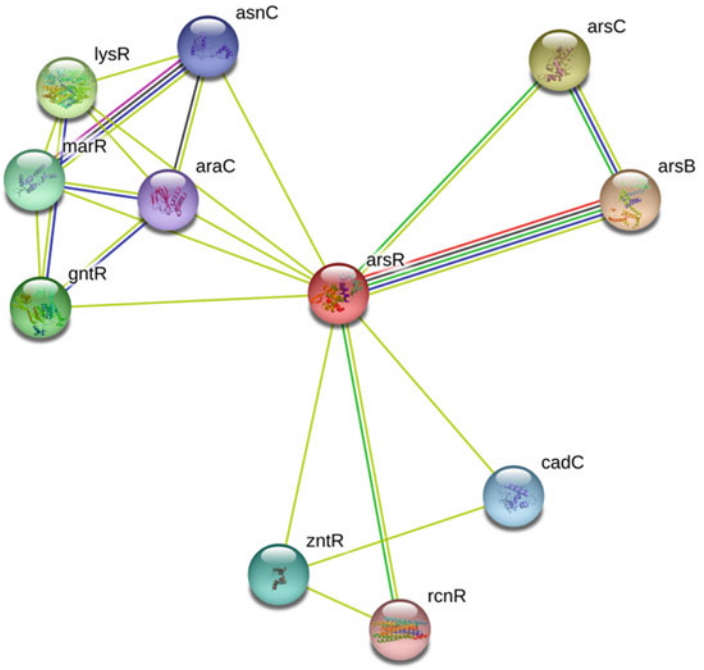
ars Operon

ars operon possess mechanism for As resistance which is either plasmid or chromosome located (Silver and Phung 2005; Stolz et al. 2006). Such operons are extensively studied in several Gram-negative and Gram-positive bacteria and are found to be nearly homologous. As microbes are constantly exposed to varied range of metals and metalloids since ages that leads to selective pressure in order to evolve resistance mechanism operons which are conserved. The presence of *ars* operon in bacterial and archeal species indicate the ubiquitous presence of As in the environment. However, they are also found in those microorganisms which thrive in As free surroundings. It contains generally three or five genes organized as one transcriptional unit. In *Escherichia coli* plasmid R773 (accession number J02591) isolated from urinary tract infection patient, the operon comprises of five genes in an order *ars*RDABC controlled by single promotor (Hedges and Baumberg 1973; Ben Fekih et al. 2018). *ars*R is responsible for encoding arsenic inducible repressor. ArsR which is a member of SmtB/ArsR family binds with promotor and the transcription of operon occurs with interaction between ArsR and arsenite that cleaves repressor protein within DNA. *ars*D acts as a negative regulatory protein which is a weak repressor (Wu and Rosen 1993). *ars*A and *ars*B encode ATP dependent arsenite efflux pump. arsC works as arsenate reductase that reduces it to arsenite which is released out by transport system (Carlin et al. 1995). These five genes have also been found in *Acidiphilium multivorum* plasmid KW301 (accession number AB004659) and *Bacillus* sp. (Fig. 10.2a)

Chromosome of *E. coli*, *Pseudomonas stutzeri*, *Pseudomonas aeruginosa* and plasmid pI258 and pSX267 of *Staphylococcus* species consists of *ars*RBC while cistron *ars*D and *ars*A are absent as illustrated in Fig. 10.2b (Rosenstein et al. 1992; Ji and Silver 1992). The cistron encodes polypeptide ArsR, ArsB and ArsC with molecular weight of approximately 12 kDa, 37 kDa and 24 kDa, respectively. This



A.



B.

Fig. 10.2 String analysis showing protein-protein interaction in (**a**) *Bacillus* sp. Input protein is ArsD (arsenical resistance operon repressor ArsD; COG0841 Cation/multidrug efflux pump, 118 aa) with predicted functional partners: ArsA (Arsenical pump-driving ATPase; 591 aa), ArsC

operon is also present in transposons of *Bacillus subtilis* JH642, *Acidithiobacillus caldus*, *Leptospirillum ferriphilum* (Ben Fekih et al. 2018). Prithivirajsingh et al. (2001) cloned arsenic resistance gene in *Pseudomonas fluorescens* (MSA11 and MSA12) and suggested that gene *ars*C requires glutathione reductase, glutathione (GSH), glutaredoxin and ArsC protein. Presence of As-resistant gene operons in plasmids and transposons provide an opportunity of transfer via horizontal gene transfer.

It might be that during anoxic condition on the earth, *ars*RB operon first evolved that conferred primitive cells to minimize arsenite toxicity. After the appearance of oxic condition, arsenate prevailed in environment and thus *ars*C evolved. This gave rise to *ars*RBC operons that enabled detoxification of arsenate. *ars*D originated during later phase of evolution of life on earth where *ars*RDABC operon lead to tighter regulation of arsenic tolerance. Besides traditional genes for *ars* operons, there are various additional genes encoding proteins responsible for arsenic detoxification or resistance like *ars*H, *ars*I, some proteins like Acr3, AqpS and transporters of major facilitator superfamily (MFS). Acr3 is an arsenite efflux pump present in prokaryotes, fungi and some plants. However, ArsB is confined to prokaryotes only. These two are excellent examples of convergent evolution as the transporters and As^{5+} reductase enzyme families have evolved independently but address the same stress, i.e. As exposure (Mukhopadhyay et al. 2002). With advancement in technologies governing prokaryotic genome sequencing, it was concluded that *ars* operons are evolving as a result of convergent evolution (Silver and Phung 2005). Role of *ars* operon in encoding aquaglyceroporin (AqpS) whose function is similar to ArsB transporters is established to extrude arsenite (Mukhopadhyay et al. 2014).

Zhao et al. (2015) demonstrated the utility of As-dedicated multi operons in *Rhodopseudomonas palustris* strain CGA009. Expression of operon *ars*2 and *ars*3 was differentially regulated and enhanced upon increasing As^{3+} concentration up to 1 mM. Marine bacteria also process *ars* operon (Singh et al. 2014). Marine isolated *Vibrio* showed presence of *ars*C gene with 98–99% homology with *ars* operon of *E. coli*. Extremely resistant strain of *Brevibacterium linens* AE038-8 can tolerate inorganic As species, i.e. up to 75 mM of arsenite and approximately 1M of arsenate even in minimal media (Maizel et al. 2016). This is because of the occurrence of ACR3, *ars*C gene and *ars*O. Yang and Rosen (2016) recently described the role of *ars*M, *ars*I and *ars*H which encodes As (III) S-adenosylmethionine methyltransferases, C–As bond lyase and methylarsenite oxidase, respectively, for organic arsenicals detoxification.

Dissimilatory arsenate reduction is prominent in bacteria and archaea only where As (V) being electro positive in nature gets used in respiratory chain for growth and

Fig. 10.2 (continued) (Arsenate reductase; helps in catalysing reduction of arsenate [As(V)] to arsenite [As(III)], 139 aa), ArsB (Arsenic efflux pump; 436 aa), ArsR1 (COG0640 Predicted transcriptional regulators, 116 aa), ADC51661.1 (COG0798 Arsenite efflux pump ACR3 and related permeases, 318 aa); (**b**) *Escherichia coli.* Input protein is ArsR with major predicted functional partner viz. ArsB and ArsC

survival (Ahmann et al. 1994). As (V) respiration is quite evident in proteobacteria, thermophilic and Gram-positive eubacteria present in different environmental conditions (Stolz et al. 2006). After reduction to As (III), it gets potentially oxidized with the help of arsenite oxidase which was first reported in *Bacillus arsenoxidans* (Green 1918). Arsenite acts as electron donor hence reduces oxygen or nitrate (Richey et al. 2009; Sun et al. 2010). Currently, two different arsenite oxidase enzymes have been reported, viz. AoxAB (AroBA or AsoBA) and ArxAB. This oldest procedure of detoxification method is carried out by heterotrophic and chemoautotrophic bacteria while ArxAB is restricted to purple sulphur bacteria, ectothiorhodospiraceae family (Oremland et al. 2002; Kulp et al. 2008; Huang et al. 2012). The small and large subunit of arsenite oxidase encoded by genes called as *aio*A and *aio*B, although dedicated nomenclature has not been assigned to the genes. The process of As (III) oxidation occurs in bacteria's periplasm. In periplasm, sensor kinase aoxS detects arsenite and triggers aoxR which is a regulatory protein (Oremland and Stolz 2003). This results in activating transcription factors for As (III) oxidase in bacteria and expression of *aio*A and *aio*B genes (Huang et al. 2012).

Arsenic methylation is another detoxification procedure used by bacteria, fungi, archaea, algae, plants, animals, humans and recently in some protozoans (Shariatpanahi et al. 1981; Michalke et al. 2000; Wang et al. 2004; Yin et al. 2011a, b). The organisms convert As (III) into methylated form of As which is volatile. The volatile compounds are mono-, di-, trimethylarsine (MMA, DMA and TMA). Some non-volatile compounds include methylarsonate and dimethylarsinate. The process is considered to be detoxification procedure, however, the products like MMA and DMA are more toxic than inorganic form (As (III/V). Thus some researchers do not consider this process as a detoxification procedure (Bentley and Chasteen 2002; Stolz et al. 2006; Dopp et al. 2010). The physiological function and biochemical basis of methylation is still unclear. *ars*M encoded As (III)-S-adenosylmethyltransferase, ArsM protein catalyses the formation of As methylation and its homologs are quite widespread (Qin et al. 2006). The multistep process involves S-adenosylmethionine as a methyl donor to As (III) through ArsM protein. Here, glutathione acts as electron donor. Demethylation process is being carried out in some of the microbes in order to use it as source of energy. Such process is observed in species of *Pseudomonas*, *Burkholderia*, *Mycobacterium*, *Alcaligenes,* etc. but mechanism is still not clear (Maki et al. 2004; Yoshinaga et al. 2011).

10.3.3 Arsenic Detoxification in Animals

As toxicity can be seen in animals as binding of As (III) with sulfhydryl group induce alteration in protein structures thereby inactivates several critical enzymes. Arsenite inhibit pyruvate dehydrogenase thus block citric acid cycle. This damages electron transport chain. Soil contaminated with As adversely affects invertebrates. PCS genes are found in few species of metazoans belonging to mollusca, chordate, annelida, cnidaria and echinodermata (Clemens 2006; Clemens and Persoh 2009). However, very little is known about their functional attributes. According to study

conducted by Liebeke et al. (2013), *Lumbricus rubellus* produces PCs when exposed to arsenic in dose dependent manner, however, not regulated transcriptionally. There are evidences of response due to metal stress which are reported in aquatic animals after exposure to As. Cytotoxicity and oxidative stress are evident in fishes like *Clarias batrachus* and polychaeta (Bhattacharya and Bhattacharya 2007; Ventura-Lima et al. 2009a). Taking into account, the aquatic animals minimize As toxicity by increasing antioxidative responses and even alters antioxidant system which can be seen in zebra fish (*Danio rerio*), gold fish (*Carassius auratus)* and common carp (*Cyprinus carpio*) (Bagnyukova et al. 2007; Ventura-Lima et al. 2009b).

In mammals, arsenite gets methylated via arsenite methyltransferase where S-adenosylmethionine acts as methyl donor (Thomas et al. 2001; Akter et al. 2005). The conversion of As in less/non-toxic form occurs with the help of methylarsonate reductase that require GSH which is an isoform of glutathione-s-transferase (GST). GST omega genes are found in humans (identical to monomethylarsenic acid reductase, MMA^V), aquatic animals like *Takifugu rubripes*, *Tetraodon nigroviridis*, *D. rerio*, *Xenopus tropicalis,* etc. (Ventura-Lima et al. 2011). The osmolarity of cells are governed by aquaporins. In invertebrates, these channel proteins, viz. AQP7 and AQP9 are found in kidney and liver, respectively. The aquaglyceroproteins are found to uptake As (III). Similarly four human aquaporins (AQP3, AQP7, AQP9, AQP10) can uptake arsenite (Liu 2010).

10.4 Chemistry of Siderophore Metal Chelation

Siderophores are non-ribosomal peptides widely known to chelate iron to make it accessible to their producers (Neilands 1995). It encompasses various classes of molecules bearing different functional groups such as catechol containing catecholate siderophores, alkylamine or hydroxylated ornithine containing hydroxamate siderophores, carboxylate siderophores with citric acid and some siderophores termed mixed type containing combinations of these functional groups (Khan et al. 2018). Besides iron chelation, siderophores are also capable of binding with other metals. However, this binding differs in terms of binding affinity, chirality, denticity and other physiochemical parameters. Also, different classes of siderophore might bind in different ways with metals including iron. Denticity (κ), i.e. number of atoms from a ligand or chelator bound to metal plays a key role in metal-siderophore complexation. They might form bidentate, tridentate or a hexadentate complex with iron (Boukhalfa and Crumbliss 2002). Another aspect is the chirality at the metal centre or peptide backbone that plays important role during recognition by cell surface receptor (Matzanke et al. 1984; Raymond et al. 2015). Such stereospecificity was observed in case of rhodotorulic acid (RA; hydroxamate type of siderophore) where transport of iron complexed with RA proves much efficient than the complex with its enantiomer (Matzanke et al. 1984). Metal–ligand interactions including metal-siderophore interaction are widely studied in context of hard and soft acid and base theory (Pearson 1963). According to this theory, based on charge density, charge-to-size ratio, polarizability and nature of interactions

metals are categorized into hard and soft acids/bases. Also, hard acids (high +ve charge and smaller ionic size) are known to bind with hard bases (small anionic neutral molecules) while softer ones (transition metal with +1/+2 charge) are known to bind bases categorized as soft (large anionic neutral molecules).

Beginning with iron, its ferric form is a hard lewis acid and forms complex with siderophore by binding generally with its hard oxygen donor (however, sometimes nitrogen or sulphur are also involved) that governs the iron hydrolysis making it accessible for utilization (Dhungana and Crumbliss 2005). Siderophore forms bi-, tri- as well as hexadentate complex with iron of which hexadentate is thermodynamically most stable structure. However, a tetradentate structure is easier to reduce than hexadentate complexes which are also essential for efficient iron transport (Boukhalfa and Crumbliss 2002). Siderophores chelates iron in both ferric (Fe^{3+}) and ferrous (Fe^{2+}) form by mineral dissolution facilitated either by ligand exchange or by reduction, respectively (Dhungana and Crumbliss 2005). During Fe^{3+} ion chelation, for metal dissolution, a ligand exchange event occurs whereby an iron chelating moiety of siderophore replaces oxygen/hydroxide groups of ferric ions (Hersman 2000; Kraemer 2004). In yet another mechanism of reduction ferric ion is reduced to ferrous and then its chelation by siderophores occurs (Albrecht-Gary and Crumbliss 1998; Dhungana and Crumbliss 2005), thermodynamically shifting the equilibrium of solubility making iron more soluble and also making iron-hydroxide protonation easier. Iron dissociation is further enhanced by introducing dissociation in first co-ordination shell of iron by displacing already present labile water molecules in the shell.

Of all the known siderophores, enterobactin is known to form strongest complex with iron using its three catecholate moieties arising from triserine lactone backbone. Generally, siderophores upon protonation releases bound metal but such is not the case with enterobactin. Protonation results in conversion of catecholate mode of enterobactin to salicylate mode of enterobactin in turn allowing metals to remain co-ordinated with the siderophore (Cass et al. 1989; Raymond et al. 2003). Another factor that governs the stability and complex formation of iron and siderophore is cyclization. Macrocyclization forms a metal-binding pocket and are known to form more stable complex with iron than a linear form of siderophore. For example, a macrocyclic siderophore alcaligin (a dihydroxamate siderophore from *Bordetella* sp.) binds with a stability constant of 10^{37} M^{-1} and forms 32 times more stable complex than linear RA at physiological pH (Hou et al. 1998; Brickman and Armstrong 2007). Siderophores produced by the same organisms might also bind with iron with different affinity, e.g. two siderophore from *Pseudomonas* sp., namely pyoverdine and pyochelin binds iron with an affinity of 10^{24} M^{-1} (neutral pH) and 2×10^5 M^{-1} (in ethanol) respectively (Neilands 1981; Cox et al. 1981). Also the stoichiometry of siderophore versus iron differs for these two siderophores as pyoverdine forms complex with iron in a ratio of 1:1 while for pyoverdine iron complex the ratio is 2:1 (Tseng et al. 2006).

Siderophores also binds with copper ions as seen in case of bacterial siderophore such as those of *Bacillus megaterium* and cyanobacterial siderophore of *Anabaena flosaquae and A. cylindrica* (McKnight and Morel 1980; Arceneaux et al. 1984).

However, unlike ferric ions copper is a softer acid and forms complex with siderophores with softer donor atoms (Johnstone and Nolan 2015). Strong copper-hydroxamate complexes were detected when cultures were deprived of iron in turn leading to release of hydroxamates (McKnight and Morel 1980). Certain bacteria are known to produce siderophores that enhance copper toxicity while others aids in Cu (II) binding and in turn provide resistance against copper. For example, uropathogenic strains of *Escherichia coli* principally produce enterobactin that chelates iron and also are responsible to chelate and reduce Cu(II) to more toxic Cu(I) form (Henderson et al. 2009; Chaturvedi et al. 2012). Such conversion proves fatal to these pathogenic strains. However, at the same time these strains produce another siderophore yersiniabactin that binds cupric ions preventing their conversion to cuprous form by enterobactins. This occurs probably by utilization of thiazolines/thiazolidine present in yersiniabactin. In yet another siderophore from *Pseudomonas* sp. known as pyochelin (Pch) two Pch ligands are involved for a cupric bischelate formation; one forms a tetradentate complex while other binds loosely to cupric ion (Brandel et al. 2012). Apart from Pch *Pseudomonas* sp. are also known to produce another siderophore pyoverdine which shows greater affinity towards iron unlike Pch that prefers divalent ions such as Cu (II) due to presence of nitrogen binding sites that prefers softer metal ions.

Similar to copper, zinc is also prevalent in divalent form and is known to form tetrahedral or octahedral complexes (Steinbrueck et al. 2020). Zinc gets chelated by siderophores, however, with lower affinity than iron (Braud et al. 2009). The formation of a complex between Zn (II) and pyochelin occurs either through interaction between phenolate oxygen or via deprotonated thiazoline/thiazolidine units (Brandel et al. 2012). In *Pseudomonas putida* siderophore called pyridine-2,6-dithiocarboxylic acid (ptdc) are known to be secreted that bind with zinc by using its soft sulphur donor atom via formation of a tridentate binding pocket involving two sulphur and one nitrogen atom (Sebat et al. 2001; Cortese et al. 2002). Namiranian et al. (1997) reported a red shift from 455 nm to 459 nm when Zn (II) was added to a pyochelin and subjected to fluorescence. They suggested that Zn (II) forms complex with phenolate of pyochelin in ground state that breaks upon excitation. The small shift of 4 nm suggested weak complex between pyochelin anion and Zn (II).

Another metal, manganese widely present in three oxidation states, i.e. Mn (II), Mn (III) and Mn (IV) is also known to form complex with siderophores. Siderophores possessing different functional groups are known to oxidize manganese and form strong Mn (III)-siderophore complex (Harrington et al. 2012). Not only does co-ordination between iron, copper, zinc and manganese have been studied with siderophore but there are a number of other metals such as cobalt, gallium, silver, aluminium, cadmium, etc. that forms complexes with various types of siderophore. Khan et al. (2020) reported bioaccumulation of cadmium ions that forms a thermodynamically stable complex with triacetylfusarinine C (a hydroxamate siderophore from *Aspergillus nidulans*) with a binding energy (E_{total}) of −44.24 kcal/mol. In yet another instance several other metals including those mentioned have been confirmed to bind pyochelin siderophore, however, with

affinity lower than iron (Braud et al. 2009). Binding of arsenic with siderophores of different origins has been studied widely.

10.5 Siderophore Mediated Arsenic Mitigation

Like iron and other heavy metals siderophores are known to bind arsenic also. This property of siderophore acting as a metallophore is being analysed to use for mitigation of arsenic and minimizing its toxic effect (Fig. 10.3). Numerous bacteria such as *Pseudomonas* are known to oxidize and reduce different forms of arsenic, i.e. As (III) and As (V) mitigating its toxic effect (Ghosh et al. 2015). Such activity has been successfully co-related with siderophore producing capacity of these bacteria. The amount of siderophore production varies among different strains of arsenic resistant *P. fluorescens* grouping them into high, moderate and low siderophore producers. Higher siderophore production led to better oxidation of As (III) while low siderophore producers were efficient in As (V) reduction, thus resisting both the forms of arsenic in an efficient way. This has been attributed to activation of As (III) oxidase by iron internalized via siderophore mediated uptake mechanism.

Mobilization of arsenic serves one of the important factors in mitigating arsenic toxicity as it is known that As (V) is less mobile than As (III). In one instance, arsenic resistant bacteria, i.e. *Staphylococcus* sp. TA6 possessing ars operon and thus resistant to arsenic with high siderophore production capacity showed much stronger reduction of As (V) than non-siderophore producing mutant strain of *Pseudomonas* (Das and Barooah 2018). Such strong reduction occurs in an arsenic rich environment whereby siderophore is basically responsible for releasing As (V) from arsenopyrite by scavenging iron from it. Further, this free As (V) gets reduced to As (III) by arsenate reductase enzyme upon getting inside cells via phosphate channels. This toxic form of arsenic then gets expelled out by arsB transporters. In another instance, siderophore acts similarly upon scorodite composed of iron and As (V) resulting in mobilization and further mitigation of arsenic toxicity (Drewniak et al. 2008).

One of the deleterious effects of As in plants involves formation of iron arsenate ($AsFeO_4$) when As interacts with iron plaques formed on root surfaces of plants (Liu et al. 2006; Bhattacharya et al. 2012). Siderophores produced by microbes at rhizospheres solubilize these plaques either through proton promoted (protonation of O/OH groups of iron) or by ligand promoted (involving organic or inorganic ligands) mechanisms (Kraemer 2004). In another study, three different bacteria namely *Bacillus pumilus*, *Bacillus thuringiensis* and *Pseudomonas* in combination with leonardite (oxidation product of lignite with high affinity towards As) successfully reduced accumulation of As in rice grains (Dolphen and Thiravetyan 2019). Bacteria producing more siderophore, i.e. *B. pumilus* were better in reducing As accumulation in grains than *Pseudomonas* followed by *B. thuringiensis.* Also, efficiency of reducing As accumulation was much better in combination of leonardite and microbes when compared with administration of leonardite alone. Expression of silicon and phosphate transporters also responsible for As (III) and As

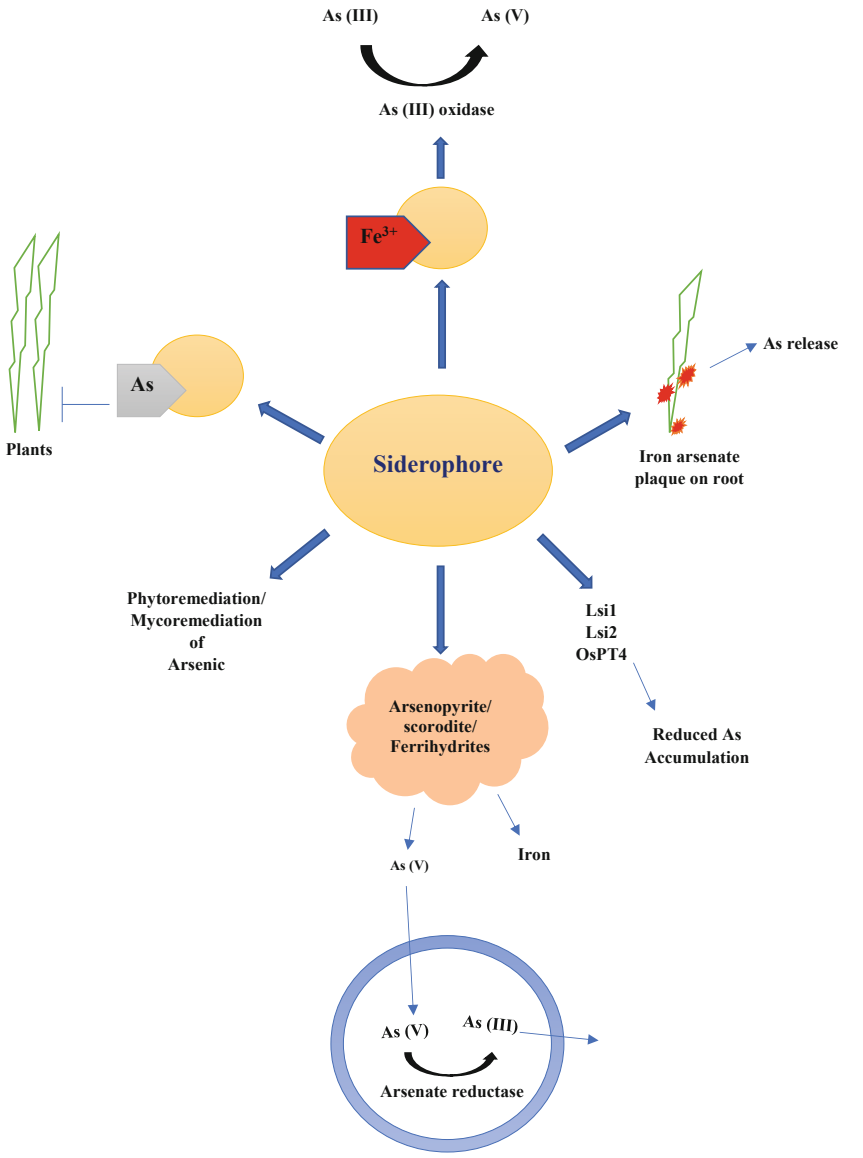


Fig. 10.3 Schematic representation of siderophore mediated As mitigation

(V) uptake, i.e. Lsi1, 2 and OsPT4, increases upon As exposure in these plants. Addition of leonardite together with siderophore producing bacteria causes downregulation of these transporters further reducing As accumulation and toxicity.

Arsenic in its As (III) form presents high binding affinity with siderophores isolated from different actinobacteria (Retamal-Morales et al. 2018). Exogenous

application of siderophore isolated from different organisms or co-culture of siderophore producing microbes is being tested nowadays for their ability to reduce toxic effects of arsenic in different organisms. As is known to damage cellular membrane and increase ROS generation as evident in level of antioxidative enzyme (SOD, POD, etc.) production in wheat (Zhang et al. 2007). Siderophore produced from fungus, i.e. *Aspergillus nidulans* mitigates the harmful effect of As and restored the SOD, CAT, POD as well as MDA level in wheat genotype NW1014 growing under arsenic stress (Kumari et al. 2019). Such inhibition was attributed to greater affinity of siderophore towards arsenic than towards iron. Formation of siderophore-arsenic complex rendered entry of As inside plants reducing toxic effect of As.

Arsenic hyperaccumulator *Pteris vittata* gets benefitted in terms of biomass upon addition of siderophore producing bacteria like *Delftia sp.*, *Variovorax* sp. among others in the rhizosphere (Lampis et al. 2015). Application of siderophore from *P. aeruginosa* releases arsenic from ferrihydrites (composed of iron and arsenic) which further forms complex with available siderophore (Jeong et al. 2014). The siderophore-arsenic complex gets transported to leaves as seen in *Pteris cretica* which can easily be removed. These approaches suggest use of these plants along with siderophore producing bacteria as a means of phytoremediation in arsenic contaminated soils. Also, siderophore produced from *Pseudomonas azotoformans* also serves as washing agent in arsenic as well as other heavy metal contaminated soil removing about 92.8% of arsenic without damaging soil microbial community (Nair et al. 2007).

Not only bacteria siderophore from some saprotrophic fungi like *Purpureocillium lilacinum*, *Absidia spinosa* among others have been investigated for their capacity of As mycoremediation (Ceci et al. 2020). These fungi possess high tolerance against As and are able to produce siderophore at the same time suggesting similar utilization of siderophore as in bacteria for As mobilization. However, exact mechanism and suggested co-relation between siderophore mediated mycoremediation of As needs to be established. We may state that mitigation of arsenic toxicity in microbes, plants and environment is possible using a number of different siderophores from numerous organisms, however, more clear understanding of mechanisms and development of efficient methods to use them is still required.

10.6 Conclusion

The toxicological effects of arsenic in the surrounding possess serious threat affecting millions of people worldwide. Contamination deteriorates environment, agricultural sector, health even at low concentration. In order to cope up its deleterious effect organisms have evolved detoxification system. Oxidation, reduction and biomethylation of arsenic play a crucial role in converting arsenic into less toxic form. The biological based heavy metal minimization approach is turned out to be most effective, economic and environmental friendly. Last few years have further revealed the role of secondary metabolites in arsenic mitigation. Siderophore which was earlier believed to chelate iron is now considered as metallophore due to its

ability to chelate several other elements including arsenic. Although binding affinity of different siderophores based upon chemical structure and origin with arsenic varies, it is interesting to explore the interaction and mitigation mechanisms. This will further help the investigators to develop genetically engineered microbes and plants based upon their potential application to remove arsenic which is yet not established.

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Mechanisms of Arsenic Transport, Accumulation, and Distribution in Rice

11

Akshay Shinde and Kundan Kumar

Abstract

Arsenic (As) is a prevalent form of metalloid in the environment, which exists in its organic as well as inorganic forms. Arsenic is a well-known carcinogen and its prolonged exposure and intake may lead to several health disorders in humans. Contamination of arsenic in the soil results in arsenic accumulation in the food crops and thus enters the food chain. Rice being a staple food in many countries is at a higher risk for arsenic accumulation since it is capable of accumulating various heavy metals as well as metalloids present in the soil, out of which, arsenic is the most common. Several transporters were identified in rice roots which were found to have a function in arsenic uptake and translocation to grain. Rice, OsLsi1, and OsLsi2 are widely studied silicon transporters which actively participate in collection and transport of arsenic. Proteins from the Nodulin-26 like Intrinsic Protein (NIP) family, namely, OsNIP2;1, and OsNIP3;2 and Plasma membrane Intrinsic Protein (PIP) family, namely OsPIP2;7, OsPIP2;6, and OsPIP2;4 also play a vital role in arsenic translocation from soil to root and root to grain. In the plant, arsenic efflux from root to shoot occurs through xylem while the transport from shoot to grain occurs through phloem. In the rice grain, the rice bran and brown rice were found to have more arsenic concentration as compared to polished rice. This chapter highlights the critical factors responsible for uptake, transport, distribution, and accumulation of arsenic in rice.

Keywords

Arsenic · Rice · Transport · Rice grain · Aquaporin · Accumulation

A. Shinde · K. Kumar (✉)
Department of Biological Sciences, Birla Institute of Technology & Science Pilani, K. K. Birla Goa Campus, Zuarinagar, Goa, India
e-mail: kundan@goa.bits-pilani.ac.in

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11.1 Introduction

Arsenic (As), a well-known carcinogen, is introduced into the soil by numerous environmental factors as well as human activities and thus considered as a global contaminant (Mandal and Suzuki 2002; Zheng et al. 2013). Arsenic in the contaminated crops or drinking water has a major health impact on humans and animals (Ng et al. 2003) as well as phytotoxic to plants leading to decline of crop growth and yield (Islam et al. 2017). Arsenic is a metalloid, present in the nature in its organic and inorganic form. The inorganic form constitutes of oxygenated and complexation of As with sulfur and iron, viz. As anions or arsenopyrite (FeAsS) abundantly (Brewster 1992). The inorganic form mainly comprises of arsenate [As (V)], which is pentavalent in nature and arsenite [As(III)], which is trivalent. Arsenate is found in aerobic environments, while arsenite occurs in anaerobic environments. However, inter-conversion among them occurs with respect to the changed pH, redox potential of soil, and the existing microflora (Zhao et al. 2010; Nearing et al. 2014). The uptake of As by the rice plant is affected by the concentration of Fe, Mn, N, S, P and also the pH of the soil (Abedi and Mojiri 2020). As(III) readily cohere to sulfhydryl groups that are present on cysteine residue, thus hampering number of crucial metabolic processes such as ATP synthesis, oxidative phosphorylation, and fatty acid metabolism. Moreover, the fastening of As(III) to glutathione, a known reducing agent, would lead to decrease in the levels of glutathione and thus increase in reactive oxygen species (ROS) (Bhattacharjee et al. 2008). Arsenate, a phosphate analogue, substitutes inorganic phosphate which hampers synthesis of nucleotides and also energy regulation of the cell by interfering with ATP synthesis (Mead 2005). Among the organic forms, methylated arsenic species, viz. monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) are prevalent in nature (Meharg and Hartley-Whitaker 2002). Arsenate is predominantly present in the rice straw followed by As(III) and MMA (Abedin et al. 2002a). Apart from those, other organic arsenic species derived from preservatives, and chemicals like herbicides and pesticides may also be present. Most of the study on arsenic in plants is being focused upon rice since it is the crucial source of As intake through diet and is cultivated in areas having water-logged soil that contains high amounts of As. As(III) is the most commanding arsenic species in reductive environment in mostly flooded paddy soils (Takahashi et al. 2004; Xu et al. 2008). Flooding in paddy soils results in a rise of As bioavailability to rice plants via mobilization of arsenite throughout the soil (Xu et al. 2008). The concentrations of arsenite in the soil of flooded rice ranges from 0.01 to 3 μM which is higher in comparison to arsenate level present in aerobic environment (Zhao et al. 2009). It is anticipated that approximately 100 million individuals are exposed to water containing arsenic over the WHO safety limit of 0.01 ppm (Nordstrom 2002). The range of 5 mg/kg–2553 mg/kg arsenic is present in agricultural field by As-comprising pesticides and defoliants (Anawar et al. 2018).

Majorly two species, *Oryza glaberrima* (African rice) and *Oryza sativa* (Asian rice) are cultivated in various parts of the world (Pathaichindachote et al. 2019). Rice is the chief diet food consumed by major part of the world's population and is

described as a natural sponge, knowing its ability to accumulate number of metalloid and heavy metals present in the water and soil (Zheng et al. 2013). Due to the rising population in Asia, the production of rice is expected to rise by 60–70% by the year 2050 (Ma et al. 2019). Shrivastava et al. (2020) suggested that there is considerable amount of As toxicity by consuming rice and products made from rice as a staple dietary source. In comparison to other cereal crops, rice paddy accumulates more arsenic because arsenite is mobilized in flooded soil and then taken up by the silicon uptake pathway. Arsenic is accumulated in larger amounts in the consumable parts of rice, where the concentration in grains is the highest, which ranges from 0.08 to 0.20 mg/kg (Zavala and Duxbury 2008). Reports on As contamination throughout the world showed 150 million people being affected and include many countries such as Bangladesh, Argentina, china, India, Chile, Columbia, and Turkey (Bundschuh et al. 2012; Gan et al. 2014; Tong et al. 2014; Welna et al. 2015). The accumulation of As in soils in Taiwan (157,000 μg/L in root) and Bangladesh (51,900 μg/L in root) is significantly higher compared to other countries (Abedi and Mojiri 2020). As indicated by the organization for toxic substances and disease registry list 2017, As is one of the most toxic metals to the human beings. Around two hundred million humans in 70 nations are exposed to this metalloid (Sodhi et al. 2019).

Toxic effects of As are based on the form of As species and vary from one form to other (Jomova et al. 2011). Both the organic and inorganic forms of As are available in the rice grains, out of which, inorganic As (iAs), DMA, and As(III) are the most common forms. Moreover, rice grain may also contain MMA, As(V), and in some cases tetramethylarsonate. Organic forms of arsenic include different subgroups such as arsenic betaine, methylated species, arsenolipids, and arsenosugars (Heuschele et al. 2017). It was found that inorganic As exposure is linked to various epigenetic alterations in specific genes throughout the genome. Most of these genes are functional in development of a disease, especially having the potential to either prevent or cause cancers. These disease-associated genes have some important functions, such as monitoring optimum utilization of nutrients by the cell, assisting in DNA repair or triggering programmed cell death (Zheng et al. 2013; Bastias and Beldarrain 2016). Disruption of such vital genes may lead to detrimental health consequences in near future. There is an urgent need to develop strategies to decrease the widespread contamination of As in the food chain. This requires a better understanding of the mechanisms that are responsible for the uptake and transport of arsenic in the rice plant and its accumulation and distribution into the rice grain. Many options are explored to reduce the toxic As uptake by rice including plant breeding, water management, genetic approaches, and Si management (Saifullah et al. 2018). This chapter focuses on the mechanism of uptake and transport of arsenic in rice and its extent of accumulation in the edible parts such as rice grains. The representative genes from *O. sativa* involved in As uptake, accumulation and distribution are given in Table 11.1.

Table 11.1 The representative genes from rice which are involved in arsenic uptake, transport and accumulation

Gene category	Gene name	Source	Manipulation	Consequences	Reference
Phosphate Transporter	*OsPht1;8* (OsPT8)	*O. Sativa*	Knockout	Decreased As(V) uptake; increased As (v) tolerance	Wang et al. (2016)
Aquaporins (As(III) transport)	*Lsi1(OsNIP2;1)*	*O. Sativa*	Knockout	Decrease in the As accumulation in straw of field grown rice	Ma et al. (2008)
Arsenate reductase	*OsHAC1;1 & OsHAC1;2*	*O. Sativa*	Overexpression (rice)	Increase in the As efflux into the external medium; Decrease As accumulation in rice grain	Shi et al. (2016)
Glutaredoxin	*OsGrx_C7 & OsGrx_C2.1*	*O. Sativa*	Overexpression (rice)	Increase in the As tolerance; Decreased As accumulation	Verma et al. (2016)
NRAMP transporter (Fe/Mn/Cd/As transport)	*OsNRAMP1*	*O. Sativa*	Overexpression (rice)	Increase in the As tolerance and accumulation	Tiwari et al. (2014)
ABC transporter (Cd/Pb /As transport)	*OsABCC1*	*O. Sativa*	Overexpression *(Arabidopsis)*	Increase in the As tolerance	Song et al. (2014)
ArsB/NhaDpremease (AsIII efflux)	*Lsi2*	*O. Sativa*	Knockout	Decrease in the As accumulation	Ma et al. (2008)
ArsM/AS3MT family (As methylation)	*RpArsM*	*R. palustris*	Overexpression (rice)	Produced methylated volatile arsenic	Qin et al. (2009) and Meharg et al. (2009)
CRT-like transporter (Glutathione hemostasis)	OsCLT1	*O. Sativa*	Knockout	Lower As accumulation in roots but higher or similar As accumulation in shoots	Yang et al. (2016)
Inositol transporter (As transporter)	*AtINT2/4*	*A. thaliana*	Knockout	Lower shoot As accumulation	Duan et al. (2016)
Plasma membrane intrinsic protein	*OsPIP2;4, OsPIP2;6, OsPIP2;7*	*O. Sativa*	Overexpression (*Arabidopsis)*	Enhanced arsenite tolerance	Mosa et al. (2012)

11.2 Arsenic Transport in Rice

11.2.1 Arsenic Uptake

The highest amount of As taken up by rice plant is As(III) followed by MMA, As (V) and DMA (Marin et al. 1992). These As species are taken up and transported with the help of plant cell through specific transporter proteins (Mitra et al. 2017). Rice plant transports silicon from the soil as a part of its requirement to protect and strengthen its stalk and hull. However, the mechanism by which silicon is taken up in rice is responsible for the uptake of arsenic as well, since both the elements follow the same pathway of transportation. The forms of arsenic that are taken up by rice depend upon the water and soil chemistry as well as the variety of rice growing in the field. Therefore, certain varieties of rice are more susceptible than others and hence accumulate more arsenic (Zheng et al. 2013). In most plants grown under water-logged environments, taking up of As(III) is the major cause of As toxicity. Arsenic in its organic form is present in a tiny amount, and mainly consists of arsenic in methylated forms, such as DMA and MMA. Trivalent MMA(III) is partially reduced in the rice roots by MMA(V), although only MMA(V) is translocated to shoots (Guillod-Magnin et al. 2018; Kumar et al. 2019). However, plants take up these compounds in lesser amounts when compared to the inorganic As species (Raab et al. 2007). Li et al. (2009a) demonstrated that OsLsi1 is crucial for the uptake of DMA and MMA by the rice roots. The rice mutant having loss of function for OsLsi1 had reduced the uptake activity for MMA and DMA by around 80% and 50%, respectively (Li et al. 2008). There are four significant elements that are responsible for As accumulation in rice: P, Si, S, and Fe (Zhao et al. 2009). In the biogeochemical pattern of As, Iron (Fe) plays a significant role. Iron oxyhydroxides in the plant root surface or in the soil, acts as a solid adsorbent. A reducing environment is created by the presence of Fe oxyhydroxides, releasing As, which is further adsorbed by the rice roots resulting in higher bioavailability of the metalloid. To transfer O_2 from shoot to root, rice plant develops aerenchyma, which results in oxidation of ferrous to ferric iron and thus Fe oxides or hydroxides precipitation takes place on the surface of the roots (Pan et al. 2014). The Fe covering can sequester metals in wetland plant roots, structure a buffer zone and hence modify the passage of arsenic into the plant roots (Hansel et al. 2001; Liu et al. 2004; Rahman et al. 2014).

11.2.2 Translocation of Arsenic from Root to Rice Grains

The transport of As in the xylem of rice plants co-relates with the As accumulation in the shoots. Xylem harbors several membrane proteins that function in loading of As into the xylem, however, key transporters of As are yet to be explored.

11.2.2.1 Xylem Loading

In rice, Si and As(III) follow the same pathway for xylem-mediated loading and root uptake. Xylem loading of As(III) in the roots of rice plants is by OsLsi2 (Ma et al. 2007; Ma et al. 2008), and OsLsi2 mutations in the rice grains affects the concentration of As(III) in xylem sap and grains significantly. On the other hand, marginal effects are seen in the As(III) uptake by the roots. This suggests that OsLsi2 has a role in As(III) efflux to the xylem (Ma et al. 2008). Khan and Gupta (2018) demonstrated that rice seeds primed with Si and As, helped the plant to tolerate the As stress for a longer duration. The expression of OsLsi6, OsLsi2, and OsLsi1 was higher in the case of As(III)+ Si treatment when compared to Si + control, but lesser than only As(III) treatments, which finally leads to the reduced accumulation of As in the presence of Si. Reports also show the role of NRAMP (natural resistance-associated macrophage protein) in the accumulation of As via xylem-mediated loading (Tiwari et al. 2014). Expression of OsNRAMP1 conferred tolerance to As(III) in *Arabidopsis*. However, in rice, the function of OsNRAMP1 in transport of As is not clear. Inorganic phosphorous (Pi), As(V) generally enters the rice roots by phosphate transporters (PHTs), essentially PHT1 (phosphate transporter1) type transporters (Luan et al. 2018). Constructive expression of phosphate transporter (OsPht1;8) showed increase in the xylem loading and As(V) uptake. Significant increase in As(V) translocation was seen from roots to shoots by the overexpression of OsPht1;8 (Wu et al. 2011; Li et al. 2015).

The transport of As(V) through xylem from the root to shoot utilizing X-ray absorption spectroscopy imaging was demonstrated by Smith et al. (2008). After the translocation of As(V) to shoots, it is transported by phosphate transporters (Punshon et al. 2017). Phytochelatins complexes the As(III) and eventually sequestered in the vacuoles (Zhao et al. 2010). In addition to sequestration and complexation in root vacuoles, transport of As(III) occurs through the xylem to the shoot (Su et al. 2010; Ren et al. 2014). Translocation of arsenic into grains depends on the rate by which As is taken up by the roots, concentrations of As present in soil, forms, and xylem flow rate, complexes with phytochelatins, cultivar to reduce As and sequester into vacuoles (Suriyagoda et al. 2018). Thiol complexation interferes with As(III) movement but not with organic As species. Additional, factor recommended to be accountable for mobility changes is hydrophobicity of organic and inorganic As. MMA(V) and DMA(V) were the only pentavalent organic As species existed in the xylem sap (Li et al. 2009b; Ye et al. 2012). Even though, few reports show xylem transport of As, there is almost no data that shows the procedure of phloem mediated transport of As to grains. DMA(V) and MMA(V) have likewise been observed in phloem sap and their concentration was relatively higher than xylem sap (Ye et al. 2012). A transcription factor OsARM1 (ARSENITE-RESPONSIVE MYB1) is responsible for the uptake and transport of As(III) from the soil and also from root to shoot translocation in rice through regulating the expression of OsLsi6, OsLsi2, and OsLsi1. OsLsi6, OsLsi2, and OsLsi1 were significantly upregulated in OsARM1-knockout lines in comparison to wild type and downregulated in OsARM1-over-expressing lines (Wang et al. 2017).

Arsenic concentration in the node and internode of *lsi2* mutant and wild type of excised panicles as well as soil grown plants were analyzed with the help of synchrotron mX-ray fluorescence (m-XRF) (Chen et al. 2015). *lsi2* mutants have lesser As accumulation in phloem of the top and internode compared to wild types. Similarly, in *lsi2* mutant, lower As distribution in grain was found in excised panicles containing As(III) compared to wild types. Whereas, when DMA was supplied externally there was no difference noticed. The production of PC is inhibited by L-buthionine sulfoximine (BSO) hinders the synthesis of PC leading to increase As accumulation in grains. Therefore it was concluded that rice nodes acts as filters and limits As(III) translocation to the grain with crucial roles of PC and Lsi2 levels (Chen et al. 2015).

11.2.2.2 Phloem Loading

The As translocation was studied in excised panicles from shoot to grain, which revealed that 90% of As(III) transport is involved in phloem activity and 55% of DMA transport to the grain (Carey et al. 2011). It suggests that translocation of inorganic As is majorly via the phloem, while transportation of DMA is via both xylem and phloem (Carey et al. 2010). DMA and MMA showed the highest translocation to the rice grain. While As(III) was not at all translocated and As (V) was translocated in very minute amount and was promptly reduced to As(III) in the flag leaves (Carey et al. 2011; Norton et al. 2012). Hence for the accumulation of As in grains, phloem transport plays a crucial role (Carey et al. 2010; Song et al. 2014). However, till date, the transporters that carry out As species from the phloem and influx it inside the grains are not identified (Punshon et al. 2017). Arsenic transportation follows a similar route by which nutrient transport is facilitated in rice (Krishnan and Dayanandan 2003). The transfer takes place in the nodes. These nodes have various kinds of vascular bundles which control the transfer of minerals to panicles and leaves (Yamaji and Ma 2017). In the intravascular transfer of As(III) the efflux transporter Lsi2 plays a crucial role (Chen et al. 2015). Lsi2 is more expressed in roots and nodes, higher accumulation of As in companion cells of phloem and enlarged vascular bundles in rice nodes was observed (Moore et al. 2014). For hampering the transfer of As(III) to the grains, vacuolar sequestration in roots and sequestration of As(III)-PC complexes in phloem companion cells of nodes are essential. Since, DMA is neither permeable through Lsi2 nor complexed by PCs, hence this mechanism is not applied to DMA. Carey et al. (2010) fed broken panicles with As(III) or DMA to the developing rice caryopsis to investigate the role of inorganic As and DMA transport. In spite of the concentration of DMA(13.3 mM) to AS (III) (133 mM), only one-tenth in the feeding solution, DMA was more efficiently transported to rice grains. However, higher As accumulation (17-folds) was seen in rice grain by the DMA treatment. The stem-girdling method of phloem removal caused As reduction of 55% in the grains and 90% and 55% in the As(III) and DMA treatments, respectively. This concluded that essential ways of DMA transport are phloem and xylem, while for AS(III), phloem alone is crucial. Study conducted by Carey et al. (2011) stated that iAs in grains is less transported via phloem, but efficient transport of organic species occurs.

The characterization of rice OsPTR7, a peptide transporter was performed (Tang et al. 2017). Transporter was significantly expressed during grain filling stages of nodes, roots, and leaves. Under field conditions, WT plants had 35% more As in the form of DMA in grains, while no DMA was found in mutants of OsPTR7 in grain. Hence, OsPTR7 is considered as a grain transport of DMA and transporter for root to shoot translocation at longer distances (Duan et al. 2016). AtINT2 and AtINT4 (inositol transporters) might be responsible for As(III) accumulation in seeds (Duan et al. 2016). The most mobile As species in plants is DMA which can be easily transported from root to shoot. The *OsPTR7* plays an important role in transport of DMA in the xylem and phloem (Abedi and Mojiri 2020).

11.3 Major Intrinsic Proteins (MIPs) in Arsenic Transport

MIPs plays vital role in arsenic translocation and transport. The family of MIPs has been divided into five subfamilies, of which, PIPs and NIPs have been well characterized in rice for As transport (Kumar et al. 2015).

11.3.1 Plasma Membrane Intrinsic Proteins (PIPs)

PIPs comprise of the most ample subfamily of plant MIPs. PIPs maintain water homeostasis as it forms water intrinsic channel of the plasma membrane (Maurel et al. 2015; Saddhe et al. 2018). Apart from water, PIPs also transport molecules such as urea, H_2O_2, CO_2 and also different metalloids of uncharged forms including arsenite (Mosa et al. 2012). PIPs are classified into two subgroups, namely PIP1 and PIP2, having the identity sequence of more than 50% (Chaumont et al. 2001; Mosa et al. 2016; Kumar et al. 2018). The level of expression of five rice PIPs, viz. OsPIP2;7, OsPIP1;3, OsPIP2;6, OsPIP2;4, and OsPIP1;2 and 13 of *Brassica juncea*, viz. five from subgroup PIP1 and 8 from subgroup PIP2, was decreased by arsenite (Mosa et al. 2012; Srivastava et al. 2013). This decrease in expression of specified PIP genes was directly related with a reduced water concentration in plants under the As(III) stress, which ultimately resulted in hindrance of the growth of seedling (Srivastava et al. 2013). OsPIP2;7, OsPIP2;6, and OsPIP2;4 proteins increased influx of As(III) when expressed in *Xenopus laevis* oocytes. OsPIP2;7 OsPIP2;4, and OsPIP2;6 were overexpressed in *Arabidopsis* and exhibited increased tolerance to As(III) and led to its active influx and efflux in plant roots. However, long-term As (III) treatment in plants had no evidence of As accumulation (Mosa et al. 2012). On the other hand, an increased ROS level in plant root was seen at the same time, and it was shown that ROS propelled the subduing of PIP2 transcript accumulation in the root (Wudick et al. 2015). Further studies should be conducted to explain whether the oxidative stress generated by As toxicity or direct As(III) stress cause change in levels of PIPs expression.

11.3.2 Nodulin-26 like Intrinsic Proteins (NIPs)

NIPs constitute one of the five subfamilies of the plant MIPs (Maurel et al. 2008). Transporters of NIP subfamily are permeable to arsenite (Ma et al. 2008). NIPs have lower permeability to water and can transfer different uncharged solutes that include boric acid, silicic acid, urea, ammonia, glycerol (Wallace et al. 2006), and toxic metalloids such as arsenite (Isayenkov and Maathuis 2008; Ma et al. 2008). NIPs show similarity to a bacterial homologue of aquaporin GlpF, which is also able to transport arsenite (Wallace et al. 2006). The rice genome constitute 10–13 members of the NIP subfamily (Forrest and Bhave 2008; Maurel et al. 2008). The aromatic/arginine (ar/R) selectivity filter and the highly conserved asparagine-proline-alanine (NPA) motifs regulate the substrate selectivity of aquaporins (Wallace et al. 2006; Maurel et al. 2008; Karle et al. 2020). NIPs have been divided into two or three subgroups based on the pore structure at ar/R selectivity filter region (Wallace et al. 2006; Mitani et al. 2008). The archetype nodulin 26 is the NIP I subgroup which is porous to lactic acid, water, and glycerol. The subgroup NIP II has larger pore size compared to the NIP I subgroup, and is porous to solutes such as formamide, urea, and boric acid, however, has lower permeability to water (Wallace et al. 2006). NIP III have smaller sized residues on the ar/R regions which make them permeable to silicic acid and thus have the largest pore diameter. However, arsenite permeability is observed in all NIP subgroups, which suggest that ar/R selective filters do not control the transport of arsenite and there is a possibility of having more proteins permeable to arsenite. The transport of arsenite into rice root cells is through Lsi1, while Lsi2 causes efflux of arsenite towards the xylem (Ma et al. 2008). Lsi2 was first known to be a Si efflux transporter and present at the proximal side, in contrast to Lsi1 (Ma et al. 2007). Therefore, the Lsi2 transporter necessitates the influx of silicic acid from external medium to stele in the Si transporter pathway, and the Lsi2 mediates the efflux of Si towards the stele (Ma and Yamaji 2006; Ma et al. 2007). When compared to the wild types a tremendous reduction (66–75%) in the pooling up of As in shoots was seen in two independent *lsi2* mutants (Ma et al. 2008). Moreover, As(III) level in xylem sap was much lesser then those of xylem sap in wild-type plants. The effect of Si to the nutrient solution was studied which resulted in inhibition of transport and accumulation of arsenite to the xylem and the shoots in the wild-type rice, but not in the *lsi2* mutant plants (Zhao et al. 2009). Similar study was performed for *lsi1* mutant. The concentration of As in the mutant shoots was 71% lower and in the roots was 53% lower than the wild type. A decrease in As concentrations in both shoot and root of wild-type plants was observed to larger extents upon the addition of silicic acid but decreased As was not observed in case of the mutants. To confirm if the decreased As accumulation in mutant roots was not an effect of As translocation, a short-term arsenite uptake study for 30 min was performed. The results obtained stated that, when compared to the wild types the mutant plants showed 57% lower uptake of As by the roots, thus indicating Lsi1 play a role in arsenite influx to the roots. The major As species present in the xylem sap in case of the *lsi2* mutant and wild type was found to be As(III), and the concentration in mutant plant was only 9% of the wild type. Ma et al. (2008) reported that Lsi2

have a very crucial role in As transport to the shoot in comparison with the Lsi1 and firmly suggested that the root to shoot translocation plays a critical step in the control of As accumulation in shoots. Rice Lsi2 was found to have a similarity to *E. coli* ArsB which functions as an $As(OH)_3$-H antiporter and shared 18% identity. However, there is a fundamental difference in the arsenite transport system between both of them at the organism level, viz. arsenite is effluxed by bacteria for detoxification, whereas the Lsi2 mediated efflux of arsenite which results in pooling it up in grains and shoot. Hence, transporters for influx and efflux were identified in the roots of rice. These transporters are involved in accumulation and uptake of As(III) (Ma et al. 2008).

Bienert et al. (2008) demonstrated complementation analysis of various NIP genes in yeast. It was noticed that the expression of LjNIP6;1 and LjNIP5;1 from *Lotus japonicas*, AtNIP6;1 and AtNIP5;1from *A. thaliana* and OsNIP3;2 *and OsNIP2;1* from rice showed an increase in yeast sensitivity to antimonite and arsenite, and increased As accumulation in the yeast cells. Physiological studies recommend that OsNIP2;1 (Lsi1) is involved in transport of As(III), which has a role in Si uptake pathway. An increase in As(III) uptake was seen on expression of Lsi1 in the yeast and *Xenopus* oocytes, while in short-term analysis there was a decrease in As(III) uptake of about 60% due to loss in functions in rice Lsi1. An increase in As (III) uptake was noticed in the *Xenopus laevis* oocytes upon expression of rice aquaporins such as OsNIP2;2 (Lsi6) and OsNIP1;1 but these had minute expression levels in rice (Ma et al. 2008). Similarly, an increase in sensitivity towards As(III) was noticed in yeast upon heterologous expression of OsNIP3;2 and OsNIP2;1 (Bienert et al. 2008). These data suggest that As(III) and Si share the same transport pathway for entering the rice root cells because arsenite and silicic acid both have a high *p*Ka value of 9.2 and 9.3, respectively, and both molecules are tetrahedral in shape having similar size. As(III) transport activity was possessed by OsNIP3;3 and HvNIP1;2 in yeast cells (Katsuhara et al. 2014). Expression of HvNIP1;2 and OsNIP3;3 in yeast cells caused an increase in sensitivity to 5 mM As(III) in yeast DACR3 mutants that needed the As(III) efflux transporter ACR3 (arsenical compound resistance 3), which indicated that HvNIP1;2 and OsNIP3;3 are transporters of As(III) (Ali et al. 2012). Rice treated with As(III) did not induce the expression of OsNIP3;3. Further research is needed for confirmation of OsNIP3;3 function in rice (Katsuhara et al. 2014).

11.4 Transporters of Arsenic Other Than PIPs and NIPs

A protein named Natural Resistance-Associated Macrophage Protein 1 (NRAMP1) from rice was proposed to facilitate the translocation and uptake of As(III) from root to shoot. OsNRAMP1 may enable the transfer of As(III) to xylem resulting in As(III) xylem movement from root to shoot. OsNRAMP1 gene expression in *A. thaliana* and yeast resulted in enhancement of As and cadmium accumulation (Tiwari et al. 2014). Hence OsNRAMP1 accompanied by OsLsi2, helps in As(III) loading in xylem as well as transportation of As(III) from root to shoot. The presence of a

putative peptide transporter (PTR7) was postulated in rice, having function of transporter of DMA from roots to grains. A significant gene expression of PTR7 was found in rice leaves, roots, and first node during grain ripening. Moreover, low level of DMA was observed in grain of OsPTR7 mutant as compared to the wild-type grain which contained 35% DMA (Tang et al. 2017). Zhou et al. (2008) demonstrated that overexpression of a homolog of *Arabidopsis* PHR1 and a MYB-CC transcription factor upregulates a numerous Pi transporter genes in rice when grown with enough Pi supply, further results in huge accumulation of P in the shoots. Phosphate transporter 1 (Pht1) family is engaged in expression of over 100 phosphate transporters, which strongly express in the roots (Dutta and Bandopadhyay 2016). Furthermore, the effects of Pi transporters such as PT8 or PHR2 overexpression and the mutation of PH1 on Pi and As uptake were studied in rice. The study revealed that in hydroponically grown rice loading and uptake of arsenite in xylem occurs via Pi pathway. However, the phosphate uptake pathway does not appear to facilitate much to arsenic uptake and transport to grains of rice plants grown in flooded soil (Wu et al. 2011).

11.5 Proposed Mechanism of Arsenic Transport in Rice

Arsenic has an ability of translocation in rice plants from the region of roots to grain. The inorganic form of arsenic, As(III) mainly translocate from roots to shoot, that accounts 60–100% of the whole arsenic (Pickering et al. 2006; Zhao et al. 2009). Limited translocation occurs in roots as As(V) gets reduced to As(III), which along with PCs form complexes and is excluded to the vacuoles (Zhao et al. 2009). Plants that accumulate metals can transport arsenic very fast and effectively through xylem towards the grain. This infers that the xylem is stacked with this metalloid, transfers it to the vacuoles and because of the qualities of the root cell tonoplast (Rascio and Navari-Izzo 2011). Arsenate penetration is attainable due to its similarity to the Pi transporters which belongs to the PHT1 family (Ali et al. 2009). Arsenite is absorbed through NIPs and LSi1 transporters (Meharg and Jardine 2003; Rascio and Navari-Izzo 2011). DMA, and MMA which are the methylated forms of As are taken up through aquaporins and use the similar glycerol mechanism (Rahman et al. 2011). Arsenate is reduced by As reductase (AR) to As(III) in the root cells and in-turn form oxidized form of glutathione(GSSG) from (GSH). Arsenite is transformed into trimethylarsine oxide (TMAOIII) and trimethylarsenic oxide (TMAOV). The methylation path make As volatile species that are delivered into the atmosphere. Another As detoxification pathway is seen by PC synthesis due to the buildup of three amino acids: glutamate (Glu), glycine (Gly), and cysteine (Cys). The segregation of the As III-PC compound take place with the help of ABC transporters within the vacuole (Rahman and Hassler 2014). Toxicity of As(III) is much higher compared to As (V) and has the ability to bind to peptides and proteins containing thiol groups, mainly phytochelatins and glutathione and thus an inactive compound is formed (Tsai et al. 2009). The mechanism of sequestration of As(III) by the vacuole is unknown (Kumar et al. 2015). The proposed mechanism of uptake, transport,

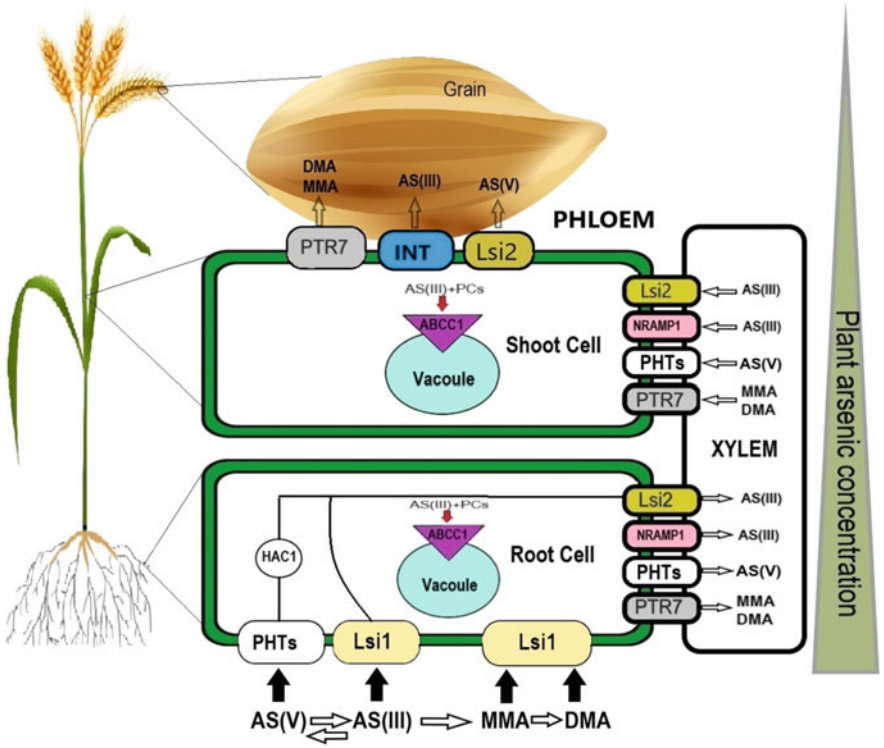

Fig. 11.1 Schematic representation of uptake, transport and accumulation of different As species in rice. [Modified from Chen et al. 2017; Awasthi et al. 2017; Saifullah et al. 2018]

detoxification, and accumulation of arsenic in rice plant is shown in Fig. 11.1. The transport from root to shoot along with xylem and phloem loading of different arsenic species has been shown.

11.6 Arsenic Accumulation

Rice is known to be a strong Si accumulator due to its active Si uptake pathway, which allows uptake of arsenite along with Si. Lsi1 being an aquaporin function as a passive influx transporter, on the other hand Lsi2 functions as an anion channel which is an energy-dependent efflux transporter. The *lsi1* and *lsi2* mutant plants were studied for As accumulation in rice by Ma et al. (2008). It was observed that the *lsi2* mutants contained lesser concentrations of As in grain and straw with respect to the wild type, however, there was no significant difference between the *lsi1* mutant and wild type. Hence, it was concluded that Lsi2 was more crucial than Lsi1 as the former mediates the efflux of arsenite towards xylem, while the latter functions accumulation and short-term arsenite influx in rice. Arsenate is reduced to arsenite in

the root cells, and is then transported to the xylem via Lsi2, which is Si/arsenite effluxer for which Si plays a role of a potent competitive inhibitor. Applying silicic acid fertilizers to rice fields may help to mitigate the complication of excess transfer of As from soil to grain (Zhao et al. 2009). In case of methylated arsenic species, it was observed that the influx of MMA and DMA into rice roots was significantly low when compared to arsenite and arsenate (Abedin et al. 2002b). A similar finding was reported in *Zea mays* by Abbas and Meharg (2008) with respect to DMA. The uptake rate of DMA and MMA was lower than arsenite and arsenate, however, their translocation from root to shoot was quicker. The reason postulated was poor thiol complexation of DMA and MMA which leads to lesser retardation during translocation (Raab et al. 2007). Moreover, DMA was highly accumulated into the rice grain with respect to its rate of transport from root to shoot and majorly distributed around the pericarp/aleurone/subaleurone zone (Zhao et al. 2009). Furthermore, the stem-girdling results showed that phloem transport is the major reason for most of the arsenite transport to the grain, with phloem interruption reducing grain As concentration by 90% (Carey et al. 2010). The effect of sulfur on As accumulation in rice was studied. It was found that high S supply resulted in low As accumulation in the shoot, improved plant growth by alleviating the stress symptoms through activating antioxidant defense system, and enhanced thiol metabolism, which can create a hindrance for the translocation of As from root to shoot (Dixit et al. 2016).

Rice bran, which makes up 7–10% of whole grain weight, contains 24–70% total As in whole grain. The average arsenic percentage in bran is 45% of whole grain, which suggests that As is preferentially concentrated in the bran. However, even in the rice bran, the distribution of arsenic is not uniform. It is accumulated in a small area on the surface that is located at the ovular vascular trace (Meharg et al. 2008; Lombi et al. 2009). It is reported that nutrient transport to the endosperm is facilitated through ovular vascular trace which might be the way for As transport into the endosperm (Krishnan and Dayanandan 2003). It has been suggested that for the redistribution of As to grains, the processes of phloem loading and unloading are essential. In experiments conducted to study translocation of As species from shoot to grain, 90% of the As(III) was accounted by phloem transport and 55% of the DMA to the grain (Carey et al. 2010). Despite thiols being present at sufficient concentrations in the phloem sap, thiol complexes were not formed by As(III) since phloem had a neutral pH (7.5–8.0) (Ye et al. 2010). Moreover, in ovular vascular trace (OVT) accumulation of As(III) along with Mn and Fe was observed, and DMA was not seen in the OVT, but it was spread into the endosperm and across the external parts of the grain (Carey et al. 2010; Carey et al. 2011). However, no As species were present in the embryo.

A putative vacuolar As(III)-PC transporter called OsABCC1 was reported to confine to the phloem companion cells in rice nodes which are important for distribution of nutrients (Moore et al. 2014). It was reported that knockout lines of *osabcc1* tend to accumulate lower level of arsenic in the nodes but higher arsenic level in their grains compared to wild type (Song et al. 2014). These outcomes recommended that OsABCC1 sequesters As into the vacuoles of rice nodes and hence hindered the As translocation into grains (Li et al. 2015).

Arsenate reductase (AR) is an important enzyme in plants, which converts As (V) to As(III). In plants a numerous AR genes are present, two of them being in rice, viz. OsHAC1;1 and OsHAC1;2 which are the orthologs of HAC1 (Shi et al. 2016). In roots, OsHAC1;2 and OsHAC1;1 are expressed, but their localization differs as OsHAC1;1 is abundant in pericycle, epidermis and root hair while OsHAC1;2 is abundant in outer cortex layers, epidermis, and endodermis. Among the two, OsHAC1;1 is significantly expressed in stems and nodes (Xu et al. 2017). Another protein HAC4 was recognized as As(V) reductase in rice (Xu et al. 2017). The mutation in OsHAC1;2, OsHAC1;1 (Shi et al. 2016), and OsHAC4 (Xu et al. 2017) resulted in lower levels of As(V) reduction in roots and further increased As accumulation in shoots and decreased As(III) efflux, while over expression of these genes resulted in contrasting effects in the rice plant (Awasthi et al. 2017). Hence, to avoid accumulation of arsenic in the rice grain, such transporters can be targeted which can sequester the arsenic into the roots or shoots and hence unable to translocate and accumulate it into the edible parts of the plant.

11.7 Arsenic Distribution in Rice Grain

The intake and transport of arsenic from root to grain results in distribution of various types of arsenic species in different parts of the plant which depends on their affinity to the particular plant tissue. A study involving analysis of 121 samples having 12 different rice types revealed that As(III) had the highest concentration in rice grain, which was accompanied by DMA, followed by MMA and As(V). On the contrary, As(V) was found to be the predominant species in rice straw, followed by As(III) and DMA (Latowski et al. 2018). Arsenic concentrations in plant parts were found to be the highest in the flag leaf, with decreasing levels in straw, brown rice, husk, and polished rice. A similar distribution pattern was observed in other studies performed (Liu et al. 2006; Rahman et al. 2007; Xu et al. 2008). During cultivation, the concentration of As in rice straw increased in all sample sets. This observation was consistent with the experiments performed by Zheng et al. (2011). Xu et al. (2008) showed that the As accumulation in the straw intensified for rice plants which were grown under flooded conditions after flowering. The concentration of As was higher the straw than in polished and brown rice, and this finding was in accordance with previous reports. On comparison, the polished rice showed one third lesser concentration of As than brown rice. It can be co-related to the bran removal, as the rice bran accumulates more arsenic as compared to the endosperm (Lombi et al. 2009). In brown rice, bran As was found to be mainly inorganic, while endosperm mostly contained organic species, such as DMA (Sun et al. 2008).

Silicic acid is also crucial for the uptake and distribution of arsenic in rice. The effects of silicic acid on the concentration of As in grain and straws were in line with other studies (Guo et al. 2005; Li et al. 2009b). The transporters responsible are present in the exodermis and endodermis of rice roots, which were earlier known to be silicic acid transporters (Ma et al. 2007). Lsi1 and Lsi2 are present at the distal side and at the proximal side of endodermis and exodermis, respectively. Higher

uptake of Si and As occurs in roots due to the coupling of the above transporters (Ma and Yamaji 2008). Once As travels from endodermis to stele, it is further translocated to the shoot via xylem. Ma et al. (2007) demonstrated that the expression levels of Lsi1 and Lsi2 decreased by supplementing Si, which might result in lesser uptake of As(III). Another hypothesis postulated was that the decrease in As (III) uptake is because of competitive inhibition between silicic acid and As(III) (Guo et al. 2009; Li et al. 2009a, b; Zhao et al. 2009). Application of silicon to paddy soils reduces the concentration of As in polished rice and straw, despite the concentration of As in the soil being higher. The decrease in As level in polished rice was completely dependent on decrease in As(III) concentration while there was no effect of Si application on the concentrations of As(V) and DMA. Other studies also revealed that soil fertilization with silicic acid is beneficial since it reduces the concentration of As in rice straw and grain (Fan et al. 2013; Tripathi et al. 2013; Bastias and Beldarrain 2016). The diminished As(III) movement to the shoot was the aftereffect of either decrease in transporter density because of reduced expression of Lsi1 and Lsi2 or competitive inhibition of As(III) take up by Si at Lsi2, or a mix of both (Lombi et al. 2009; Fleck et al. 2013; Chen et al. 2017). Thus, it can be stated that silicic acid plays a crucial role in distribution of arsenic in rice grain.

Rice nodes are one of the factors that help in the regulation of distribution and storage of As to the rice grain (Yamaji and Ma 2014; Zhao et al. 2012). Study conducted by (Moore et al. 2014) showed As concentration in the nodes was found to be higher as compared to the internodes and leaves. In line with the previous reports (Chen et al. 2015) revealed that the rice nodes acted as As(III) filter by limiting the distribution of arsenite. The PC-As(III) complex transport to vacuoles is mediated by the ABCC transporter which is confined in tonoplast of phloem cells in nodes. *osabcc1* knockout mutants showed lower As accumulation in nodes but higher in grains when compared to wild type (Song et al. 2014). As OsABCC1 is a vacuolar PC-As(III) transporter, it sequesters PC-As in vacuoles in nodes of wild type and does not sequester in mutant. OsABCC1 was reported to be localized in nodal vascular bundle of phloem companion cells thus confirming that the translocation of As into grains is inhibited by OsABCC1 via vacuole sequestration of As (Moore et al. 2014).

Arsenic transport and accumulation was found to be hampered by sulfur (S) supply, however, variable results were seen (Hu et al. 2007; Zhang et al. 2011; Dixit et al. 2016). Srivastava et al. (2016) studied the effect of different concentration of sulfur (S) supply on As distribution and accumulation in rice plants. A considerable decrease was found in the accumulation of As at zero S (0.003 mM) supply compared to normal S (0.798 mM). This was followed by the changes in the arsenic subcellular distribution. At zero S supply, increased synthesis of thiols including phytochelatins was observed. Thus, availability of S is a crucial factor to tackle As stress and when the supply of S is limited, the plants continue to rely on thiol metabolism. Zhang et al. (2016) showed 44% decrease in grain As concentration when supplied with high amount of sulfur. The high sulfur supply resulted in downregulation of the aquaporin genes OsTIP4;2 (Tonoplast Intrinsic Protein) and phosphate transporter OsPT23,while upregulation of phytochelatin synthase genes

(OsPCS13, OsPCS3, and OsPCS1). The study suggested that high sulfur supply led to high amount of PCs synthesis and hence transport As into the vacuoles. Moreover, sulfur supply seemed to reduce As(III) and As(V) uptake in roots by down regulating aquaporin channel and the phosphate transporter, respectively. Yang et al. (2016) and He et al. (2016) identified a rice transporter which was found to be localized to plastids and named OsCLT1 (Chloroquine-resistance transporter Like Transporter). When the mutant *Osclt1* lines were exposed to As(V)or As(III), they showed lower level of PC2 compared to WT and also a decrease in concentration of As. Thus, the biosynthesis is regulated by OsCLT1 of phytochelatins by monitoring homeostasis of glutathione (Awasthi et al. 2017). Similar to silicic acid, supplementation of sulfur to the soil alters the distribution of arsenic in the rice grain by reducing As accumulation of the grain.

Rice varieties from distinct parts of the world vary considerably in arsenic accumulation, distribution, and speciation. Williams et al. (2005) initially performed the comparative study of rice for arsenic distribution. Quantification of arsenic in rice grain was performed using High Performance Liquid Chromatography (HPLC) along with (ICP-MS) inductively coupled plasma mass spectrometry. The rice samples from European Union (EU) and the US was found to have huge amounts of DMA with contrast to Indian and Bangladeshi rice (Williams et al. 2005). The Chinese rice had a higher amount of inorganic arsenic species. Meharg et al. (2009) reported that rice of Ghana (20 ng/g) had lower amount of arsenic concentration which was followed by India (50 ng/g). On the contrary, Thailand, USA, and Italy had elevated arsenic concentration, with Bangladesh and China being intermediate. Vast survey was performed by Zavala and Duxbury (2008) for rice from the USA along with a few samples for Thailand, Pakistan, India Spain, Italy, and Venezuela produced rice. The survey revealed a similar kind of results as obtained by Meharg et al. (2009). Another finding related to the rice color revealed that arsenic concentration in brown, white and other colors is 0.196–0.111 mg/kg, 0.127–0.087 mg/kg, and 0.07–0.05 mg/kg, respectively (Zavala and Duxbury 2008). The brown rice has the highest amount of arsenic due to larger concentration of metalloid in the outer layers (Meharg et al. 2008).

11.8 Conclusion

Rice being a staple food is consumed worldwide and any toxicity entering the food chain through food should be treated with great concern. Arsenic being a potent carcinogen and having a greater affinity towards rice has become a major subject of interest for investigating its transport mechanisms and finding a solution to reduce the arsenic accumulation in the edible parts of rice. In the past few years, research has progressed to study the mechanism of arsenic contamination in rice and the factors responsible for it. However, many of the details regarding the study are yet to be revealed and also a lot of factors need to be investigated with respect to the transport and accumulation of arsenic in rice grains. Use of silicone fortified fertilizers is one of the affordable solutions so far. However, there is a need to explore and find a way

that can alleviate the effects of arsenic contaminated soils on the crops and can sustain in the long run.

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The Healing Art of Arsenic in Various Malignancies

12

Archana Chaudhary and Rizwanul Haque

Abstract

Malignant growth is a significant weight of illness around the world. Internationally, one in every five men and one out of six women will become a potential victim of malignancy prior to the age of 75. The World Health Organization (WHO) is alerted of a worldwide "tsunami" of malignant growth and declared that by 2035, around 24 million individuals will have the ailment. Along with recognizable discoveries in therapy as well as in counteraction of cardiovascular illnesses, malignancy has or will turn into the main executioner in numerous places of the world. Malignant growth is a main source of monetary misfortune through sudden passing and inability around the world in view of the immense whole spent on treatment yet additionally in lost monetary and social action. Arsenic trioxide (As_2O_3) is an aged medication that has lately been restored as a therapeutic option for different malignancies. All in all, arsenic is known to be a natural toxic substance fit for evoking an assortment of risky antagonistic impacts. In spite of its present reputation as a toxic substance, arsenic is viewed as one of the world's most miracle medications, utilized for quite a long time as a therapy for diseases running from contamination to malignancy. Arsenic trioxide (As_2O_3) is a successful forthright enemy of disease, has been utilized as a medication for more than 2000 years, and has been revived due to its exceptional therapeutic efficacy in case with APL (acute promyelocytic leukemia). Arsenic trioxide (ATO) alone or in blend with different therapeutics has been found to be effective against different cancer types of human origin. Notwithstanding, the specific systems by which ATO hinders malignancies are not completely

A. Chaudhary · R. Haque (✉)
Department of Biotechnology, School of Earth Biological and Environmental Sciences, Central University of South Bihar, Gaya, Bihar, India
e-mail: rhaque@cub.ac.in

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clarified. In this chapter we will explain the likely mechanisms of action about the healing craft of ATO towards different human malignancies. These data will most likely urge clinical examiners to sanely join ATO with extra chemotherapeutic agents in treating patients determined to have malignant growth is a main sources of death on this planet.

Keywords

Arsenic trioxide (ATO) · Malignancies · Therapeutics

12.1 Introduction

Malignant growth is yet one of the pronounced well-being confrontations around the world. Reports recommend that every year, tens of millions of whole population are determined to have malignant growth around the globe, and the greater part of the patients inevitably lose the battle against it. The current situation implies that cancer positions the second most basic reason for death following cardiovascular sickness. At this moment, 14 million people a year are analyzed to have harmful development. WHO says that it will increase to 19 million by 2025, 22 million by 2030, and 24 million by 2035 (Ma and Yu 2006). Researches around the world showed that ATO additionally has bioactivity against several tumor types, and its system of activity may incorporate DNA damage, apoptosis, and changes in stress-related proteins and so on (Walker et al. 2016). Arsenic is a strange compound of the world's covering; it is criticized by the environmentalist and classified as a cancer-causing agent. It is an established fact that arsenic and its compounds have been used as a cure and rejuvenator for many diseases yet shockingly it lost its prime spot in medication during mid-twentieth century. Aside from this, in the late 1990s, these compounds were restored by Chinese clinical investigators as well as subsequently adapted by western oncologists (De Thé et al. 2012). Arsenic has a key part in different cancer treatments particularly in hematopoietic cancer along with some positive response in solid tumors also verified (Yang et al. 2020). Presently, the therapy of any malignant growth incorporates medical procedure such as surgery and radiation, sometimes upheld by adjuvant chemotherapy or hormone treatment. Although critical investigations have been made in understanding the pathogenesis of this ailment, remedial issues, for example, the selective killing of normal versus tumor cell growth (Falzone et al. 2018). Our earth is gifted with a natural reservoir of arsenic which has been utilized as a remedial agent for over 2400 years for different ailments. Analysts at Harbin Medical University, China in the 1970s effectively found its capacity to fix intense promyelocytic leukemia. This urged various researchers to test the adequacy of arsenic trioxide in the treatment and control of any solid tumors and other hematological malignancies (Lo-Coco and Cicconi 2011). In this chapter we have summed up the results of clinical preliminaries that use ATO alone or just as in blend with different spices in patients determined to have different tumor types. Furthermore, this part likewise gives a conceivable

mechanism of action by which ATO might be helpful as a chemosensitizer in mix treatments.

12.2 Historical Background of ATO in Medicine

Arsenic has obtained a situation ever, both as a suggested poison and as a miracle medicine. Few decades back arsenic is once in a while hears word in terms of toxicity. For more than 2400 years, arsenic and its compounds, for example, orpiment and arsenic sulfides minerals are used to medicate ulcers and particular sorts of infections (Adams 2008). Since then, arsenic and its different forms have been discovered to be helpful in treating illnesses, for example, malignancy and syphilis. However in recent years, the poisonous reports of arsenic have grown up drastically with more than 20 nations from various parts of the world declaring arsenic contamination. So arsenic is a metalloid that has been notable as a "poison" or a "healer" since forever. English pioneer Thomas Fowler during the 1700s built up a solution of ATO in potassium bicarbonate (1% w/v) that was applied to treat dermatitis, asthma, psoriasis, pemphigus, iron deficiency, lymphoma, and leukemia (Ho and Lowenstein 2016; Adams 2008; Hu et al. 2005). In 1878 researchers found "Fowler's solution" was helpful to bring down white blood cell count in those with chronic myelogenous leukemia and relieved in 10 weeks. After this examination Fowler's solution was applied as a centerpiece in the therapy for blood cancer until it was winning by radiations in the twentieth century. However, ATO therapy constructs a hurried return in 1931 after a record of those nine patients with CML praises to the treatment at Boston City Hospital (Adams 2008). The patients' white platelet tallies tumble from a few hundred thousand for each cubic millimeter to about normal; their spleens and livers decreased in size. Bone marrow biopsy specimens betray ordinary hematopoiesis and patients had an overall feeling of comfort. The therapy's remeasure was fleeting after analysts outline interminable arsenic toxicity in five of the six patients medicated for CML. Based on these reports, the analysts endorse cautious patient assessment with the utilization of the solution. In time, the utilization of arsenic trioxide limited and was again restored—this time by radiotherapy and cytotoxic chemotherapy (Antman 2001; Ho and Lowenstein 2016).

12.3 Arsenic in Ayurveda Medicine

Arsenical have long history of use in pharmacological utilities and conventional practices. Arsenical compounds are deliberately added to Ayurveda formulations as main agile ingredients or an auxiliary agent to assist the effectiveness of herbal drugs (Panda and Hazra 2012). Clinical demonstration due to arsenic containing Ayurvedic medicine has also been reported from our country. Several efficacy aspects and side effects of arsenic compounds used in Ayurveda are scattered in classical text of Ayurveda and modern literature. Arsenic trioxide is now welcomed

in allopathic medicine as first line therapeutics representative in case of hematopoietic cancer and other malignancy.

12.4 Arsenic Trioxide Against Various Tumors

Arsenic trioxide is a chemotherapeutic negotiator of idiopathic capacity applied to medicate leukemia that is lethargic to initial line agents. Researchers have found that arsenic in blend with a current leukemia drug cooperates to focus on a master malignant growth controller (Jagust et al. 2019). Numerous investigations showed that As_2O_3 additionally has some significant function in shutting down the development of other solid tumors too. While arsenic at a specific dose in public drinking water has been connected convincingly to a variety of cancer, surprisingly, its presence at different dosages has been connected to abnormally low paces of different tumorigeneses (Hughes et al. 2011). ATO, when given at a clinically safe dose, the medications successfully repressed various malignancy driving pathways and eliminate cancer stem cells (Kozono et al. 2018) in cell and creature models just as patient-inferred tumor models of different tumor subtypes.

12.4.1 Leukemia

12.4.1.1 Arsenic a Key Enzyme Blocker in Acute Promyelocytic Leukemia

Acute promyelocytic leukemia (APL) reports for around 5–10% of cases of acute myeloid leukemia (AML) (Mohammad et al. 2014). This intricacy is one of the basic enduring reasons for early death in the time of initial detection and start of treatment. Arsenic trioxide is the current expectation or a chemotherapeutic agent that has been appeared to trigger apoptosis in various tumor cell lines. ATO is extremely powerful against a particular kind of blood cancer holding chromosomal translocation between 15 and 17 (Cingam and Koshy 2020; Zhou et al. 2007). It has been shown that this medication is successful against all phases of leukemia, including suppression induction in initial therapy. It is additionally valuable in the combined phase of treatment. Various clinical trials are going to decide the optimum and ideal approach for this medication as a monotherapy or in amalgamation with different medications (Cingam and Koshy 2020). Later on, its indication may stretch out to different malignancies. Researcher around the world worked with models of leukemia, breast, and liver malignancy, and they had the option to find that the blend of ATO with ATRA (all-trans retinoic acid) was appeared to apply synergistic cytotoxicity against Fms-like tyrosine kinase 3 inside pair replication, leukemic cells through co-restraint of Fms-like tyrosine kinase 3 signaling pathways these mix of the ATO-ATRA additionally obliterated a catalyst known as Pin1. Pin1 assumes a key function in regulating the signaling network in malignancy; it induces more than 40 proteins that feed disease tumors, while likewise hindering more than 20 proteins that would typically smother tumor development. This enzyme is overactive in many

kinds of malignancy found in people especially so in cancer stem cell, which drive tumor development and frequently lead to malignant growths' protection from conventional medicines. ATO ties to Pin1, hindering its activity and eventually results in enzyme deformation. Simultaneously, ATRA additionally ties to Pin, debases it and permitting it to encourage and expand cells' take-up of ATO. This prompts the increased expression of a protein explicit to cell membrane, which supports cells retention of ATO (Alimoghaddam 2014). In larger part of the APL cases a new chromosomal aberration, t(15,17), is the most extreme hereditary deformation, and PML-RARαchimeric gene development has an essential function in APL pathogenesis. Directed treatments generally disorganize these fusion genes or its signaling pathways in cells to cope with this ailment. So also, patients with recently analyzed APL and chimeric fusion protein of PML/RARα are generally restored after standard all-trans retinoic acid (ATRA) with chemotherapy. A few reports recommend that predominance of ATRA and arsenic trioxide combination for the treatment of patients with APL as relapse free survival, event free survival, backslide free endurance, and reduced hematologic poisonousness contrasted with ATRA + chemotherapy. Combinational therapy of ATRA and arsenic trioxide differentially tie PML/RARα protein, the proteasomal debasement of which promptly activates terminal differentiation, and resulting apoptosis in acute promyelocytic leukemia APL (Alimoghaddam 2014; Sever and Brugge 2015).

Ongoing ex vivo and in vivo investigations of APL strongly indicates that different mechanisms are proposed for the effect of ATO in leukemic cells such as.

12.4.1.2 Induction of Differentiation

Arsenic trioxide prompts the let go of blood cancer cells into peripheral blood in certain patients and a huge number of naive cells, which may increment leukemic cells to greater than 100,000 per mm^3 (Alimoghaddam 2014; Pavlovic et al. 2015; Portilho et al. 2016). During suppression induction, bone marrow does not set off hypoplastic, and bone marrow creates without cytotoxicity to hematopoietic cells (Alsaleh et al. 2018).

12.4.1.3 Triggers Apoptosis

Arsenic trioxide persuades apoptosis in leukemic cells at a suggested dose (between 0.5 and 2 mmol). The direct mechanism by which ATO induces apoptosis is by triggering cytotoxicity in leukemic cell or indirectly by affecting various regulatory pathways in this cell type. All things considered arsenic causes the arrangement of ROS (responsive oxygen species) and reduces GSH substance of cells. It likewise straightforwardly harms RNA and DNA. Arsenic can persuade mitochondrial caspase framework for the initiation of apoptosis which can be averted by azidothymidine (Alimoghaddam 2014).

12.4.1.4 Other Related Mechanisms

Arsenic has anti-angiogenesis approach and can cut the quantity of new vessels framed while leukemia changes. It additionally has some spin-off on telomere length

and telomerase activity, just as on microvascular robustness of bone marrow during remission introduction (Alimoghaddam 2014; Portilho et al. 2016).

12.4.2 Breast Cancer

Breast cancer is one of the most widely recognized diseases among women and one of the main sources of cancer related death among them around the world. Ongoing reports recommend that arsenic trioxide downregulates DNA methyltransferase-1 expression in this type of malignancy and upregulates estrogen receptor α whose expression profile has been epidemiologically seen to extend disease-free survival and determine a general understanding of apoptosis (Shi et al. 2017). In human breast malignant cell line MDA-MB-435S ATO in mix of antiestrogen tamoxifen (TAM) therapy hampers the cell proliferation both in vivo and in vitro. Researches additionally propose that in breast cancer ATO improves 89Sr radiation therapy initiated apoptosis by mostly directing the Bcl-2/Bax proportion. ATO has function in interruption of rapamycin (explicit inhibitor of mTOR)—provoked ERK and Akt (Ser473) phosphorylation, which at last results in the improvement of the rapamycin's anticancer effect in vivo. Scientist additionally implies that arsenic trioxide when co-incubated with cotylenin A (CN-An), a growth controller of plant, shows a great antitumor impact on breast cancer cells in vitro condition. This combinational treatment of ATO-CN-A altogether downregulates expression of survivin and upregulates caspase-7 by mostly conciliating ROS production. Several cancer preventing agents, for example, melatonin, increase ATO-initiated apoptosis by activating ROS production which triggers MAPK activation incorporating JNK and p38 in human breast cancer. In MCF-7 cells arsenic alongside cryptotanshinone (a characteristic quinoid diterpene secluded from Salvia miltiorrhiza roots) remarkably induces apoptosis by umpiring endoplasmic reticulum (ER) stress as well as ROS production. ATO-persuaded cell cycle arrest is mostly because of demethylation and adjustments of cell cycle-related genes. Arsenic mixes downregulate malignant growth property of breast cancer cells. However, the specific mechanism of arsenic-mediated anticancer effect still not been completely clarified. Ongoing reports showed that arsenic could regulate microRNAs in human malignancies. One such miRNA is let-7a which is strongly upregulated in response of ATO in breast cancer cell and this activated let-7a consequently suppress cell development and provoked apoptosis related genes, for example, caspase-3, p53, and Bcl-2 (B-cell lymphoma 2) which retarded cell invasion and metastasis. In expansion, this microRNA additionally controls mammosphere arrangement limit by Ras/MAPK (mitogen-actuated protein kinase)/ERK and by Ras/NF-κB (atomic factor kappa B) pathway in breast cancer stem cell. Let-7a has an extreme role in tumor suppression through targeting on HMGA1 (high versatility bunch A1) in breast cancer (Shi et al. 2017; Darakhshan and Ghanbari 2013; Sweeney et al. 2012). Thus, ATO induced let-7a may be another potential objective in the therapy of human breast cancer.

12.4.2.1 ATO and let-7a in Notch Signaling

The oncogenic part in numerous tumor types can be best described by Notch signaling pathway. Various reports suggest that arsenic trioxide has been accounted to disturb Notch signaling pathway in various human malignancies. For instance, ATO exhausted the malignant cell growth population in gliomas through suppression of Notch pathway. ATO likewise prompts the hindrance of neurosphere repopulation got from glioblastoma by suppressing Notch pathway (Shi et al. 2017). Hu et al. found that ATO restrained the expansion of myeloma cell line through downregulation of Notch signaling pathway (Hu et al. 2013). Yang et al. revealed that ATO shows anti-lung cancer activity via suppression of Notch-1 (Yang et al. 2013). In accordance with these discoveries, it was investigated that arsenic and its compounds downregulate the expression of Notch-1 in breast cancer cells. These reports distinguished that arsenic trioxide could repress Notch-1 expression in human tumors. Researchers have investigated that Notch-1 repressed let-7a expression. Out and out, ATO applies its anticancer effect via means of hindrance of Notch-1/let-7a in breast cancer. It is notable that arsenic trioxide is essentially utilized for PML (promyelocytic leukemia) therapy (Shi et al. 2017). Along these lines, further examination is needed to investigate whether arsenic applies its physiological capacity by upregulating let-7a using mouse models in this cancer type.

12.4.3 Prostate Cancer

Around the world, prostate malignant growth is the most usually analyzed male threat and the fourth driving reason for malignancy demise in men. In 2018, this added up to 1,280,000 recently analyzed cases and 359,000 deaths around the globe from this ailment (Leslie et al. 2020). Luckily, the limit of prostate diseases has moderate development rate and is short-grade with generally little danger and diminished aggressiveness.

12.4.3.1 ATO in Prostate Disease

It was accounted that ATO boosts the radiation affectability by moderating suppression of the Akt/mTOR signaling pathway in androgen-subordinate (LNCaP) and PC-3 (androgen-autonomous) human prostate cancer cells both in vitro and in vivo. Notwithstanding this ATO likewise suppresses the expansion of PC-3 by repressing the Hh (Hedgehog) signaling pathway and the anticancer impact was strengthen by an exemplary Hh pathway inhibitor cyclopamine in vivo (Tai et al. 2017). ATO + RAD001 (mTOR inhibitor) combination therapy synergistically activates both autophagy and apoptosis in prostate malignant cells, where upgraded autophagy was joined by activated Beclin1 mRNA expression and ATG5-ATG12 upregulated form, LC3-LC2 and Beclin1, as detailed by Tai et al. (2017). The mix of ATO + RAD001 altogether suppresses LNCaP xenograft tumor expansion than monotherapy without improving weight loss. The inhibitor of PI3K-AKT-mTOR pathway, for example, Rad001, has not demonstrated therapeutic adequacy as a

single agent in prostate malignant growth. ATO triggers the autophagy pathway in this cancer type (Tai et al. 2017). It synergizes with Rad001 to activate cytotoxic cell death of prostate malignancy cells alongside synergistic acceptance of apoptosis and autophagy as the basic mechanism. This upgraded autophagy is joined by enhanced Beclin1 mRNA stability and activation of ATG5-ATG12 conjugates, LC3-2 and Beclin1. ATO and Rad001 likewise can synergistically repress malignancy in prostate malignancy xenograft animal model (Leslie et al. 2020; Tai et al. 2017). These reports approve a new mechanism to grow the current targeted therapeutic agents for the treatment of prostate malignant growth. ATO with Rad001 synergistically stimulates the cytotoxic effect in prostate malignancy, accordingly altogether gives a noble therapeutic possibility to advance prostate disease.

12.4.4 Cervical Malignancy

Cervical malignancy is the most well-known disease among females around the world. Radiotherapy has been commonly utilized for the ministration of patients with cervical malignant growth. ATO + radiation therapy was expectably reported to apply an antitumor impact on cervical malignant growth cells in vitro or potentially in vivo. Studies propose that ATO diminishes radiation-accelerated metastases rate presumably by means of subduing radiation-prompted MMP-9 expression and furthermore upregulates the phosphorylation level of Bcl-2 as well as translocation of Bax protein to mitochondria, which were joined by activation of JNK and MAPKs including p38 (Segovia-Mendoza et al. 2015; Wei et al. 2005). Since NAC unmistakably upsets the ATO-intervened cell killing just as MAPK induction, ROS generation may assume a significant function in ATO-radiation-stimulated apoptosis. Notwithstanding arsenic and its compounds like ATO, TAO (tetra arsenic oxide), and As4O6 was appeared to possibly apply an antitumor impact on cervical malignancy. ATO in blend with radachlorin/photodynamic treatment helpfully dysregulates and restrains the multiplication of mouse TC-1 cells, where p53 tumor silencer and the p21 inducible protein improved particularly in mix treated tumor cells both in vitro and in vivo. ATO was likewise shown to synergistically reduce growth and development of CaSki (human cervical carcinoma cell line) when co-incubated with CDDP. The mix ATO-CDDP treatment significantly expanded the rate of apoptosis, as comparatively saw in different kinds of malignant growth cells when arsenic trioxide was combined with CDDP (Kang and Lee 2008; Kim et al. 2012; Byun et al. 2013).

12.4.5 HCC

HCC (hepatocellular carcinoma) is the sixth most frequent tumor and the subsequent driving reason for cancer demise especially in males around the world. Hepatocellular carcinoma (HCC) is the most well-known kind of essential liver malignancy, including 75–85% of cases (Bray et al. 2018). A few multikinase inhibitors, for

example, Sorafenib, can upgrade the survival rate of patients with cutting edge HCC. As per Zhai et al. (2015) ATO in collaboration with sorafenib hinders the multiplication and advances the apoptosis of liver cancer cells by decreasing the sorafenib-mediated upregulation of Akt or potentially its downstream factors, like glycogen synthase kinase-3β, ribosomal protein S6 kinase, mTOR, and eukaryotic translational initiation factor 4E-binding protein 1. ATO was additionally shown to intensify the anticancer impact of genistein (Chen et al. 2011a), 3′-azido-3-′-deoxythymidine (AZT) (Chen et al. 2011b), oridonin (Chen et al. 2012), MDM2 inhibitor nutlin-3 (Zheng et al. 2014), metformin (Yang et al. 2015), as well as survivin mutant (T34A) (Ling et al. 2017) in HCC cells.

12.4.5.1 ATO in Liver Cancer

Arsenic and its related compounds are strong anticancer specialist applicable for both leukemia and solid tumors treatment. The concentration of arsenic needed to inhibit human xenografts in mice is extraordinarily higher than that used to medicate APL in people. Paradoxically, As_2O_3 at low concentration stimulates angiogenesis, which may be required to improve tumor development. Obviously, recommended dose of As_2O_3 is needed to get patients to avoid toxicity and unfortunate symptoms. In the current examination, we researched As_2O_3 concerning its harmfulness and consequences for malignant growth, cell apoptosis and angiogenesis utilizing H22 hepatocellular carcinoma cells in a mouse model of HCC. As_2O_3 hindered tumor development and angiogenesis and improved cancer cell apoptosis at dose more than 1 mg/kg; however, mice shed weight and not able to thrive at dosages of 4 mg/kg and more prominent. Arsenic trioxide has evident antitumor activity on HepG2 liver tumor. The system of arsenic trioxide may basically be prompting liver malignant growth cells to go through apoptosis, which might be identified with downregulated bcl-2 genes and upregulated bax expression (Liu et al. 2006). It is likewise revealed that As_2O_3 limits the development of tumor cells by activating apoptosis more in malignant cells when contrasted with normal cells. These findings recommend that it may be a promising therapeutic option against liver malignant growth which further needs to be tested by in vivo examinations (Sadaf et al. 2018).

12.4.6 Lung Malignant Growth

Since 1985, lung malignant growth has been the most widely recognized disease around the world, both as far as rate and mortality. Globally, cellular breakdown in the lungs is the largest contributor of new malignant growth examine (1,350,000 new cases and 12.4% of absolute recent disease cases) and to death rate (1,180,000 death and 17.6% of all tumor related death). The 5 year endurance rate is under 15.6%, and instead of the fact that there has been some advancement in endurance during the past few decades, the endurance rate that has been realized in other regular malignancies is yet to be attained in lung cancer (Dela Cruz et al. 2011). Apoptosis of A549 (human lung cancer cell line) by mediating the NF-κB pathway and the mitochondrial pathway and by intervening p53-induced suppression of surviving

was firmly triggered in response of ATO in mix with sulindac treatment (Zhang et al. 2018; Jiang et al. 2004). This blend synergistically enhances the cytotoxicity in human lung cancer cell lines NCI-H1299 and NCI-H157 by interceding reactive oxygen species-induced MAPK phosphorylation and through phosphorylation of Bcl-xL as well as by c-Jun NH2—terminal kinase-subordinate (Park et al. 2008; Jin et al. 2008). Various reports propose that a nonselective cyclooxygenase inhibitor like indomethacin (an auxiliary isoform of sulindac) induces the ATO-intervened cytotoxic impact in A549 cells by activation of ERK and additionally p38 MAPKs (Mandegary et al. 2013). A glutathione inhibitor like buthionine sulfoximine (BSO) likewise strikingly inspires ATO-mediated apoptosis in lung cancer cell line (A549), in which the apoptosis was identified with the amplified level of ROS (Han et al. 2008). Besides, joined ATO-CDDP therapy triggers apoptosis and synergistically represses the expansion of human A549 and H460, with CI esteems 0.5 and 0.6, separately, where CI $<$ 1.0 (Li et al. 2009).

12.4.7 Pancreatic Disease

Pancreatic disease is the seventh driving reason for cancer related death around the world. It spreads mainly in more developed nations. The possible reason for huge contrasts in death rate of pancreatic tumor is not totally clear yet; however, it might be due to shortfall of appropriate diagnosis, therapy, and recording of malignancy cases (Rawla et al. 2019). It is commonly acknowledged that the counter leukemic impact of ATO is mediated by apoptosis induction. Arsenic trioxide likewise represses multiplication and prompts apoptosis in solid tumor of different types including inadequately separated and very much separated pancreatic malignant growths. Nonetheless, little consideration has been paid to the action of the apoptosis-induced effect of ATO, especially in pancreatic disease which is a significant reason for malignant growth demise in the western world. Studies report that arsenic trioxide chunks multiplication and activates apoptosis in pancreatic malignant growth cells at less, non-poisonous concentration. The mechanisms by which ATO triggers apoptosis was by activating caspase-3, caspase-7, and caspase-9 along with breakdown of the downstream caspase-3 target poly ADP ribose polymerase (PARP) as described in PANC-1 cell that have been recently demonstrated to be responsive to ATO. The expression profile of anti-apoptosis proteins, Bcl-2 and Mcl-1 decreases, while Bax expression enhanced in a time dependent manner. Subsequently Bcl group of proteins, like activation of the caspase cascade and other mitochondrial pathway is responsible for arsenic-prompted apoptosis. Information acquired by flow cytometric examination show changes of cell cycle distribution from a G0/G1 phase arrest to G2/M phase arrest after 24–72 h following arsenic treatment. Simultaneously the sub-G0/G1 cell population of apoptotic cells was enhanced. Arsenic altogether upregulates P21 protein expression as well as downregulates the level of cyclin A, cyclin D1, and cyclin B1; however, expression of CDK4, CDK2, CDK6, and cyclin E was not influenced. Arsenic trioxide particularly increases the expression of GADD45 and GADD153 in a period subordinate

manner. ATO has significant function in apoptosis induction in pancreatic cancer cells by triggering the caspase cascades by means of the mitochondrial pathway, GADD activation, and by adjusting cell cycle progression and changes in a various cell cycle-modulating proteins (Li et al. 2003). This matured natural drug might be important for therapy of pancreatic disease. Researchers revealed that a sesquiterpene lactone from the clinical spice feverfew like parthenolide (PTL) triggers apoptosis in human pancreatic disease cell lines BxPC-3 and PANC-1 by interceding ROS production and subsequent caspase stimulation by means of the mitochondrial pathway (Wang et al. 2009). ATO and PTL combinational treatment fundamentally suppresses tumor development rates of PANC-1 xenografts in contrast with those treated with either ATO or PTL alone. Studies additionally showed the purpose for the restricted viability of arsenic on cytotoxicity in pancreatic ductal adenocarcinoma which most likely as a result of the high-cell ROS scavenging activities. It is likewise described that a hypoxia-inducible factor-1 inhibitor (like-PX-478) strongly boosts the anticancer and pro-apoptosis impact of ATO on BxPC-3 and Panc-1 pancreatic malignant growth cells in vitro by directing ROS accumulation (Wang et al. 2009; Lang et al. 2016).

12.4.8 Oral Cancer

Diseases of the oral cavity and pharynx represent 3% of all tumors in the USA. Oral malignant growth generally incorporates disease of the lip, tongue, salivary organs, and different locales in the mouth, while pharyngeal disease incorporates tumors of the nasopharynx, oropharynx, and hypopharynx. Over 90% of oral or pharyngeal tumors are squamous cell in cause. Oral cancer is a definitive basic head and neck neoplasm and is primarily connected with helpless guess, notwithstanding a few headway in its symptomatic and therapy systems. As referenced above ATO was clinically depicted as a combinatorial medication with chemotherapy as well as a platinum-based antineoplastic medication cisplatin (CDDP), combination of both compounds retains cancer type CI value mechanism of activity (Ota et al. 2018; Kumar et al. 2008; Nakaoka et al. 2014). More similar combination like ATO with buthionine sulfoximine (BSO) in ovarian malignancy it brought about reduction of GSH, likewise improves ROS level alongside upregulation of different stress-related pathways (Ong et al. 2011). ATO with bortezomib (BOR) and p38 inhibitor (SB203580) likewise leads to downregulation of anti-apoptotic proteins, for example, Bcl-2 in myeloma malignancy type (Wen et al. 2010; Ota et al. 2018). Recent reports additionally characterized that arsenic trioxide triggers apoptosis as well as diminishes intracellular nicotinamide adenine dinucleotide levels in patients with oral cancer, when ATO applied moreover with specific inhibitors, for example, nicotinamide phosphoribosyl transferase inhibitor (NAMPT) (Wang et al. 2017a, b). Tsai et al. demonstrated that the mixture of ATO and DTT (dithiothreitol) therapy brought about developed number of pro-apoptotic molecules Bak and Bax while reduction of p53 and Bcl-2, which at last resulted to a suggested cell death of oral malignancy cells with no damage on ordinary cell type (Tsai et al. 2017).

12.4.9 Ovarian Malignant Growth

Ovarian malignant growth (OC) is the seventh most ordinarily analyzed tumor type among female world. Epithelial OC is the most prevalent cancer subtype, with five significant histotypes that vary in pathogenesis, origination, molecular alteration, risk factor, and prognosis (Reid et al. 2017). The death rate from ovarian disease is nonsensical among malignant cancer of the female genital tract. In this kind of malignancy growth ATO when applied with CDDP which is one of the standard chemotherapeutics option for ovarian disease, or potentially RAD001 (mTOR inhibitor) have strong cytotoxic and cell killing effect against this specific tumor type (Zhang et al. 2009; Liu et al. 2012a, b; Ota et al. 2018).

12.4.10 Glioma and Glioblastoma (GBM)

GBM (glioblastoma) is the most aggressive malignant primary cerebrum cancer. This kind of malignant growth is uncommon in kids but its frequency is higher in middle age of 64 years. GBM rate is 1.6% more in males contrasted with females. This is generally situated in the supratentorial area (frontal, worldly, parietal, and occipital projections) and is once in a while situated in cerebellum. It has been examined that genetic and ecological elements are significantly related with GBM. Risk factors includes prior radiotherapy, diminished susceptibility to allergy, immune genes and immune factors, and some single nucleotide polymorphisms distinguished by genomic examination (Tamimi and Juweid 2017). Recent examinations explain that ATO essentially includes in the upregulation of DR5 (death receptor 5) which is a death receptor of tumor necrosis factor-related apoptosis-induced ligand (TRAIL) in a group of human glioma cell lines yet not in astrocytes (Ota et al. 2018). These reports likewise shed light on function of ATO in improvement of autophagy by rising mitotic arrest and regulation of ERK1/2 and PI3K/Akt signaling pathways. It likewise brings about suppression of glioma cell development with a CI < 1.0. ATO treatment activates G2/M phase cell cycle arrest in human fibrosarcoma and osteosarcoma. Certain normal polyphenols like silibinin when applied in mix with ATO significantly inhibit invasiveness and activate apoptosis in U87MG a human GBM cell line, this combination likewise downregulates cathepsin B, MMP-2, uPA, MMP-9, survivin, Bcl-2, layer type 1-MMP, and CA9 expression (Dizaji et al. 2012) and declines the feasibility of A-172 by refereeing intracellular ATO accumulation (Gülden et al. 2017). Literatures depict that c-Myc is likewise required for the regulation of CSCs (cancer stem cells) of several tumors like GBM (Wang et al. 2008). Yoshimura et al. legitimized that ATO + 10,058-F4 (c-Myc inhibitor) coordinately enhances differentiation of GBM CSCs and relapsed GBM CSC tumor development in vivo (Yoshimura et al. 2015).

12.4.10.1 ATO in Gliomas

ATO mix therapy regimen appears to have more suppressing efficacy compared with single therapy on all kinds of malignant growth fundamentally in GBM. In GBM this treatment principally downregulates the anti-apoptotic proteins like Bcl-2 and upregulates pro-apoptotic proteins like caspase-3 and Bax (Moloudi et al. 2017). These molecular discoveries describe that the planned therapy mechanism may trigger the characteristic pathway of apoptosis. Additionally, in vivo animal examines are expected to affirm the capability of ATO for the therapy of GBM disease.

12.4.11 Lymphoma

Lymphoma particularly non-Hodgkin lymphoma (NHL) is the fifth most normal malignancy in several developed nations like the USA, with around 55,000 new cases assessed for the year 2000. The expanding occurrence of NHL is generally unexplained (Baris and Zahm 2000). Reports connote that arsenic alone and in blend with BOR have likely anticancer impact in mantle cells which is a hopeless B-cell non-Hodgkin lymphoma (Ota et al. 2018; Abou-Merhi et al. 2007; Darwiche et al. 2001). ATO with cucurbitacin B, from trichosanthes kirilowii maxim, synergistically upregulates the rate of apoptosis by draining STAT3 phosphorylation in Burkitt lymphoma cell lines (Bornhauser et al. 2007) both in vivo and in vitro.

12.4.12 Multiple Myeloma (MM)

Although MM (multiple myeloma) is uncommon cancer, yet it is the second most basic hematologic harm. MM is a disease of the older population and related with critical morbidity because of its end-organ destruction. It is found in the range of plasma cell dyscrasias which starts with monoclonal gammopathy of unknown significance to overt plasma cell leukemia and extramedullary myeloma (Kazandjian 2016). In MM cell lines ATO treatment in blend with desired concentration of ascorbic acid reduces GSH levels and induces ATO-mediated cell death (Shin et al. 2009). One of the most attractive combinations in the case of refractory MM patients is ATO + melphalan + ascorbic acid therapy (Doudican et al. 2012). Other important mix with ATO is different proteasome inhibitors, for example, bortezomib (BOR) and carfilzomib along with these immunomodulatory medications, for example, thalidomide, lenalidomide (LEN), pomalidomide improve the survival rate of MM patients (Du et al. 2006). Researchers additionally showed that ATO-BOR connected with augmented STAT3 depletion, activation of JNK, and upregulation of p21, p27, Bim, and p53, and downregulation of apoptotic gene like Bcl-2 (Wang et al. 2015a, b, c). The effect of ATO enhances with nutrient or vitamin E simple Trolox (Li et al. 2010) which is a MEK inhibitor PD325901 a characteristic quinoid diterpene cryptotanshinone and a phytochemical sulforaphane (Bazarbachi et al. 1999; El Eit et al. 2014; El-Sabban et al. 2000) and brought about inhibition of

MM cells it likewise upregulates cereblon (Xia et al. 2013) which is an antimyeloma target of LEN.

12.4.13 Colon Malignant Growth

Colorectal malignant growth (CRC) is the third driving cause for tumor related death on the planet, and its incidence consonantly increases in developing nations. Otherwise called colorectal adenocarcinoma, CRC normally gets out of the glandular, epithelial cells of the large intestine. ATO alongside sulindac, a nonsteroidal drug, triggers ATO dependent apoptosis by suppressing NF-κB initiation mediated by the de-phosphorylation and destruction of IκB-alpha in HCT-116 cells as announced by Lee et al. (2008). Besides mix of ATO and PI3K inhibitor LY294002 prompts a decline in the development rate of colon cancer cell lines, where ATO inhibits Hh pathway record factor Gli1 and its related gene activation including CCND1 and BCL2 (Ota et al. 2018; Cai et al. 2015).

12.4.13.1 Potential Mechanism of Action of Arsenic in Different Malignancies

Arsenic and its related mixes twins a various mechanism lead to different signal transduction pathways to impact different cell reaction, for example, growth inhibition, triggering apoptosis, angiogenesis hindrance, and some more. Arsenic may activate its biological impacts by communicating with firmly dispersed cysteine residues on basic cell proteins. Arsenic increases a potential achievement particularly in one sort of malignancy called APL. In greater part of APL cases, it is described by the t(15:17) translocation which leads to the arrangement of PML and RAR gene fusion. This combination is a delegate of several transcription factors (Yu et al. 2014; Levine 1997; Miller Jr et al. 2002). The above protein helps in the blockage of genes which is dependable of myeloid differentiation. Gene sequences of PML describe that it has cysteine rich region which aids arsenic cooperation. This PML protein typically restricted in nuclear body present inside the nucleus (Davison et al. 2002; Alimoghaddam 2014). The association of PML-RAR in leukemia prompts the suppression of nuclear bodies which at last dispersed the PML proteins into smaller fragments. ATO along with RA also hinders the myeloid separation by PML-RAR combination which executes in ATRA treatment for APL (Davison et al. 2002). Arsenic also leads to reduction of PML-RAR combination protein and it was demonstrated as a new option for the therapy of ATR as in both RA-resistant and RA-sensitive APL patients it shows total abrogation (Jing 2004; Zhang et al. 2001). Arsenic trioxide impacts the advancement of a molecular protein which co-localizes with PML in nuclear bodies and inhibits transcription of gene called Daxx (Lallemand-Breitenbach and de Thé 2010). Daxx which has a significant function in regulation of death related genes transcription in Fas initiated apoptosis (Bernardi and Pandolfi 2007; Percherancier et al. 2009). So a slight rise in arsenic concentration legitimately impacts acute promyelocytic leukemia inside nuclear bodies and adequate to induce Daxx-subordinate apoptosis. ATO additionally has some effect

on the covalent alteration of PML with SUMO-1 which is an ubiquitin like protein, so it related in the growth of PML-containing nuclear bodies in the nucleus. Accordingly it assumes a lead function in pro-apoptotic signal transduction (Zhang et al. 2001). Subsequently an ideal dose of arsenic upgrades the SUMO-1 modification of PML-RAR and eventually prompts apoptosis.

12.4.13.2 ATO on Cell Signaling Pathways

Scientific literatures already asserted that arsenic associated with upregulation of several pro-apoptotic pathways in various tumor cell lines might be subject to PML and P53. ATO enhances the P53 expression in MBC-1, a B-cell lymphoma gastric malignant cells, ultimately results in apoptosis followed by caspase activation (Kang et al. 2019; Ma et al. 2014; Zhong et al. 2018). In human T-cell lymphotropic virus type 1 cells the recommended dose of ATO brings about the accumulation of P53,G1 phase arrest, expands the level of Cip1/p21 and p27KIP1, dephosphorylation of retinoblastoma protein, and inevitably prompts collection of P53 which triggers apoptosis (Yih and Lee 2000; John et al. 2000). In human fibroblast cells, ATO prompts the double strand breaks which likewise finish up in phosphorylation or enhanced expression of P53, so it additionally helps in enhanced expression of P53 downstream proteins (P21 and others) (Ishitsuka et al. 2000; Williams and Schumacher 2016). Scientists likewise provided the insight that arsenic treatment in certain concentration insists P53 aggregation mainly because of the inclusion of phosphatidylinositol-3-kinase related proteins, inside an ataxia-telangiectasia transformed pathways (Yu et al. 2014; Levine 1997; Shiloh 2003; Zannini et al. 2014). Bcl-2 mainly involved in binding with the regulation of arsenic-mediated apoptosis, ATO strongly upregulates p53, other growth arrest related genes in apoptosis while it cause downregulation of Bcl-2 in APL patients (Carr and Jones 2016; Zheng et al. 2010; Kumar et al. 2018). Arsenic also regulates the binding of PML, Bax, p27KIP1 to nuclear bodies (Liu et al. 2016; Lam et al. 2014), alongside PML-containing cells, which synergistically move with IFNs (interferons) so that induce PML, to insists tumor cell death.

12.4.13.3 ATO in Apoptosis

ATO mainly involved in caspases activation recent reports on myeloma cells shows that caspases-9 is fundamentally initiated in arsenic-mediated apoptosis in combination with dexamethasone where as in neuroblastoma cell lines and in myeloid leukemia cells ATO prompted apoptosis by stimulating caspases-3 a definitive system by which arsenic triggers apoptosis might be by suppressing telomerase activity (Hayashi et al. 2002; Ishitsuka et al. 1999). In NB4 cells arsenic trioxides brought about decrease in the expression of telomerase genes and its activity (Xu et al. 2014; Chou et al. 2001) this may be because of quick reaction of arsenic trioxide on transcription factors, for example, Sp1 and Myc.

12.5 Arsenic and ROS

ATO upsets the natural oxidation and oxidative reduction equilibrium by managing different pathways including various redox responses with intimate oxidants and other cellular antioxidant systems. As arsenic has high affinity for thiol gatherings, proteins with approachable and firmly spaced thiol moieties with high thioldisulfide oxidation potentials might be redox-sensitive and redox-regulating distinctly mediate principal cell functions. Arsenic suggests it is both remedial and poisonous impacts by targeting redox-sensitive enzymes and proteins (Chen et al. 1998). Endogenous glutathione and thioredoxin have a significant function in regulating the redox signaling and subsequently shielding cells from toxic effects of arsenic compounds likewise recommends that arsenic incomprehensibly shares numerous properties of tumor promotors as impacts the various redox sensitive signaling molecules, for example, AP-1, P52, P21, and S-nitrosothiols which bring about the dysregulation of different cell signaling gene expressions (Pace et al. 2017).

12.6 Summary

While intensive attempts have been made for the treatment of malignancy, this threat is yet the subsequent driving reason for death in various nations and their worldwide frequency and mortality are probably going to enhance in the coming decades. Arsenic trioxide significantly modulates several mechanisms prompt different signal transduction pathways to impact different cell reactions, for example, development hindrance, enlistment of apoptosis, angiogenesis restraint, and many more. Here we have demonstrated the likely mechanisms of action about the healing specialty of ATO toward different human malignancies as shown in Table 12.1. Arsenic, alone or in mix with other anticancer therapeutics, for example, molecular targeted drugs, radiation, chemotherapy helps in the induction of apoptosis in various malignant growth cell types. Because of ongoing headway in innovations and utilization of numerous anticancer treatments quite possibly several cellular biological processes may produce an alternate dangerous population of malignant growth cells, some of which may secure a specific medication obstruction. Thus noble therapeutic options are earnestly needed to beat drug obstruction and upgrade both the disease results and the personal satisfaction for patients with disease. Currently number of clinical trials under path in a few sorts of tumorigenesis to examine the restorative capability of arsenic and it related compounds. Arsenic in its desired concentration demonstrated to have remedial potential which previously represented by APL and subsequently it is suggested as a potential guarantee for preclinical model of different sorts of malignancy as well. Moreover, studies are required to comprehend the connection between apoptosis activation and hereditary changes in malignant cells because of arsenic which may upgrades the investigations in selectivity for disease treatment. Further progressions are needed to comprehend the part of arsenic and its synergistic anticancer methodologies with other regular combination with

Table 12.1 ATO combinational therapy

Serial no	Cancer type	ATO in combinational therapy	Pathways if known	References
1	Acute promyelocytic leukemia	ATO in mix with ATRA (all-trans-retinoic acid) (ATO + ATRA)	Blend of ATO and APL prompts proteasomal debasement of PML-RARα and destroys Pin1 protein	Ota et al. (2018), Kozono et al. (2018), Mohammad et al. (2014), and Wang et al. (2017a, b)
2	Acute myeloid leukemia (AML)/FLT3	(ATO + ATRA)	Co-restraint of Fms-like tyrosine kinase 3 (FLT3) signaling pathways	Wang et al. (2017a, b)
	Lymphoma and leukemia	ATO + buthionine sulfoximine (BSO)	ROS-mediated upregulation of death receptor 5 and phosphorylation of JNK	Ota et al. (2018) and Chen et al. (2006)
3	Hepatoma	(ATO + BSO)	Decreased GSH level	Lin et al. (2005)
4	Glioma	(ATO + BSO)	Suppression of cancer stem cell (CSC) properties	Karsy et al. (2014)
5	Lung cancer	(ATO + BSO)	GSH depletion	Han et al. (2008)
6	Ovarian cancer	(ATO + BSO)	GSH exhaustion, expanded intracellular ROS production, activation of stress-related pathway	Ota et al. (2018) and Ong et al. (2011)
7	Cervical cancer	ATO (As4O6) + CDDP	Synergistic initiation of caspase-3	Ota et al. (2018) and Byun et al. (2013)
8	Ovarian cancer	(ATO + CDDP)	Upregulation of BAX and TP53	Zhang et al. (2009)
9	Lung cancer	(ATO + CDDP)	Decrease in Bcl-2 and clusterin and increase in Bax	Li et al. (2009)
10	Prostate cancer	ATO + radiotherapy	Inhibition of Akt/Mtor signaling pathway	Chiu et al. (2012)
11	Oral cancer	ATO + radiotherapy	Inhibition of metastasis, tumor growth, and angiogenesis	Kumar et al. (2008)
12	Breast cancer	ATO + radiotherapy	Bcl-2/Bax ratio	Liu et al. (2012a, b)

(continued)

Table 12.1 (continued)

Serial no	Cancer type	ATO in combinational therapy	Pathways if known	References
13	Glioma	ATO + radiotherapy	Increased mitotic arrest and regulation of ERK1/ERK2 and PI3K/Akt signaling pathways	Chiu et al. (2012)
14	Cervical cancer	ATO + radiotherapy	Inhibition of radiation mediated MMP-9 expression, ROS production induced MAPKs activation, and Bax translocation	Wei et al. (2005) and Kang and Lee (2008)

respect to ATO-based mix remedial to develop a novel consolidated treatment for malignant growth.

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Developments in Nanoadsorbents for the Treatment of Arsenic-Contaminated Water

13

Rabia Amen, Irshad Bibi, Muhammad Shahid, Nabeel Khan Niazi, Amna Zulfqar, Muhammad Farrakh Nawaz, Muhammad Bilal Shakoor, Ahmad Mukhtar, and Talha Rehman

Abstract

Arsenic is an extremely hazardous metalloid affecting the health of millions of people worldwide. Numerous technologies have been developed to remove As from drinking water/wastewater, of which adsorption is considered as the most effective technique. Nanoadsorbents such as nano-scale zero valent metals, carbon nanotubes (CNTs), and biochar/biomaterial-based nanocomposites are being widely used by the researchers for water treatment. In this chapter, recent developments in the nanoadsorbents to eliminate As from water/wastewater are discussed. Application of raw and engineered nanoparticles (NPs) such as iron

R. Amen · I. Bibi · A. Zulfqar · T. Rehman
Institute of Soil and Environmental Sciences, University of Agriculture Faisalabad, Faisalabad, Pakistan

M. Shahid
Department of Environmental Sciences, COMSATS University Islamabad, Vehari, Pakistan

N. K. Niazi (✉)
Institute of Soil and Environmental Sciences, University of Agriculture Faisalabad, Faisalabad, Pakistan

School of Civil Engineering and Surveying, University of Southern Queensland, Toowoomba, QLD, Australia
e-mail: nabeel.niazi@uaf.edu.pk

M. F. Nawaz
Department of Forestry and Range Management, University of Agriculture, Faisalabad, Pakistan

M. B. Shakoor
College of Earth and Environmental Sciences, University of Punjab, Lahore, Pakistan

A. Mukhtar
Department of Chemical Engineering, NFC Institute of Engineering and Fertilizer Research, Faisalabad, Punjab, Pakistan

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oxide/hydroxide, alumina, copper oxide, titanium oxide, bi-metal oxides and carbonaceous NPs are primarily focused. Different techniques for the physico-chemical characterization of nanoadsorbents, including Fourier transform infrared (FTIR) spectroscopy, Raman spectroscopy, X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM) and X-ray photoelectron spectroscopy (XPS) have been discussed briefly. The influence of numerous factors (e.g., pH, synthesis method, initial concentration, particle size, competing ions, and contact medium) on As adsorption capacity by nanoadsorbents are deliberated. Furthermore, the chapter also discusses As adsorption mechanisms and regeneration and separation of nanoadsorbents from water/wastewater.

Keywords

Nanoparticles and nanotechnology · Carbon nanotubes · Metal oxides · Remediation · Drinking water and wastewater treatment

13.1 Introduction

Water is an important element for the existence of life in the biosphere. The Earth has only 2.5% of water resources, of which 30% is groundwater, which is used for drinking, industrial, and agricultural purposes worldwide. However, increased urbanization and industrialization presented a significant threat to groundwater safety. Of the numerous causes of pollution, groundwater contamination due to the geogenic release of arsenic (As) is known as a major environmental and public health concern for millions of people in the world (Raza et al. 2017; Shahid et al. 2018a; Amen et al. 2020b). Arsenic is ranked first in 20 highly-hazardous substances as per the ASTDR (Agency for Toxic Substances and Disease Registry) (Jaggard et al. 2010).

The As toxicity is directly linked to its oxidation state and speciation. In water, inorganic As species are predominantly As(III) and As(V), whereas organic As species are arsenobetaine, dimethyl arsenic acid (DMA), and monomethylarsonic acid (MMA) (Niazi and Burton 2016; LeMonte et al. 2017). Chemical speciation of As relies primarily on the redox potential (E_h) and pH of aqueous medium. Arsenate is prevalent in the acidic conditions with oxidized conditions, however, the As(III) predominates in the alkaline pH under reduced conditions. Arsenite is 60 times more toxic relative to As(V), whereas the As organic species, e.g. DMA and MMA are 70 times less harmful compared to inorganic As species (Shakoor et al. 2016; Amen et al. 2020b).

Increased concentration of As in the aquatic environment is due to the natural causes including volcanic eruptions, weathering, and hot springs (Tabassum et al. 2019a; Shah et al. 2020). Arsenic is used as insecticide and to preserve wood as it is bactericidal and resistant to decay. Moreover, the primary drivers of As pollution in water are mining operations, pharmaceuticals, and electronic industries (Amen et al.

2020a). Nearly 200 million people in the world are at risk due to the naturally existing As in the groundwater and surface water (Shakoor et al. 2015). In Pakistan, approximately 47 million people are susceptible to As-contaminated drinking water according to the recent scientific report (Shahid et al. 2018b). The key causes of As build-up in the human body include As-contaminated food and drinking water. The As concentration beyond the suggested level (10 μg/L) by World Health Organization (WHO) is the reason of harmful diseases, such as arsenicosis, hyperkeratosis, diabetes mellitus, cancer, diarrhea, and hypothyroidism (Mohan and Pittman Jr. 2007; Abdul et al. 2015; Sarkar and Paul 2016; Amen et al. 2020a).

A number of treatment strategies has been suggested to tackle pervasive As, which are summarized by researchers in the form of review (Lata and Samadder 2016; Kumar et al. 2019; Sanjrani et al. 2019; Tabassum et al. 2019b; Amen et al. 2020b). Water treatment techniques for the As removal comprises membrane separation, lime-softening, electrochemical methods, coagulation/flocculation, and ion exchange. However, such procedures do have serious disadvantages like the higher cost and energy needs, excessive waste generation, higher maintenance and operational cost, inadequate contaminant removal, etc. (Thekkudan et al. 2016). Among these conventional methods, adsorption is known as the most desirable strategy due to its sustainability, efficient processing, high adsorption potential, and cost-effectiveness. Therefore, there is a need of continuous research on ease to synthesize, economically viable, environment friendly, and reproducible adsorbents for the fast and effective As removal (Fu and Wang 2011; Ray and Shipley 2015; Siddiqui et al. 2020).

Adsorption has become the most promising process amid other techniques, because it does not introduce unwanted by-products and a single adsorbent have capability to be reused after regeneration over a relatively considerable number of cycles (Raval and Kumar 2020). Different types of adsorbents have been used for adsorption including mineral products, surfactants, industrial wastes, synthetic activated carbon, and ferrous materials, etc. (Hashim et al. 2011). In order to attain the goal of fast and efficient adsorbent fabrication, scientists have produced nano-sized adsorbents. The intra-particle diffusion capability of macromolecules reduces the adsorption efficiency and potential of the adsorbent, whereas nanoparticles (NPs) possess low diffusion resistance, which increases the value of NP adsorbents (Attia and Hu 2013).

Nanoparticles have several unique attributes including fast separation, strong reactivity, catalytic potential, higher quantity of active sites, and small size that allows the removal of As more effectively than other adsorbents (Lata and Samadder 2016). Nifty nanocomposites consisting of metal oxides, polymers, and carbon were fabricated as a prospective adsorbent for the treatment of contaminated water (Hua et al. 2012; Qu et al. 2013; Ray and Shipley 2015). Their distinctive qualities like the relatively low cost, high surface-to-volume ratio, reusability, surface modifiability, and biocompatibility have allowed them to become increasingly important as effective adsorbents (Hua et al. 2012; Wang et al. 2012).

Among the metal nanoadsorbents, the iron oxide NPs generally known as magnetic nanoparticles (MNPs) are the most studied (Shen et al. 2009; Dave and Chopda

2014). Iron oxide core-based NPs including akaganéite (β–FeOOH), magnetite (Fe_3O_4), maghemite (γ–Fe_2O_3), and geoethite (α–FeOOH) are among the best adsorbents due to their convenient reusable property. This aspect allows their multiple reuses for the adsorption and thus decreases the issue of secondary pollution (Raval and Kumar 2020). The presence of iron provides them magnetic characteristics which enables them to be separated quickly from contaminated water by applying basic magnetic field. There are several drawbacks if the MNPs are of too small size because they need a large magnetic field for removal, which also increases the overall cost of treatment process (Shen et al. 2009; Thekkudan et al. 2016). The other metal oxide NPs comprise zinc, titanium, and cerium. When reduced to nano-scale, they possess higher surface area. Furthermore, the carbon nanotubes (CNTs) are also investigated to analyze their ability to remove heavy metals from the polluted water (Tian et al. 2012; Gangupomu et al. 2014). The presence of carbon makes it favorable for the adsorption due to the availability of high energy binding sites (Gangupomu et al. 2014).

Bare NPs are susceptible to oxidation via atmospheric oxygen accumulated in water which highlights the need of surface modification to stabilize the NPs and their consequent utilization as an adsorbent (Maity and Agrawal 2007). Henceforth, the NPs surface ought to be functionalized with organic/inorganic layer to enhance the biocompatibility and functionality of adsorbent and to minimize instability. Relative to the inorganic molecules, organic molecules layering improves the possible usage of NP through retaining their magnetic characteristics and assembling of reactive functional groups (hydroxyl, aldehyde, amino, and carboxyl groups) (Dong et al. 2009).

The modified NPs possess higher adsorption capacity because modification imparts characteristics in the surface layer that promote improved adsorption (Wang et al. 2012; Qu et al. 2013; Ray and Shipley 2015). The polydispersion and size regulation are useful characteristics which must also be taken into account when designing new methods of separation as they play a major role in specifying the NP properties. We have summarized the recent developments in the usage of different NPs to remove As from water/wastewater.

13.2 Nanoadsorbents Application for As Removal

Different types of NPs including metal oxide, metallic, bimetallic, zeolite, ferrite, carbonaceous, polymer-based NPs, etc. are studied to evaluate their potential to eliminate metal(loid)s from the contaminated water (Fig. 13.1). The As is primarily removed using NPs by the process of adsorption on their surfaces. Different types of nanoadsorbents along with their adsorption capacity are mentioned in Table 13.1. Below is the detailed account of the various kinds of NPs reported in the scientific investigations for As removal from water.

Fig. 13.1 Flow chart indicating the removal of As using nanoadsorbents

13.2.1 Metal Oxides

13.2.1.1 Iron Oxide/Hydroxide NPs

The metal oxides are further divided into metallic NPs, bimetallic NPs, and metal oxide NPs (Fig. 13.2). Iron oxide NPs are very likely used to remediate a broad spectrum of contaminants based on low cost, simple processing, and modification. Nano-iron oxides possess chemical inertness, high surface area-to-volume ratio, biocompatibility, low toxicity and are superparamagnetic due to which they could conveniently immobilize different adsorbents on their surfaces for enhanced operation (Sanaei et al. 2020). Some iron compounds such as granular ferric hydroxide (GFH), hematite, iron oxide-layered materials, and goethite are considered as ideal adsorbents for As adsorption, as low amount of As leaching has been indicated from the depleted adsorbent (Lata and Samadder 2016).

Raval and Kumar (2020) coated the iron oxide NPs to fabricate bilayer nanoadsorbent (bilayer-OA@FeO NPs) to remove As(V). The bilayer-OA@FeO NPs exhibited maximum adsorption capacity (32.8 μg/g) for As(V). Various forms of iron oxides, for example, wustite (FeO), α-Fe_2O_3, Fe_3O_4, and g-Fe_2O_3 and iron hydroxides including bernalite ($Fe(OH)_3$), feroxyhyte (d-FeOOH), b-FeOOH, and

Table 13.1 Nanoadsorbents application for the removal of arsenic (As) from water/wastewater

Adsorbent	Preparation	Temperature	pH	Time (min)	Size range (nm)	Surface area (m^2/g)	Adsorbate	Adsorption capacity (mg/g)	References
Mesoporous magnetic γ-Fe_2O_3	–	–	–	–	–	35.7	As(III)	73.2	Chen et al. (2014a, b, c)
Goethite nanoparticles	Wet-chemical synthesis method	298 K	3.0	240	<10	167.8	As(V)	76	Ghosh et al. (2012)
Iron-impregnated granular (AC)	–	25 °C	7.0	–	–	–	As(V)	1.66	Chang et al. (2010)
Iron-modified (AC)	–	20 °C	_	–	–	–	As(III)	38.8	Chen et al. (2007)
Surfactant-modified zeolite	–	25 °C	–	–	–	–	As(V)	0.0743	Mendoza-Barrón et al. (2011)
Cupric oxide nanoparticles	–	–	9.3	–	–	–	As(III)	26.9	Martinson and Reddy (2009)
Fe-hydrotalcite supported magnetite nanoparticle	Co-precipitation	–	–	–	50	–	As(III)	0.12	Türk and Alp (2014)
Chitosan-Fe_3O_4 NPs	Sol-gel method	–	–	–	–	52.48	As(V)	79.49	Raza et al. (2020)
Oak leave FeO NPs	–	–		20			As(V)	32.05	Kamath et al. (2020)
Black tea FeO NPs	–	–	–	20	60-70	18.33	As(V)	18.98	Kamath et al. (2020)
Green tea FeO NPs	–	–	–	20	30-40	3.26	As(V)	13.70	Kamath et al. (2020)
Eucalyptus leaves FeO NPs	–	–	–	40	35-50	22.57	As(V)	39.84	Kamath et al. (2020)

Pomegranate leaves FeO NPs	–	–	–	60	70-80	0.83	As(V)	11.65	Kamath et al. (2020)
NC-PEI-GA	–	–	3.0	10	–	10.25	As(V)	255.19	Chai et al. (2020)
Maghemite nanoparticles	Co-precipitation	27	–	–	–	–	As(III)	17.5	Siddiqui et al. (2020)
Starch functionalized nanoparticles	Co-precipitation	35	–	–	–	–	As(III)	8.90	Siddiqui et al. (2020)
CNC-PEI-Fe(III)	–	–	–	–	–	7.06	As(III)	149.42	Xi et al. (2020)
Ascorbic acid coated Fe_3O_4 nanoparticles	Hydrothermal process	RT	2.0–7.0	30	<10	179	As(III)	46.06	Feng et al. (2012)
Magnesium ferrite nanocrystallites	Solvothermal process	RT	7.0	–	–	~438	As(V)	10	Tang et al. (2013)
Titanium dioxide nanoparticles	Sol-gel method	–	–	–	108	–	As(V)	20.4	Deedar and Aslam (2009)
Iron-doped titania nanoparticles coated on glass beads	Liquid impregnation method	–	7	–	30–40	–	As(III)	0.59	Danish et al. (2013)
CuO nanoparticles	Microwave irradiation	–	6.0–10.0	30	12–18	85	As(V)	22.6	Martinson and Reddy (2009)
Cerium oxide nanoparticles	Precipitation process	298 K	3.0–11.0	30	4	198	As(III)	170	Li et al. (2012)
Magnesium oxide nanoflakes	Hydrothermal process	–	–	360	>100	115.9	As(III)	506.6	Liu et al. (2011)
CuO nanoparticle	Thermal refluxing technique	298 K	8	300	–	52.11	As	1.0862	Goswami et al. (2012)
Zirconium oxide nanoparticles	Hydrothermal process	303 K	5.0	720	~5	327.1	As(III)	83	Cui et al. (2012)

(continued)

Table 13.1 (continued)

Adsorbent	Preparation	Temperature	pH	Time (min)	Size range (nm)	Surface area (m^2/g)	Adsorbate	Adsorption capacity (mg/g)	References
Multiwall carbon nanotube–zirconia nanohybrid	Microwave accelerated reaction	–	6	360	–	–	As(V)	5	Ntim and Mitra (2012)
Multiwalled boron nitride nanotubes	Sonochemical synthesis	RT	6.9	720	~20 to 50	~95.9	As(V)	0.96	Chen et al. (2011)

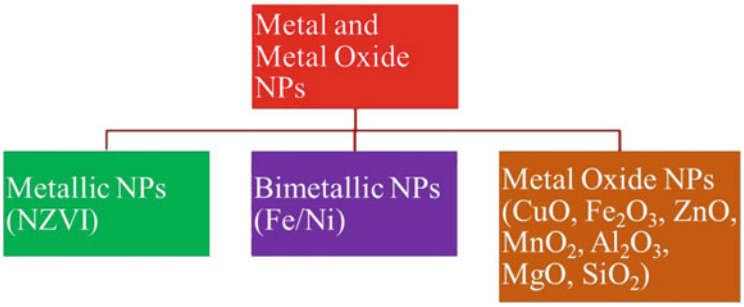

Fig. 13.2 Schematic representation of different types of metal oxides

α-FeOOH, are reported by Nassar (2012). These iron NPs are taken out of water using high magnetic gradient separation (HGMS) method after adsorption due to their magnetic properties. Mamindy-Pajany et al. (2011) analyzed the As (V) adsorption on magnetite, goethite, and hematite. They indicated that the adsorption capacity was directly proportional to the iron concentration in the adsorbent, and goethite possess maximum adsorption compared to hematite and magnetite, whereas ZVI exhibited lowest adsorption capacity for As(V). This was due to high iron contents in goethite than hematite and magnetite.

Chen et al. (2014a, b, c) have developed ultrafine porous α-Fe_2O_3 NPs with high refined surface hydroxyl groups to remove As(V) from wastewater. They faced the issue of poor aggregation and adsorbent separation, which was resolved by forming magnetic γ-Fe_2O_3 nanostructures via atmospheric calcination of Fe_3O_4/phenol–formaldehyde resin. In another study, the ascorbic acid was used to coat the Fe_2O_3 NPs for As removal, which enhanced the porosity and productively hindered the Fe release into solution (Feng et al. 2012).

13.2.1.2 Alumina NPs

The alumina (A_2O_3) is one of the crucial metal oxides that exists in natural soils and possesses variety of structures i.e. α, β, ɤ, □, and χ. The α-Al_2O_3 is used in conventional techniques as a natural adsorbent having high stability. Alumina is considered as a prominent adsorbent possessing solid interatomic bonding as it has interesting characteristics, like electrical insulation, thermal conductivity, corrosion resistance and its compressive strength is very high. Saha and Sarkar (2012) fabricated chitosan-grafted polyacrylamide (CTS-g-PA) alumina NPs adsorbent for the As removal. The modification of NPs by grafting new functional groups is done due to numerous benefits, such as (1) to enhance sorption sites density, (2) to alter the pH range for metal removal, (3) to modify the sorption site and uptake mechanism according to the targeted metal. Darban et al. (2013) used precipitation method for the fabrication of nanoporous g-alumina using low-cost raw material (kaoline) which possess surface area of 201.53 m^2/g and particle size of 22–23 nm. This alumina powder exhibited high potential for adsorption and regeneration.

13.2.1.3 Copper Oxide NPs

The copper oxide (CuO) is considered as promising nanoadsorbent as it effectively removes As from water without oxidation of As(III) to As(V) and changes in the pH. Moreover, it performs well under the influence of co-existing ions. Such NPs can be regenerated quickly and retrieved for As removal from water. The sand was used as a support material with cupric oxide for a batch study in the polypropylene centrifuge tubes for the removal of As. The outcomes suggested the use of CuO NPs in the field applications for As removal from water (Reddy et al. 2013; Lata and Samadder 2016).

13.2.1.4 Titanium Dioxide NPs

The titanium dioxide (TiO_2) NPs are chemically stable, non-toxic, simple to synthesize and cost-effective. They present photocatalytic behavior, rendering them an effective water/wastewater treatment agent. Titanium is used in the form of TiO_2 and nanoporous titania for As removal in numerous studies (Hung et al. 2007). The surface complexation model (SCM) was used to describe the characteristics of nanoporous titania adsorbent (NTA) surface. Using SCM, Han et al. (2010) reported the type of surface specie involved in the noticeable removal of As at a defined pH. The monodenate surface complexes have been found more productive across a large pH spectrum for As adsorption, whereas bidenate surface complexes adsorbed the As(V) at pH 8 (Han et al. 2010).

The specific organic polymers were used to fabricate economical magnetic polyaniline and strontium-titanium (MP-$SrTiO_3$) composites. The surface area for metal adsorption was increased due to integration of accumulated magnetic NPs and $SrTiO_3$ in the coatings of polyaniline. From 50 ppm As(III) solution, the fabricated composite eliminated 95.24% of As(III). The electrostatic interaction among positively charged nanocomposite and As ions due to the existence of imine–N and amine–N< groups on polyaniline results in As elimination. The maximum removal of As(III) (67.11 mg/g) was observed at pH 6, temperature 303 K, contact time 250 min and at 2 mg/mL of adsorbent dosage (Nodeh et al. 2018).

13.2.1.5 Bi-Metal Oxide NPs

The hybrid bi-metal oxides possess an increased adsorption capacity due to synergetic effect of both metal oxides compared to individual metal oxide. Different metal oxide hybrids have been used to remove As, including Fe-Mn (Kong et al. 2014), magnetite-graphene oxide (Chandra et al. 2010), Fe-Ti (Gupta and Ghosh 2009), Mn-Co (Zhang et al. 2010), and Fe-Cu (Zhang et al. 2013). Parsons et al. (2009) produced $MnFe_2O_4$, Fe_3O and Mn_3O_4 NPs and recorded comparatively improved adsorption potential in bi-metal oxides. Zhang et al. (2010) utilized a technique of chemical co-precipitation for the production of $MnFe_2O_4$ and $CoFe_2O_4$ magnetic NPs. The paramagnetic characteristic of these nanomaterials allows them to be separated easily after adsorption and desorption by applying the external magnetic field. Chandra et al. (2010) produced magnetic-graphene oxide hybrids to remove As and observed that the As(III) was separated via surface complexation while As (V) removal was because of electrostatic attraction. The adsorption of As(V) was

higher when pH < pHzpc indicating the presence of higher number of positively charged functional groups, however, in As(III) case, the pH > pHzpc represents more availability of negatively charged As which reduced its adsorption.

Ghosh et al. (2012) used hydrazine sulfate to modify the goethite NPs (HS-GN) for As(V) removal from wastewater. The 99% of As(V) was eliminated from the water using 6 g/L of HS-GN from 50 mg/L of initial As concentration at 240 min of contact time. The HS-GN was successfully regenerated using NaOH solution (pH 10.3) without losing the adsorption effectiveness. Fast magnetic separation was accomplished through doping Mg(II) into α-Fe_2O_3 via solvothermal technique to generate ultrafine superparamagnétic nanocrystallites. Improved adsorption of As (III) and As(V) at 10% concentration of Mg was detected in lower As equilibrium concentration which is credited to modification of microstructure using Mg(II) (Tang et al. 2013). Deedar and Aslam (2009) produced pristine and iron-doped TiO_2 NPs via sol-gel method and evaluated their efficiency for As removal from water. The iron-doping assist to increase the TiO_2 NPs adsorption potential by avoiding increase in particle size and thereby preserving the surface area needed for the adsorption. The titania NPs having high affinity for As have been fabricated via the fluid impregnation technique (Danish et al. 2013). Both forms, pristine and metal-doped titania, presented 90% As removal with an initial metal concentration of 2 mg/L in water. The influence of NPs coated glass bead for As(III) elimination in fixed bed columns was also studied under optimized conditions (Parsons et al. 2009). The NPs coated glass beads were easily regenerated using 10% NaOH solution.

13.2.2 Carbonaceous NPs

Carbon-based NPs are being utilized largely for the removal of heavy metals for the past few decades (Bassyouni et al. 2020). Many types of NPs, for example, CNTs, carbon fiber, activated carbon (AC), and graphene have exhibited very important characteristics in the course of wastewater treatment by successfully eliminating the As from the samples.

13.2.2.1 Carbon Nanotubes

The most effective carbon-based NPs are the CNTs discovered by Iijima (1991). CNTs have very remarkable properties such as distinctive structure, mechanical, electrical, physiochemical, and semiconducting properties. CNTs have been utilized widely in the process of wastewater treatment for eradicating the dyes and heavy metals due to their exceptional properties and distinctive structure (Li et al. 2003; Madrakian et al. 2011). These are grouped as single-walled and multi-walled carbon nanotubes as indicated by their superstructure (Fig. 13.3). A single layer of graphene sheet in cylindrical form is single-walled carbon nanotube while multiwalled carbon nanotubes are made of several layers of graphene sheets in the form of cylinder. The space between the adjoining layers of graphene in multiwalled CNTs is 0.34 nm (Lal et al. 2020). The distinctive properties of carbon nanotubes can be enhanced through surface modification by conjugating different kind of metals. This results in the

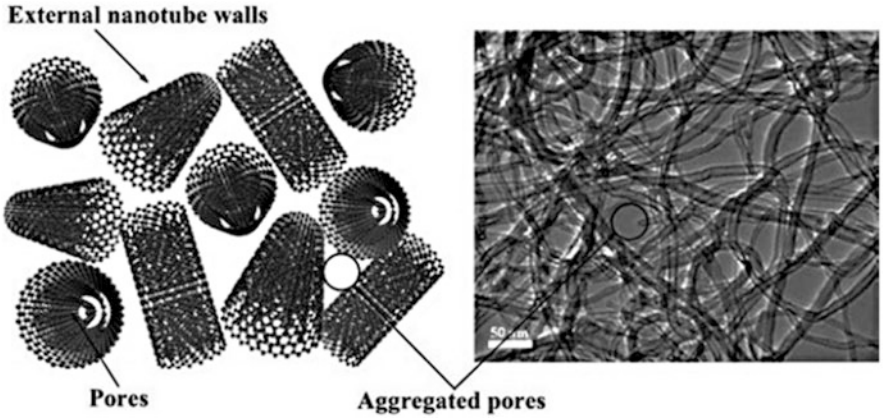

Fig. 13.3 Structure presenting adsorption sites on MWCNTs (Reproduced with permission from Bassyouni et al. (2020))

increase of many surface functional groups with specific surface area and improved dispersion rate. Carbon nanotubes can be modified through oxidation, consolidating with organic compounds and combining with other metal ions in order to increase the sorption capacity (Mubarak et al. 2014). The process of adsorption of metal ions on carbon nanotubes was credited to the chemical and electrostatic interaction between surface functional group of carbon nanotube and metal ions (Lal et al. 2020).

The deep eutectic solvents (DESs) consisted of glycerol and N,N-diethyl ethanol ammonium chloride were used to functionalize the CNTs to remove As(III) from wastewater (Al Omar et al. 2017). Through the deployment of response surface methodology central composite experimental design setup, the optimal requirements for the removal of As(III) (17 mg/g) by consuming 20 mg of adsorbent dosage were found to be at pH 6.0 and contact time of 55 min. Budimirović et al. (2017) established the multistage functionalized multiwalled carbon nanotubes (MWCNTs) by successive modification using iron hydroxide followed by improved terminal amino groups on the surface to remove the As(V) (Budimirović et al. 2017). This research showed the 91–97% elimination of As using the modified MWCNTs at a pH level of 7.12 because of the interaction between negatively charged monovalent anion $H_2AsO_4^-$ and positively charged adsorbent surface.

Polystyrene nanocomposites were modified using CNTs and 4-aminophenyl methyl sulphone were used as nanofillers, followed by analyzing their capabilities for the sorption of As(V) and their biodegradation behavior. The results revealed the development of a link between CNT and polystyrene that can effectively remove As (V) with 99% efficacy (Kausar 2017). A technique has been established by Aranda et al. (2016) to determine the very less quantity of As(V) in wastewater adsorbed on tertiary amine aliquot modified MWCNTs using X-Ray fluorescence (XRF) method. For best detection limit, better selectivity, reproducibility, wide range of pH, and

exception of organic solvents to estimate the trace amount of As in wastewater, the researchers recommended the application of this technique (Aranda et al. 2016).

Many studies on alteration and functionalization of CNTs have been conducted to control the accumulation issues and insolubility problems in aqueous conditions. Particularly, the quick and successful elimination of heavy metal ions from wastewater through integration of the CNTs adsorption behavior with the magnetic properties of iron oxide is of considerable importance. A magnetic iron oxide carbon nanotube was made via a solid phase technique and afterwards it was functionalized using glutathione via a simplistic chemical technique to improve the adsorption ability of 19.12 mg/g As(III). Chen et al. (2014a, b, c) have established a one-pot solid phase synthesis method to prevail monotonous, unproductive, and ecologically unfavorable liquid phase synthesis. This also helps to enhance magnetic iron oxide CNTs for the effective removal of As (Chen et al. 2014a, b, c). The developed magnetic iron oxide carbon nanotubes carry the properties of perfect adsorbent, such as high specific surface area, greater dispersibility, and desired magnetic characteristics including great capacity of adsorption, i.e. 24.04 mg/g As(V) and 47.41 mg/g for As(III).

A graphene@CNT@iron oxide nanostructure was developed by Vadahanambi et al. (2013) by microwave route and further functionalized it with amino groups, that displayed extraordinary efficient As removal because of its permeable structural composition and high ratio of surface-volume (Vadahanambi et al. 2013). The data of As adsorption was well-fitted to Langmuir model and displayed the highest capability of adsorption such as 111 mg/g for As(III) and 66 mg/g for As(V). The adsorption of As on the synthesized MWCNTs highly depends on the availability of surface functional groups, such as carboxyl, amino, and hydroxyl groups. This adsorbent exhibited a great performance without any significant decrease in the adsorption capability up to five cycles as indicated by recycling studies. In a research, a network of carbon nanotubes layered with TiO_2 was developed by using the filtration steam hydrolysis technique and additionally assessed for the removal of As from water (Liu et al. 2014). A thick layer of TiO_2 about 5.5 nm completely enclosed the surface of carbon nanotube and increased the surface area by two times up to 196 mg/g that is more beneficial than the immaculate carbon nanotube.

The sorption potential of Cu/MCE (MCE-mixed cellulose ester) was compared with the Cu/CNT for As(III) elimination. The Cu/CNT removed 90% of As(III), however, the adsorption potential of Cu/MCE for As(III) was comparatively lower (75%). The adsorption of As(III) occurs in two stages. Firstly, the conversion of As (III) to As(V) occurs by Cu and after that As(V) is adsorbed efficiently on the membrane (Fig. 13.4). Veličković et al. (2012) studied the carbon nanotubes functionalized with Polyethylene glycol (PEG) for As removal from wastewater. They showed that the maximum As adsorption was 13 mg/g at initial concentration of 10 mg/L. The magnetron sputtering technique was used to embed the Cu on the CNTs membrane (Cu/CNTs) without any chemical treatment (Luan et al. 2018). The As(III) removal with Cu/CNT was contrasted with mixed cellulose ester (Cu/MCE) that had comparative absorptivity. The efficiency for removing the As(III) with

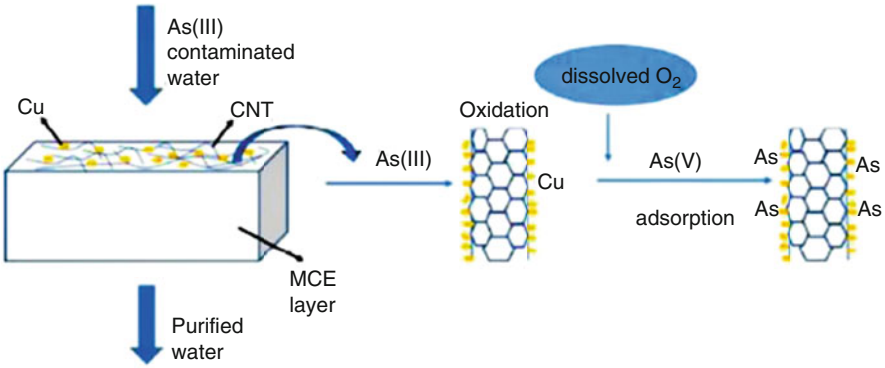

Fig. 13.4 Arsenic removal mechanism using Cu/CNT membrane (Reproduced with permission from Chen et al. (2014a, b, c))

(Cu/CNT) was more than 92% while efficiency noted with (Cu/MCE) was only 75%. The elimination of As ions from the water occurred in two stages. Initially, As (III) was oxidized to As(V) by Cu and afterwards, the As(V) was efficiently absorbed on the membrane.

Ntim and Mitra (2012) applied MWCNTs and zirconia nanohybrids to remove As (III) and As(V). The maximum adsorption capacity for As(V) and As(III) was 5 mg/g and 2 mg/g, respectively. The removal rate for As(V) was greater than As(III). This process of adsorption is finely depicted by pseudo-second-order kinetics. The optimal pH for removing the As(V) is 6. At this pH, the dominant As species was $HAsO_4^{-2}$ and the pHPZC (point of zero charge) (the pH at which the net charge on adsorbent surface is zero) for MWCNTs-zirconia nanohybrid was 6.9 (Ntim and Mitra 2012). This huge difference in charge produced a strong attraction and enhanced the adsorption for As(V). On the contrary, A(III) kept up a practically steady elimination rate in the pH range of 5–8. Past reports displayed that CNTs modified by iron oxide have a great ability of As adsorption (Mishra and Ramaprabhu 2010; Ntim and Mitra 2012).

The thermodynamic studies revealed that process of adsorption is endothermic. The most extreme adsorption limits of As(V) elimination were seen as 24.69 mg/g utilizing e-MWCNTs/Fe^{2+} and 14.45 mg/g by using e-MWCNTs/Fe^{3+} at 45 °C. The ideal pH for As(III) adsorption was seen as pH 8. At this pH level, the kinetic energy for As(V) adsorption was more rapid than As(III). Usually, e-MWCNTs/Fe^{2+} accomplished higher adsorption capabilities than e-MWCNTs/Fe^{3+}, because the surface of the adsorbent turns out to be more positive at higher iron load (Maiti et al. 2012). Hence, more attraction was found towards the negatively charged As species that were referenced previously. The enhanced As(III) removal rate at pH 8 may be credited to the presence of As (III) as a negative anion which advances the adsorption on the active site of iron oxide surface (Issa et al. 2010).

Mixture of MWCNTs and MnO_2 (manganese dioxide) (MWCNT/MnO_2) was fabricated for the As(III) and As(V) removal from water (Saleh et al. 2011). During As removal, the MnO_2 oxidizes As(III) and itself gets reduced from Mn(IV) to Mn (II). Consequently, this nanoadsorbent joins the oxidative characteristics of MnO_2 with the adsorption properties of MWCNTs for the higher As removal from wastewater (Saleh et al. 2011).

The Fe-MWCNTs is produced by doping MWCNTs with Fe°. The Fe-MWCNTs eliminated 77% of As(V) and 74% of As(III) in 60 min at pH 6–7. In water, Fe° oxidized from Fe^{2+} and Fe^{3+} hydroxides, results in As removal through complexation. The maximum adsorption capacity for As(III) and As(V) was 200 mg/g and 250 mg/g, respectively (Alijani and Shariatinia 2017).

13.2.2.2 Graphene-Based NPs

The graphene has an extraordinary potential of adsorption and earned significant consideration in the process of water treatment. The use of graphene is very economical and beneficial as it could be easily produced from graphite and hence lowers the ultimate cost of water treatment process. Graphene has a large surface area with a structure of a sp^2 hybridization and available in the form of carbon sheets. After adsorption of pollutants, the isolation of graphene from the water is a tough task that can prompt recontamination or nano-toxicity. To improve the graphene characteristics, scientists have been investigating numerous functionalized graphene materials (Sweetman et al. 2017). Graphene oxide (GO) is an excellent adsorbent with various hydrophilic oxygenated functional groups, such as carboxyl (–COOH), epoxy (C–O–C), hydroxyl (–OH), and carbonyl (–C=O) (Gao 2015). By using a modified Hummers method, it is very easy to obtain graphene oxide from the graphene by reacting with acid (Han et al. 2013). The oxygenated functional groups on GO increase its permeability for water resulting in enhanced adsorption (Hu and Mi 2013).

To remove organic and inorganic contaminants from wastewater, the modification of graphene oxide with the magnetic NPs is being studied extensively. The utilization of water-dispersible magnetite reduced graphene oxide to eliminate the As from wastewater has been reported by Chandra et al. (2010). The maximum adsorption capacity according to Langmuir model was 13.10 mg/g and 5.83 mg/g for As(III) and As(V) removal, respectively. In another study, the magnetic iron oxide@GO was produced using 51% of iron, the highest adsorption capability of 26.76 mg/g and 54.18 mg/g for As(V) and As(III), respectively, was reported (Yu et al. 2015). The As(V) linked to the functional groups containing iron oxides during the adsorption phenomenon and the Fe and As dispersal was interrelated as suggested by the elemental dispersion map created through the XRF method.

Yu et al. (2015) reported the 3D nanostructured Fe_3O_4 aerogel/grapheme fabrication to remove As for wastewater treatment. The aerogels display a significant adsorption ability up to 40.048 mg/g for the As(V). The superlative adsorption characteristics of nanohybrids of magnetic manganese ferrite ($MnFe_2O_4$) and single-layered GO for As removal are reported by Kumar et al. (2014). The heavy metals are removed by the GO-$MnFe_2O_4$ adsorbent efficiently and the

nanoadsorbent is retrieved from the water with magnet. The conversion of As(III) to As(V) is ascribed to the existence of a massive numbers of the available functional groups in the presence of Mn to assist the adsorption mechanism. The adsorption mechanism is also favored by the decrease in the pH of solution due the Mn and As (V) precipitation (Sverjensky and Fukushi 2006).

The two new hybrid nanomaterials TMF (Titania nanotube-manganese ferrite) and GMF (GO-manganese ferrite) have been introduced by Shahrin et al. (2018) for their utilization in the water treatment to remove As through adsorption. As (V) adsorption capabilities recorded by GO-manganese ferrite and titania nanotube-manganese ferrite were 102 mg/g and 80.8 mg/g, respectively (Shahrin et al. 2018). The GO-nanocomposite membranes have been fabricated by Rezaee et al. (2016) to remove As(V) from the wastewater. It was identified that the increase in GO coating decreased the adsorption capacity for As(V) which might be due to extraordinary hydrophilic nature of GO (Rezaee et al. 2016).

13.2.2.3 Activated Carbon (AC)-Based NPs

Carbonaceous materials have different forms and activated carbon is one of its types which has extremely porous inner structure and could be fabricated using diverse feedstock like nutshells, bamboo, wood, coal, and different organic materials by applying pyrolysis or chemical treatment. When the carbon material is treated for activation, its surface area increases and possesses higher ratio of binding sites which assist the adsorbent interaction with metal ions. The AC is composed of 20% oxygen or nitrogen and 80% of carbon (Figueiredo 2013). The AC generally binds to other moieties via π-π interactions; but some variations such as acidic treatment increases its binding capacity. The AC-metal composites presented greater efficiency for the removal of contaminants and heavy metals from wastewater by introducing higher adsorption sites (Reed et al. 2000). The metal saturation of ACs can be accomplished effortlessly via adsorption of already produced metal NPs on ACs or via decreasing the solution of metal salt (Reed et al. 2000; Lata and Samadder 2016).

Though the AC adsorption is the latest technology for the elimination of pollutants, but its application is costly and this could be managed through fabrication of AC using natural biomass (Hoskins et al. 2002). Economical plant *Prosopis spicigera L* resultant silver-saturated carbon (SIC) was fabricated, characterized, and explored to remove As(III) (Murugan et al. 2017). Higher pH exhibits that there is no consistent trend in the elimination of As, because the highest adsorption of As have been identified at two pH values 10 and 4 for 207.5 mg/g and 98.2 mg/g, respectively. In the acidic environment, the conversion of metallic Ag to Ag^{+} by oxidation causes reaction among AsO_3^{-} and the developed Ag_3AsO_3 precipitate on the adsorbent surface. While, in the alkaline environment, the adsorption of $H_2AsO_3^{-}$ and $HAsO_3^{2-}$ on the surface of SIC was also observed, which improved the adsorption potential. With the increasing temperature, the As removal was also enhanced, and at 45 °C the adsorption capacity for As(III) was 59.19 mg/g (Murugan et al. 2017). The adsorption data followed the pseudo-second-order kinetics model and Langmuir adsorption isotherm.

In a study, the AC was produced using shea cake to remove As. The highest adsorption capacity for As removal by shea cake AC was 7.87 μg/g which followed the Langmuir adsorption and first order kinetics model. Activated charcoal was obtained from the walnut shell utilizing phosphoric acid (5% v/v) and it was assessed for its ability to remove As from aqueous medium (Fazeli et al. 2016). This modification enhances the adsorbent surface area from 1067 to 1437 m^2/g by, with the mean pore size decreased from 3.28 nm to 2.08 nm. The 98% of As was removed in an equilibrium time of 3 min from aqueous media. The maximum adsorption capacity for As was 120 μg/g and followed Langmuir adsorption isotherm. It is proposed that the modification of AC by introducing high quantity of free carboxyl groups causes plenty of chemical and physical interactions on AC surface to absorb As ions. The ceria-coated powder was utilized for AC fabrication to eliminate As from aqueous media which exhibited high adsorption capacity for As(V) and As(III) (12.2 and 10.3 mg/g, respectively) (Sawana et al. 2017).

The robust interaction among adsorbent and As(III) is assumed to be relatively appropriate over a broad pH range. At pH 8, the maximum adsorption of As(V) has been reported, as it exists in the anionic form at pH range of 4–10 (Li et al. 2010). The highly negative nature of As supports its efficient removal by the positively charged functional groups on adsorbent surface at pH 8. Iron compounds were broadly inspected to remove As from the water (Payne and Abdel-Fattah 2005; Gallios et al. 2017). Various investigations have been done to remove As by utilizing Fe impregnated AC, which substantially enhanced their As adsorption potential. The Mn/Fe modified AC was produced through an easy and effective technique, that was then examined and characterized to remove As(V) from water (Gallios et al. 2017).

The Fe impregnation increased the adsorption efficiency of AC from 4 mg/g (pristine charcoal) to 11.05 which was enhanced further to 19.35 mg/g by the introduction of Mn on Fe activated charcoal (Fe-MnO AC). The complexation of As(V) at the particular Fe-MnO interface is the possible mechanism of As (V) adsorption on the Fe-MnO AC. The As(III) adsorption via iron oxide-layered AC is also studied (Ananta et al. 2015). The most reliable pH range for highest As (III) adsorption was detected in the range of 7.5–9.5, at which the 10 μg/L of As was eliminated in 90 min from an initial level of 100 μg/L. The pHzpc was observed at pH 8.2 for iron oxide coated activated charcoal.

The adsorbent surface becomes positively charged at the pH higher than 8.2, which enables the effective adsorption of As(III) on adsorbent surface through electrostatic interaction. The iron layered AC was utilized to examine the As behavior under optimized conditions (Raychoudhury et al. 2015). The Fe-modified AC was produced using ferric in varied concentrations, which presented 42–65% and 92–98% removal efficiency for As(III) and As(V), respectively. The Langmuir isotherm adopted well the adsorption pattern indicated 98.4 mg/g and 125 mg/g adsorption potential for As(III) and As(V), respectively. Yao et al. (2014) also reported the efficiency of Fe-modified AC for the removal of As(V), which removed 98% of As(V) in 60 min in the pH ranging from 3.5 to 8.

13.3 Characterization of Nanoadsorbents

It is important to characterize the nanoadsorbents, in order to recognize their physiochemical features and functional properties as well as the mechanism of As removal. Different analytical methods are used to characterize the nanoadsorbents including confocal micro μ-XRF, X-ray adsorption near-edge structure (XANES), Brunauer Emmett Teller (BET), X-ray diffraction (XRD), Fourier transforms infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and X-ray absorption fine structure (EXAFS) (Ijaz et al. 2020). The detail of some imperative characterization techniques is given below.

13.3.1 FTIR Spectroscopy

The FTIR spectroscopy is used for the characterization of functional groups and to study the structural properties of different sorbents including nanoadsorbents. The difference between functional groups on the nanoadsorbent surface is determined using FTIR and it also determines shifts in functional groups before and after the sorption of As. The FTIR spectra of pristine MWCNTs and carboxylate MWCNTs (MWCNTs-OCH_2CO_2H) were examined and are given in Fig. 13.5. Due to the presence of carboxylic group on the MWCNTs-OCH_2CO_2H, the strongest band was observed at 1603 cm^{-1} and 1765 cm^{-1} by the bending and stretching vibration of C=O (Fig. 13.5). The vibration band on the surface of MWCNTs-OCH_2CO_2H was more distinct which is credited to functional groups on the MWCNTs surface as a result of carboxylation (Egbosiuba et al. 2020). Wang et al. (2020) synthesized Fe_3O_4@poly(p-phenylenediamine) @TiO2 (Fe_3O_4@PpPDA@TiO_2) core-shell NPs

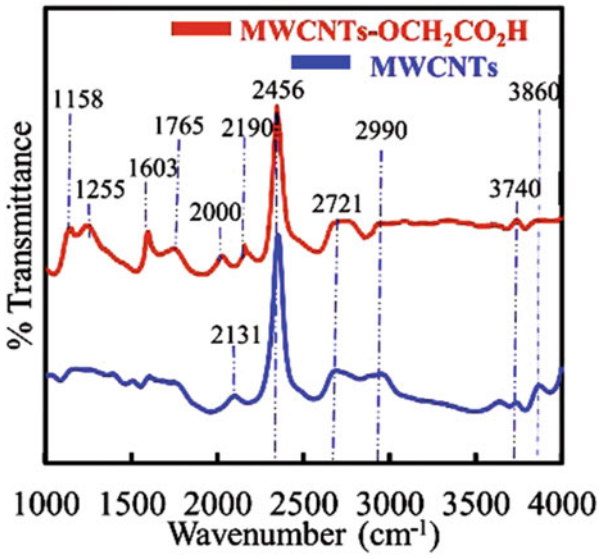

Fig. 13.5 Fourier transform infrared (FTIR) spectra of MWCNTs and MWCNTs-OCH_2CO_2H (Reproduced with permission from Egbosiuba et al. (2020))

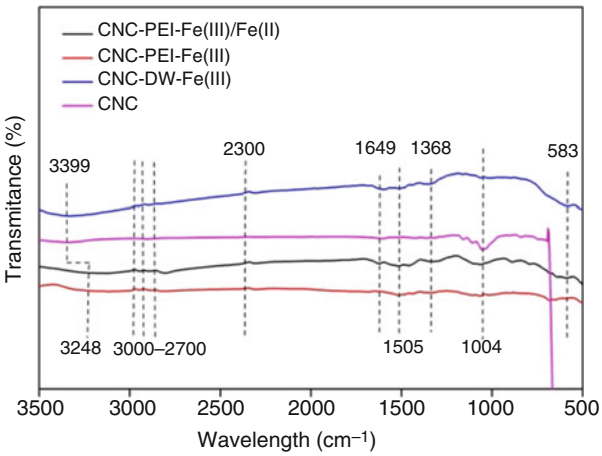

Fig. 13.6 Fourier transform infrared (FTIR) spectra of different forms of cellulose nanocrystals (Reproduced from Xi et al. (2020))

for the As adsorption. The PpPDA was characterized using FTIR, which indicated two peaks at 1502 and 1569 cm^{-1}, that is attributed to the stretching in C=N and C=C structures, respectively. The outcomes confirmed the integration of PpPDA on nanocomposites. The peak at 671 cm^{-1} confirmed the properties of TiO_2 in Fe_3O_4@PpPDA@TiO_2. The higher mass of TiO_2 hides the Fe_3O_4 properties in these types of core-shell NPs. However, the presence of Fe_2O_3 is presented via peak at 578 cm^{-1} for Fe_3O_4 PpPDA. Xi et al. (2020) fabricated cellulose nanocrystals (CNC) with various modifications with polyethyleneimine (PEI) and Fe. The FTIR spectrum showed varied O–H vibrations, as the absorbance peak for CNC and CNC-PEI-Fe(III) was observed at 3399 cm^{-1} whereas the absorbance peak for CNC-PEI-Fe(III) and CNC-PEI-Fe(III)/Fe(II) was observed at 3248 cm^{-1}. In Fe-modified CNC, the peak at 583 cm^{-1} was attributed to FeO vibration. These outcomes somehow indicated the Fe and PEI integration on CNCs (Fig. 13.6).

13.3.2 Raman Spectroscopy

The Raman spectroscopy identifies the crystalline structure of nanoadsorbents. Wang et al. (2020) analyzed chemical composition of the Fe_3O_4@PpPDA structure using Raman spectroscopy. The Fe_3O_4 phonon frequency caused formation of three peaks 396, 282 and 218 cm^{-1}. The two distinctive peaks were formed at 1530 and 1591 cm^{-1} using Raman spectra which were attributed to C–C deformation of benzenoid and quinoid rings in PpDA, respectively (Fig. 13.7). The outcomes of Raman spectra reveal the vigorous adsorption of TiO_2. The Fe_3O_4@PpPDA presented the properties of both PpDA and Fe_3O_4 representing effective fabrication of Fe_3O_4@PpPDA. However, after the addition of TiO_2, only TiO_2 characteristics were determined noticeably because of higher quantity of TiO_2 loading.

The Raman spectra of Fe@NCNT-rGO was determined at vibration frequency of 514 nm, exhibiting three peaks at 538, 226, and 496 cm^{-1} parallel to Fe moieties. The dynamic G band peak of Raman is credited to the vibrational frequency and the

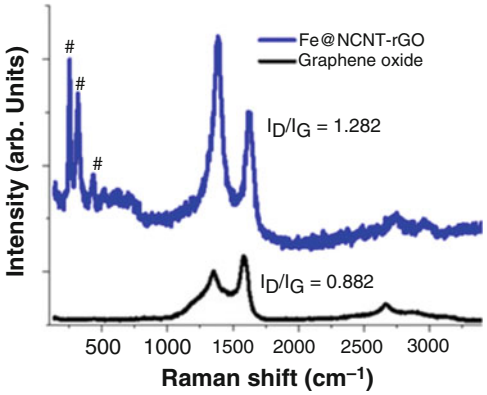

Fig. 13.7 Raman spectra of grapheme oxide and Fe@NCNT-rGO (Reproduced with permission from Sridhar et al. (2020))

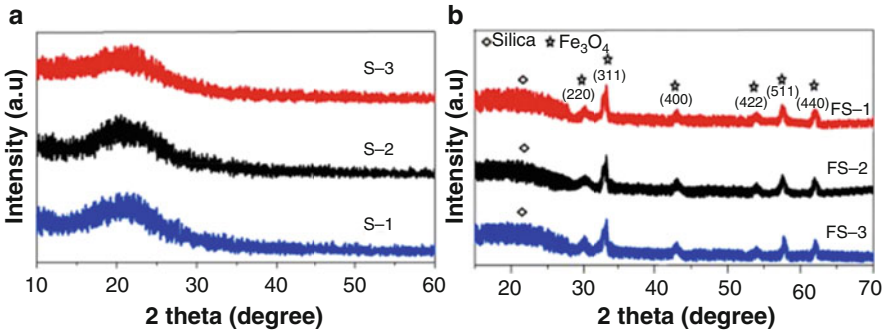

Fig. 13.8 PXRD of (a) silica (b) Fe_3O_4 quantum dot decorated silica (Reproduced with permission from Rakibuddin and Kim (2020))

disorder formed peak at 1352 cm^{-1} was attributed to the existence of CNTs on graphene structure. The reduction in I_D/I_G ratio (D band intensity ratio/G band intensity ratio) from 0.882 to 1.282 was detected in graphene oxide compared to Fe@NCNT-rGO, respectively, which exhibited the flaws in the graphene structure which occurred during its fabrication (Sridhar et al. 2020).

13.3.3 XRD

The information regarding mineral phases in nano-scale and other sorbents could be gained using XRD, which also examines the crystalline structure of the powdered materials. Rakibuddin and Kim (2020) prepared the composites of silica-nanospheres and Fe_3O_4 quantum dots (QDs) using sol-gel technique. The purities of phase and structure of QDs@silica composites and silica were determined using powder XRD (Fig. 13.8). For silica, a distinctive strong peak of (001) plane was

observed at 20.5°, representing that the nature of silica is amorphous. Just like the silica peak, distinct diffraction peaks were presented in the XRD patter for Fe_2O_3. The fabricated composites were perfectly pure in nature, as there were no impurity-related peaks. The average size of Fe_3O_4 QDs crystals was ~5 nm. The PXRD thus supports the existence of mesoporous silica and Fe_3O_4 in the composites.

The magnetite ore and $FeCl_2$ were used as a substrate to fabricate magnetic NPs by microbial synthesis using *Fusarium oxysporum* (Balakrishnan et al. 2020). The XRD spectrum confirmed the spherical structure and purity of magnetic NPs as no distinguishing impurity peak was observed. The average particle sizes of the natural magnetite ore and synthesized magnetic using microbes were 39.52 nm and 31.29 nm, respectively (Balakrishnan et al. 2020). Zeng et al. (2020) fabricated magnetic NPs using iron sludge (iMNP) and chemical reagents (cMNP). With the crystalline γ-Fe_2O_3 structure, the iMNP XRD also showed quartz phase and few wide and low intensity peaks compared to cMNP which confirmed that during fabrication the impurity from iron sludge was not removed.

13.3.4 XPS

X-ray photoelectron spectroscopy (XPS) is used for the surface examination of nanoadsorbents and makes available significant data on the percentage and form of elemental species. It is particularly known technique to identify the As distribution on nanoadsorbent surface. Xi et al. (2020) further confirmed the alterations in chemical structure of CNCs, CNC-PEI-Fe(III)/Fe(II), CNC-PEI-Fe(III), and CNC-DW-Fe(III) using XPS. In XPS spectra, the peak in C1s was altered from two sharp peaks to a large peak after the impregnation of Fe and PEI in contrast to CNC. In addition, the Fe impregnation in Fe-modified CNCs is confirmed by the shape of peaks in O1s region. The outcomes of XPS spectra revealed that the bonding of PEI with CNC was improved due to bridging effect of Fe ions. Sridhar et al. (2020) used the vitamin B_3 (Niacin) to fabricate nitrogen doped CNTs (NCNT). The Fe 2p binding region is presented in XPS spectra of NCNT which indicated two different peaks at 710.12 and 723.6 eV compared to electronic states of Fe $2p_{1/2}$ and Fe $2p_{3/2}$. Compared to Fe-ligand, Fe $2p_{3/2}$ is then deconvoluted to three peaks, i.e., covalency, iron oxynitride moieties, and Fe–N bonds. The XPS spectra confirmed the iron presence as iron carbides and iron nitride and small amount of oxynitride impurities.

Chai et al. (2020) produced nanocellulose NPs modified using glutaraldehyde (GA) and polyethyleneimine (PEI). The O 1s, C 1s, and N 1s XPS spectra of NC-PEI/GA and 2,2,6,6-tetramethylpiperidine 1-oxyl nano cellulose (TEMPO-NC) were examined to explore the linked surface chemical characteristics alterations before and after the As adsorption. The O 1s spectra somewhat enlarged while N 1s signal decreased to some extent after the adsorption of As(V). These alterations were ascribed to the reaction of PEI amino groups with As(V). The clear changes in N1s signal of NC-PEI/GA was observed before and after the As(V) adsorption (Fig. 13.9). Shift in three peaks was detected after As(V) adsorption. The outcomes

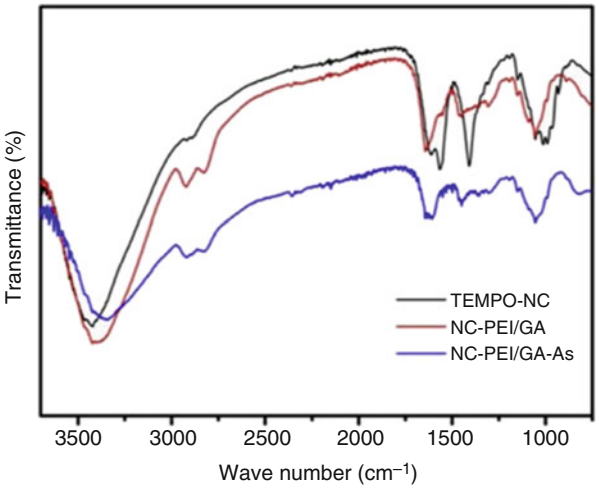

Fig. 13.9 XPS pattern of NC-PEI/GA and TEMPO-NC (Reproduced with permission from Chai et al. (2020))

confirmed the strong bond among N and As(V) atoms. A new peak was formed in NC-PEI/GA-As(V) spectrum which indicated the covalent bond between N atoms and As(V) (Chai et al. 2020).

13.3.5 SEM

Using scanning electron microscopy (SEM), the output image of nanoadsorbent is generated using electron rather than light. The nanoparticle distribution, morphology, size, and shape are studied using SEM. Balakrishnan et al. (2020) used high resolution SEM to explore the morphology and size of the microbial synthesized magnetic NPs. The micrograph represented that the structure of magnetite NPs was round, globular, and occasionally asymmetrical having narrow size range between 27.54 and 81.22 nm. The morphology of CNC-PEI-Fe(III), CNC-PEI-Fe(III)/Fe(II), and CNC-DW-Fe(III) was studied using SEM which represented the bulk presence of CNC-PEI-Fe(III) and CNC-PEI-Fe(III)/Fe(II) and high rate of polymerization. Compared to it, lower polymerization was detected for CNC-DW-Fe(III) (Fig. 13.10). So, it could be assumed that the presence of PEI makes CNC-PEI-Fe (III) and CNC-PEI-Fe(III)/Fe(II) more stable by improving the polymerization and interaction among Fe ions and CNC (Xi et al. 2020).

13.3.6 TEM

The crystalline structure and size of NPs is determined using transmission electron microscopy (TEM). Raza et al. (2020) used TEM to identify the morphology of Fe_3O_4 NPs. The Fe_3O_4 NPs were of spherical morphology having diameter of 39 nm (Fig. 13.11). The agglomeration is observed in Fe_3O_4 NPs and the reason could be

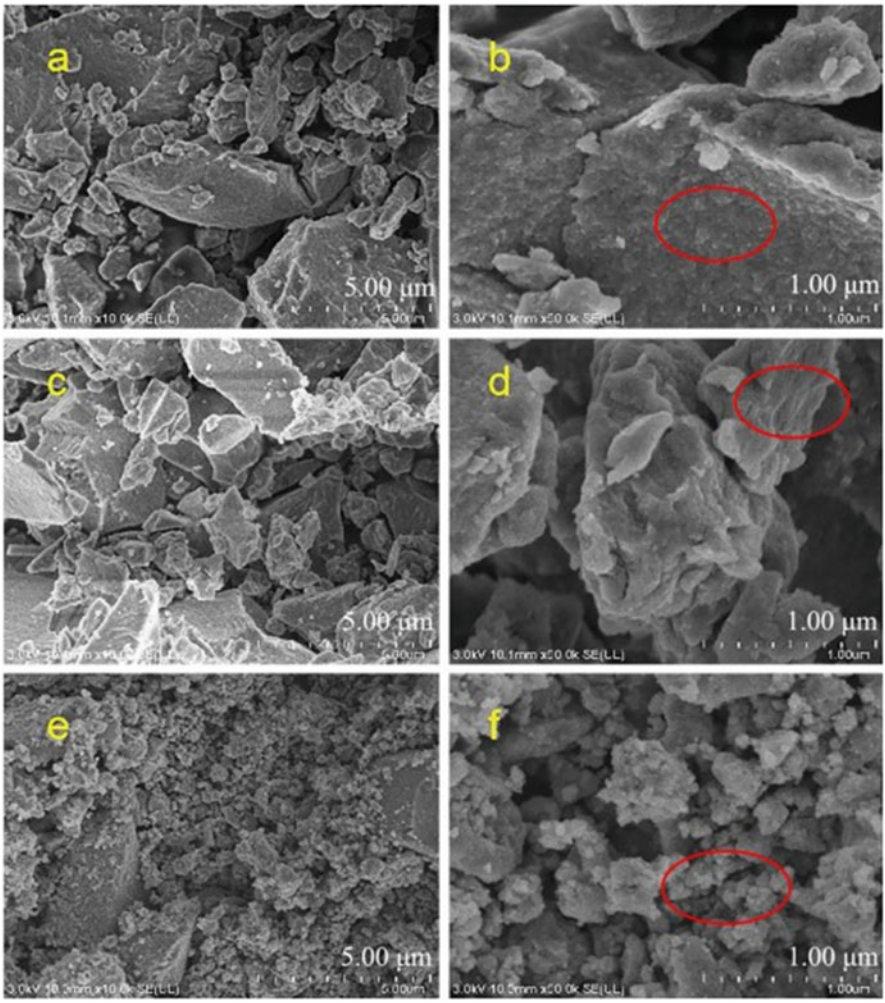

Fig. 13.10 SEM images of CNC-PEI-Fe(III)/Fe(III) (a, b); CNC-PEI-Fe(III) (c, d) and CNC-DW-Fe(III) (Reproduced with permission from Xi et al. (2020))

strong forces between magnetic NPs. In another study, starch functionalized maghemite (C2) and non-functionalized maghemite (C1) were used for the removal of As(III) from the water. The TEM analysis showed that the average particle size of C2 was 9.65 nm and C1 was 11.05 nm. The C2 formed smaller NPs compared to C1 and the morphological structure of C2 was spherical, whereas the C1 possessed large quantity of cubic NPs (Siddiqui et al. 2020). So, it was confirmed that the surface functionalization enhanced both the functional and structural properties of NPs.

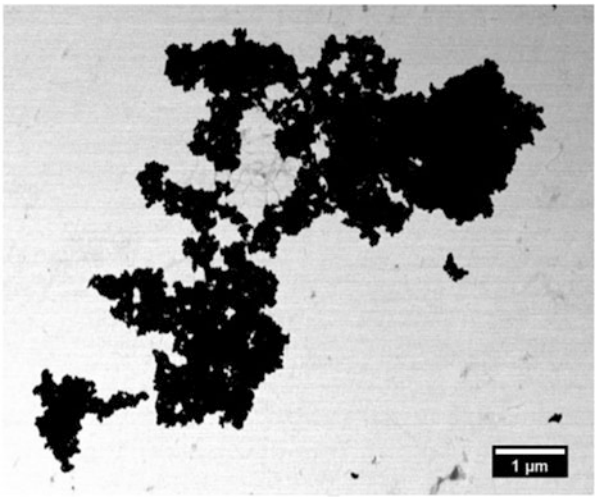

Fig. 13.11 TEM image of Fe_2O_3 NPs (Reproduced with permission from Raza et al. (2020))

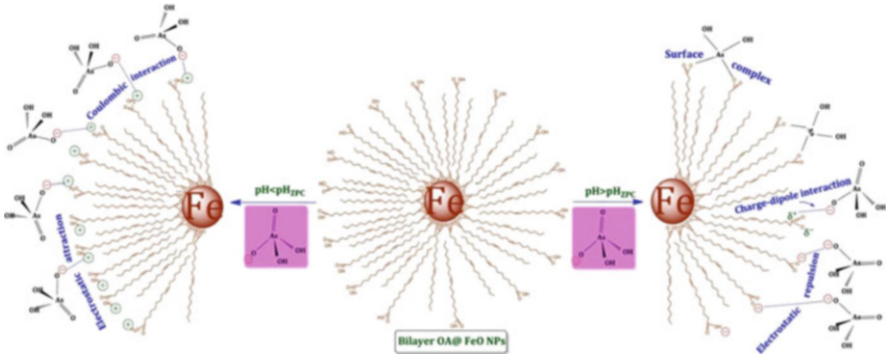

Fig. 13.12 Possible mechanism of arsenate (As(V)) adsorption on bilayer-OA@FeO NPs (Reproduced with permission from Raval and Kumar (2020))

13.4 NPs-Arsenic Adsorption Mechanisms

The adsorption procedure could be occurred in a single step or series of steps might require for its completion including pore diffusion, pore surface adsorption, and external diffusion (Gulipalli et al. 2011). The adsorption of As(V) and As(III) on the adsorbent surface takes place in three phases: (1) Surface migration, (2) deprotonation of complex aqueous As(III)/As(V), and (3) surface complexion (Zhu et al. 2009; Kong et al. 2014) (Fig. 13.12). The potential mechanisms for As (V) adsorption on bilayer-OA@FeO were inner-sphere complex creation, ion–dipole/charge–dipole interaction, electrostatic attraction, intra-particle diffusion,

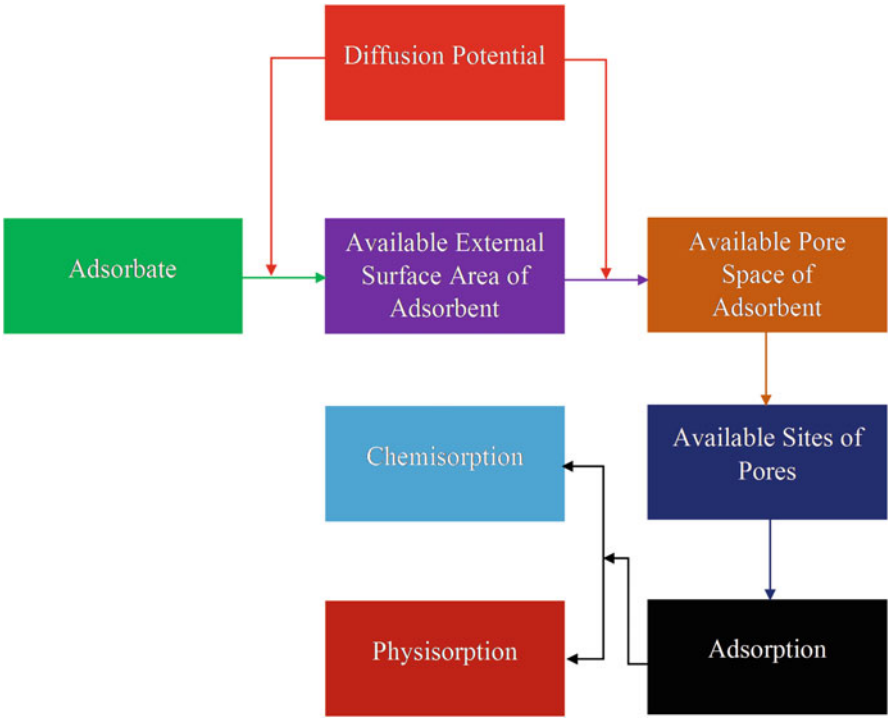

Fig. 13.13 Schematic illustration of adsorption process of adsorbate on nanoparticles

and coulombic interaction (Raval and Kumar 2020) (Fig. 13.13). The adsorbate was diffused on the nanoadsorbent surface based on the available functional groups on its outer surface. After diffusing on the adsorbents outer surface, the adsorbate diffused onto the accessible adsorbent pores. The active sites on adsorbent surface were completely occupied in the adsorption phase via physiosorption or chemiosorption mechanism.

The adsorption performance of As on alumina impregnated polymer beads was controlled through electrostatic adsorption and complexation (Saha and Sarkar 2012). Kong et al. (2014) stated the adsorption of As(V) and As(III) through the formation of inner-sphere surface complexes. The adsorption of As(V) on NC-PEI/GA was significantly attributed to NH_2 functional groups on its surface. The high amount of C-OOH and -NH_2 on the NC-PEI/GA surface results in swelling which makes available extra adsorption sites for As(V) (Chai et al. 2020).

13.5 Influence of Different Parameters

13.5.1 Impact of pH

A range of NPs have been identified so far to eliminate the As from water in pH range of 6.5–8.5 such as β–FeOOH, nano-alumina powder, Fe_3O_4 with coating of ascorbic acid, chitosan graft poly-acryl-amide of alumina nano particles, activated carbon supported by zero valent nano particles, activated carbon nanoparticles dipped with iron, $Al_2O_3/Fe(OH)_3$, and mesoporous silica-media. The bilayer-OA@FeO exhibited higher adsorption capacity of 32.8 μg/g to remove the As (V) at neutral pH (Raval and Kumar 2020). However, some other identified nanoparticles have capacity to adsorb As from water at lower pH which is good for As removal from wastewater instead of drinking water. These identified nanoparticles are; titanium dioxide, maghemites (Deedar and Aslam 2009), and zeolite impregnated magnetic NP (Salem Attia et al. 2014). Siddiqui et al. (2020) also observed the increase in As(III) adsorption by starch modified maghemite nanoadsorbents with a decrease in the pH. Mostly, multi metal (MMO) NPs show strong adsorption potential for both As(III)/As(V) and As(III), at pH range of drinking water (Lata and Samadder 2016).

13.5.2 Impact of Synthesis Method

The reduction technique is usually employed to synthesize the NZVI (Kanel et al. 2006; Chandra et al. 2010; Rahman et al. 2011). Synthesis of other adsorbents was done by different methods like hydrolysis (Vitela-Rodriguez and Rangel-Mendez 2013); polymerization (Sharma et al. 2010; Savina et al. 2011); chemical precipitation (Darban et al. 2013; Zhang et al. 2013; Türk and Alp 2014) sol-gel method (Deedar and Aslam 2009); hydrothermal method (Feng et al. 2012); sonication method (Salem Attia et al. 2014). The reverse micro-emulsion and incipient wet impregnation were used to fabricate the aluminum oxide (Jang et al. 2003; Saha and Sarkar 2012). However, CuO is usually fabricated using thermal refluxing and microwave irradiation technique (Martinson and Reddy 2009; Goswami et al. 2012). The polymerization method was used to prepare activated carbon NPs based on doped phenolic resin (Sharma et al. 2010). Incorporation of iron by polymerization process was done to improve the access of iron to As ions. More research is the much needed to develop new methods for upgrading nanoadsorbents availability to As ions in a sustainable way.

13.5.3 Impact of Initial Concentration

Numerous studies were directed so far to evaluate the higher adsorption of As on nanoparticles with maximum As availability initially to NPs for adsorption. In real circumstances, the concentrations of As in groundwater may range from lower to

higher concentrations (up to 5000 μg L^{-1}) (Shakoor et al. 2015). The adsorption of As(V) on bilayer-OA@FeO was increased from 10 to 150 μg/g when the As (V) initial concentration was increased from 10 to 150 μ/L. The reason might be due to high driving force which caused transference of higher As(V) concentration in the solution (Raval and Kumar 2020). Some of the authors evaluated higher adsorption capacities for As(V) and As(III), even though As(III) adsorption was adequate under pH range of 6.5–8.5. For instance, at 2 mg/L of initial concentration, the adsorption capacity for As(III) was calculated as 296.23 mg/g whereas for As(V), the adsorption capacity was 201.10 mg/g (Kong et al. 2014). At the initial concentration of 10 mg/L, the adsorption capacities for As(V) and As(III) were recorded as 82.7 mg/g and 122.3 mg/g (Zhang et al. 2013).

On the other hand, Deliyanni et al. (2003) observed that the As(V) adsorption capacity ranges between 100 and 200 mg/g at pH 7 with varying initial concentrations of 5–20 mg/L. The NPs of aluminum oxides showed great efficiency to eliminate high As concentrations which assisted in As elimination from highly contaminated wastewater. Siddiqui et al. (2020) investigated the variation in adsorption efficiency of starch modified maghemite nanoadsorbent for As(III) removal by varying initial concentration from 1.0 to 6.0 mg/L. They reported that with the increase in initial concentration As(III) from 1.0 to 6.0 mg/L an insignificant reduction in As(III) from 99 to 95% was detected.

13.5.4 Impact of Particle Size

Generally, the higher adsorption trend with the reduction of particle size is observed but it is not observed in all the adsorbents. For example, the particles of zeolite contain large surface area but larger crystals show higher adsorption capacity than small-sized particles (Vignola et al. 2005) because of intra-crystalline pore structure of zeolite (Rouquerol et al. 2013). Jegadeesan et al. (2010) also studied the influence of TiO_2 NPs particle size on As adsorption. They found the adsorption capacity of TiO_2 NPs for As removal is dependent on the particle size of TiO_2 NPs. The small particle size and high specific surface area of TiO_2 NPs makes it an effective adsorbent.

13.5.5 Impact of Competing Ions

It is known that As is naturally found in groundwater with other co-existing anions (SiO_4^-, F^-, CO_3^{2-}, F^-, SO_4^{2-}, PO_4^{3-}, and Cl^-) and cations (Fe^{2+}, Ca^{2+}, and Mg^{2+}). These species can influence the As adsorption in a synergistic or antagonistic way. Therefore, Raval and Kumar (2020) determined the adsorption efficiency of bilayer-OA@FeO NPs for As(V) removal in the presence of PO_4^{3-}, F^-, SO_4^{2-}, Cl^-, and NO_3^-. The As(V) removal was least affected in the presence of NO_3^-, SO_4^{2-}, and Cl^-, whereas it decreased notably in the existence of PO_4^{3-} and F^-. The decrease in adsorption capacity of As(V) by bilayer-OA@FeO NPs was might be

due to similar structure of As(V) with PO_4^{3-} and F^- which might cause competition between them for the binding sites available on bilayer-OA@FeO NPs (Raval and Kumar 2020).

To evaluate the influence of co-existing ions on the removal of As using NZVI, Tanboonchuy et al. (2012) tested six different species which includes humic acid (HA), Ca^{2+}, SO^{2-}, HCO^-, PO^{3-}, and Cl^-. They found that HA, SO_4, and PO_4 have inhibitory influence, however, Ca^{2+} has escalating effect. Occurrence of HCO^{-3} showed inhibitory influence on elimination of the both species of As. Decreased PO^{3-} and HA and increased Ca^{2+} concentrations increased the removal efficiency of both As(III) and As(V). For removal of As, phosphate and silicate were observed to show lower adsorption than NO^{-3}, SO^{2-}, and HCO^- (Kanel et al. 2006; Zhu et al. 2009). However, Savina et al. (2011) evaluated that these interfering agents have negligible impact on As adsorption capacity. Kong et al. (2014) also observed the influence of the co-existing ions (sulfate, phosphate, and silicate) on adsorption and removal of As. On the other hand, their influence on As(V) adsorption was insignificant (Martinson and Reddy 2009; Ntim and Mitra 2012).

13.5.6 Impact of Contact Medium

The NPs coated packed bed media, fluidize bed and packed beds are the varied contact mediums mentioned in literature to elucidate the application methods for As removal from wastewater. There are some articulate studies mentioned in literature for As removal and mostly mentioned and supported the pack bed column researches. However, for different types of adsorbents, both fluidize bed and packed bed column studies can be conducted. For instance, the hydraulically accepted adsorbent conductivity is the best for fixed bed, however, lower hydraulically conducted adsorbents are observed to be inappropriate for packed bed. This issue can be resolved by coating high hydraulic conductivity material by NPs. The nano adsorbents must have enough compression force to survive the hydraulic pressure that may contribute to adsorbent damage in packed bed (Chen et al. 2011).

The fluidize bed technique is also an effective technique for NPs synthesis where adsorbents are covered with such materials which curb the agglomeration of fluidize nanoadsorbents. Due to less coating, the adsorption capacity deceased and contributed in the secondary pollution due to the leaching of coated sand which compelled the usage of a binding agent named as acrylic-styrene copolymer latex (Chen et al. 2009).

Similarly, the different polymers like polyvinyle alcohol and polyacrylamide (PAM) were also found to be good binding agents. A cheaper green starch is used to stabilize and avoid the clustering of magnetic NPs. This acts as a linking media for nanoadsorbents fluctuation and precipitation while maintaining the higher adsorption capacity for As (An et al. 2011). The removal of both As(III) and As(V) from wastewater is found to be efficient with application of NPs with comparatively lower adsorbent amount and lesser time interval. The material used as nanoadsorbent must

not percolate in treated water beyond prescribed limits for drinking water, therefore a suitable coating material should be used to avoid leakage.

13.6 Nanomaterials Separation

The numerous techniques such as magnetic separation, filtration, and centrifugation are used to separate the NPs after the adsorption procedure. A stainless steel column was used in magnetic field separator for separation of magnetite NPs (Chandra et al. 2010; Khodabakhshi et al. 2011). Commonly, the magnetic NPs are impregnated with magnetic elements such as Co, Ni, and Fe which could be separated easily using HGMS (Ali 2012). Size, magnetic properties, magnetic field gradients of the NPs are the main factors affecting their separation by using HGMS technique (Moeser et al. 2004).

The Fe NPs are simply taken out from the water using magnetic separator due to their higher magnetic property (Nassar 2012). Taking into account the type and size of the membrane, many researchers preferred to use filtration technique for separation of FeO NPs, Fe_3O_4, β-FeOOH, and CNTs supported NPs (Deliyanni et al. 2003; Deliyanni and Matis 2005; Niu et al. 2005). The non-magnetic NPs can be removed effectively by using centrifugation technique due to its higher density, high efficiency, no NPs aggregation, and scalable production (Bai et al. 2010; Chen et al. 2010). Usually, NPs are able to be removed from water using a centrifuge speed range between 20,000 and 50,000 rpm.

13.7 Regeneration of Nanoadsorbents

The recycling of nanoadsorbents is key process to reduce the cost of adsorbent when used at a larger scale. Adsorbent usually gets exhausted after adsorbing As from water. Regeneration of adsorbent is required to reuse the nanoadsorbent and also for recovering As for safe disposal to protect environment. The main purpose of regeneration is to reuse the adsorbent without losing its adsorption potential which will save money and will make it economically acceptable.

Raval and Kumar (2020) used 0.1M NaOH to regenerate bilayer-OA@FeO NPs efficaciously up to five desorption cycles. The adsorption potential of bilayer-OA@FeO NPs for As(V) was 14.85% by using bilayer-OA@FeO NPs in the 5th cycle which was 5.6% less compared to fresh bilayer-OA@FeO NPs. In a study by Ali (2012), the importance of pH for adsorbent regeneration is evaluated. In this study it was observed that there is insignificant cations adsorption in the acidic solution while significant adsorption of anions is observed in acidic solution. Thus, desorption can be easily done by just adjusting pH of the solution. Nano particles can be used again after regeneration to remove heavy metals from water because they gave shown capability to maintain their adsorption capacity after number of cycles (Sharma et al. 2010).

Alkalis have been found to be more efficient desorption agents to make the modified chemical adsorbents reusable (Lata et al. 2015). The desorption potential of NaOH for regeneration of adsorbents is reported in numerous studies. Deliyanni et al. (2003) revealed that the nanocrystals of β–FeOOH had lost about 25–30% of adsorption capacity after every regeneration cycle of As (V) (Deliyanni et al. 2003). In another study, zerovalent impregnated activated carbon exhibited 2/3 of the adsorbate recovery using 0.1M solution of NaOH (Zhu et al. 2009).

Chai et al. (2020) analyzed the regeneration potential of NC-PEI/GA up to eight cycles for As(V) adsorption. Of note, the recovery efficiency in the first cycle reached 100% and was relatively stable even after eight cycles. These outcomes suggest a simple reuse of NC-PEI/GA adsorption with the NaOH solution, making it a convenient adsorbent for real acidic wastewater treatment. Zhang et al. (2013) showed that reduction in adsorption capacity for As(III) was observed to be only 10.6% and only 6.2% for As (V) after four cycles of regeneration of binary oxide of Fe-Cu. They concluded that NaOH is an effective desorption agent for binary oxide of Fe-Cu. In another study, the CTS-g-PA exhibited more better regeneration potential using NaOH (0.5M) where only 6% decrease in the adsorption capacity was observed after the regeneration cycle (Saha and Sarkar 2012).

13.8 Conclusion and Future Recommendations

The nanomaterials possess high surface to volume due to which they are extensively used to remove As from water/wastewater treatment. In this chapter, the role of various nanoadsorbents iron oxide/hydroxide, alumina, copper oxide, titanium oxide, bi-metal oxides, and carbonaceous NPs has been summarized. All types of nanoadsorbents exhibited different adsorption potential for As and for its different species.

The modified nanoadsorbents were proved as more efficient compared to pristine. The physiosorption, electrostatic attraction, diffusion, surface complexation, and ion–dipole/charge–dipole interaction are the observed mechanisms of As (V) adsorption on nanoadsorbents. Some nanoadsorbents presented excellent regeneration potential after numerous cycles without losing their adsorption capacity.

The regeneration of nanoadsorbents could minimize the overall cost of treatment, therefore more research is needed in this concern. Furthermore, more investigation is needed on a pilot-scale to evaluate the efficiency of nanoadsorbents for the adsorption of As from real water in the presence of co-existing ions.

In modified adsorbents, the strong modification for a long time is required as due to weak bonding the material used for the modification could cause its release into the water which could further deteriorate the water quality. The use of biomaterials for NPs modification is highly recommended due to their low cost and eco-friendly nature, therefore, future research is needed to explore the adsorption potential of biomaterials modified NPs for As removal.

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Understanding the Bioaccumulation and Biosorption of Arsenic [As(III)] in Plants and Biotechnological Approaches for Its Bioremediation

14

Ujjwal Kumar, Ashok K. Jha, and Ravi S. Singh

Abstract

The efforts are being made globally regarding the development of low-cost, eco-friendly, and novel methods of remediation of arsenic from aqueous medium and soil. Biotechnological approaches of bioaccumulation and biosorption have emerged as an important tool in the ongoing research including the latest application of novel CRISPR/Cas9 technology that can enhance the rate of bioaccumulation. Expression modulation of genes and proteins including transcription factor, transporter, and mi-RNAs during As(III) accumulation plays an important role in bioaccumulation besides other factors such as statistical factor, percentage removal, and adsorption isotherm. Biosorption mechanisms that include coordination, chelation, ion exchange, reduction, complexation, and movement through different parts of plants are also important. In this chapter, keeping in view the importance of bioaccumulation and biosorption by plants, we have discussed the mechanism of bioaccumulation and biosorption of As(III) in plants, different kinetic models including pseudo-first order and pseudo-second order model and thermodynamic parameters like entropy change, enthalpy change, and Gibbs free energy change determine the spontaneity and criteria of reaction and biotechnological approaches for As(III) bioremediation.

U. Kumar
P.G. Department of Biotechnology, T.M. Bhagalpur University, Bhagalpur, India

A. K. Jha (✉)
University Department of Chemistry, T.M. Bhagalpur University, Bhagalpur, India

R. S. Singh (✉)
Department of Plant Breeding and Genetics, Bihar Agricultural University, Bhagalpur, India

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Bioaccumulation · Biosorption · Adsorption isotherm · Genoremediation

14.1 Background

Resources of arsenic contamination have been explored worldwide because arsenic is the 20th most abundant metalloid found in the earth crust (NRC 1977). Its abundance is 14th and 12th in seawater and human body, respectively, that is about 5 mg kg^{-1} of earth crust which has an average concentration of 2 mg kg^{-1} in igneous and sedimentary rocks (Mandal and Suzuki 2002). The four oxidation states of arsenic are −3, 0, +3, and + 5. More than 200 minerals of arsenic are found in which 60% are arsenate, 20% are sulfides, and 20% are arsenides, arsenites, oxides, silicates, and elemental arsenic (Bissen and Frimmel 2003). Eruptions from volcanoes and sea salt sprays are also considered as source of arsenic contamination (Fitz and Wenzel 2002).

Oxidation states of arsenic exhibit a wide range of solubility, which depends on the ionic condition and pH (Finnegan and Chen 2012). More than 80% of groundwater contamination is due to As(III) (Kumar et al. 2016; Kumar and Jha 2020). When arsenic is present in +3 oxidation state, it is more toxic (Kumar et al. 2015a, b, c). Trivalent arsenic species (Arsenite) has formula reported as M_2HAsO_3, MH_2AsO_3, M_2HAsO_3, and M_3AsO_3 where M represents a universal metal cation or one equivalent of a multivalent cation. Arsenites of group-I alkali metals of periodic table are soluble and alkaline earth arsenites are sparingly soluble, whereas arsenites of heavy metals are insoluble. Arsenic is one of the carcinogenic agents which has posed alarming threat (Mueller et al. 2001).

Irrigation of crops with arsenic contaminated groundwater in South Asia leads to accumulation in plant biomass and accelerated the transfer of arsenic in the food chain that leads to adverse health effect such as arsenicosis (Williams et al. 2005). Despite this, the most widespread threat is the leaching of naturally occurring arsenic into groundwater aquifers I (Rathinasabapathi and Ma 2006). Therefore arsenic contamination in groundwater is the most common results of its higher assemblage in soils. Approximately one-third population of the world consumes groundwater for drinking and other household uses that adversely affect human health (Malik 2007; United Nations Environment Program (UNEP) 1990). Many technical applications have been established to overcome or remove arsenic contamination from water and soil resources. Some chemical and physical methods including chemical reduction, cementation, solvent extraction, electrodeposition, and reverse osmosis have been successfully implemented. But these applications require vast machinery, large setup including high operational cost and need lots of equipment. Due to their complex applicability, it is difficult to set up the unit everywhere for arsenic decontamination.

Bioaccumulation and biosorption are the two most emerging mechanism of phytoremediation techniques in a few decades that may be applicable as low-cost and eco-friendly, requiring less equipment and easy operating for removal of arsenic

from their contaminated sites. In the twenty-first century, many plant species including medicinal and aromatic plants have risen as new hope for decontaminating metallic pollutants from their active sites. These metal/metalloid bioaccumulating specific plants can be reused after bioaccumulation and their byproduct can be separated and purified after treatment. In this study we will discuss about detailed application, mechanism, and biotechnological advances in bioaccumulation and biosorption of arsenic(III) by plants.

14.2 Bioaccumulation

Bioaccumulation of arsenic by medicinal plants is a green approach using root intact live plant to remediate arsenic from contaminated site. This approach requires high growth rate, metallic or metalloid tolerant to large amount of arsenic contamination, and the metabolic capacity to accumulate large amount of arsenic in their above ground parts (more than 100–1000 mg/kg^{-1}) (Ghori et al. 2016). Arsenic species considered as nonessential for plant (Khalid et al. 2017). Plants accumulate inorganic form of As(III) or As(V) (Neidhardt et al. 2015). When As(III) enters in plant cell by their root via aquaglyceroporins (Bhattacharjee et al. 2008), As(III) translocate from root to shoot through different metal transporter export metal ions out of the root symplast into the xylem apoplast (Mills et al. 2003). In this process, translocation of metallic cations through xylem may also take place by chelation (Pilon-smits and Pilon 2002; Kim et al. 2005) including malate, citrate, histidine (Krämer et al. 2007), nicotianamine (NA) (Stephan et al. 1996; Von wiren et al. 1999). NA supports in metallic translocation in the phloem (Mari et al. 2006). The rate of arsenic bioaccumulation by plants also depends upon soil type, their pH and soil constituents. Ferric hydroxide plays an important role in stabilizing arsenic concentration in soil and aqueous medium too. This phenomenon can be shown by the following reaction (Naidu and Bhattacharya 2006):

$$Fe^{3+} + 3H_2O \rightleftharpoons Fe(OH)_3 + 3H^+$$

in the Bengal delta plain, clays, sulfates, phosphate, and sulfides of Al, Fe, and Mn are attributed to the occurrence of arsenic (Foster 2003).

In natural condition, plants essentially take up mineral nutrients together with arsenic and other contaminants from the soil or aqueous medium. Therefore equilibrium is an important factor that governs their bioavailability, i.e. their potential ability to take up and accumulate by plants. Plant nutrient uptake is an active process, requires energy to accumulate essential elements at higher level in plant tissue than in soil solution while the presence of arsenic and other toxic metals or excess of nutrients requires mechanism to modulate the accumulation of ions (Leao et al. 2017). Arsenic and other heavy metal contaminants are generally transported and accumulated in the vacuole as metal chelators. Metal ion in the soil and aqueous medium are taken up by plants into their tissues. These are reduced as metal chelate using oxygen, sulfur, and nitrogen donor ligands. The abundance of carboxylic acid

anions in the terrestrial plants cells facilitates complex formation with di- and trivalent metal ions. Generally the major charge balancing anions present in the cell vacuoles of photosynthetic tissues are malate, aconitate, malonate, oxalate, tartrate, citrate, and isocitrate. Many of these carboxylates get associated with metal concentration in plants (Ma et al. 1997; Homer et al. 1995).

Chelation compartmentalization and biotransformation are some of the mechanisms employed by plants for detoxification of arsenic (Salt et al. 1998). The external mechanism includes exudations which charge rhizospheres pH, metal speciation, and binds metal ions on the cell walls. In intracellular mechanism alteration of structural protein takes place to minimize metal toxicity and thus transport of metallic/metalloid ions to vacuoles takes place.

14.2.1 The Uptake Mechanism

For arsenic and other metallic contaminants, passive uptakes take place through micropores in the root cell to the root where degradation occurs. The apoplast is nothing but a hydrated free space in between the soil colloid and the cell membrane of the root cortex. A network of cellulose, hemicellulose, pectins, and glycoproteins in cell wall micropores has ion exchange capacity and binding sites too. Di- and polyvalent cations get attracted to these sites within root cortex cell wall. Active transport processes are responsible for translocation of the metal ions through plasma membrane of living cells to the ground parts of the plants. Endodermis forms the outer limit of the root vascular system (Mirza et al. 2014).

The As species enter from plant roots through aquaporin channels, mainly using the nodulin 26-like intrinsic proteins (NIPs, a subfamily of the aquaporin family) (Ma et al. 2008; Mitani-Ueno et al. 2011; Xu et al. 2015). In some plants N1P1:1 and NIP3 play an important action in As(III) accumulation (Kamiya et al. 2009; Xu et al. 2015). In rice plant, the Si influx transporter Lsi1 (low silicon rice 1; OsNIP2:1) is responsible for As(III) uptake, while Si efflux transporter Lsi2 (low silicon rice 2) mediates As(III) efflux (Ma et al. 1997, 2001, 2008). Besides Lsi (OsNIP2;1), other NIPs including OsNIP1;1, OsNIP2;2, OsNIP3;1 and OsNIP3;2 also show permeability to As(III) (Bienert et al. 2008; Ma et al. 2008).

Furthermore, some plasma membrane intrinsic proteins (PIOs, another subfamily of the aquaporin family), including OsPIP1;2, OsPIP1;4, OsPIP1;6 are additionally involved in As(III) transport (Mosa et al. 2012). In some other cases NRAMP (natural resistance-associated macrophage protein) transporter OsNRAMP1 is involved in As(III) bioaccumulation. Some studies state that OsNRAMP1 localizes on plasma membrane of endodermis and pericyclic cells may involve in As(III) xylem loading for root to shoot As(III) translocation (Tiwari et al. 2014).

Some other studies have reported that complexation of As(III) takes place with glutathione (GSH) or phytochelatin (PCS) (Raab et al. 2005). Fourteen different complexes with arsenic have been known in sunflower plant. Transportation of As (III) complexes takes place across tonoplast and sequestrated in vacuoles. Studies have revealed that translocation of As(III) from roots to tissue takes place via

methylation giving rise to monomethyl arsenate, dimethyl arsenate, and trimethyl arsenate in plants (Bhattacharjee et al. 2008; Mukhopadhyay and Rosen 2002; Xu et al. 2007; Wu et al. 2002: Raab et al. 2005).

Complexation of As(III) with PCs or GSH is an effective way to detoxify As(III) probably because the complexes are pumped and sequestrated in the vacuole catalyzed by the homology of multidrug resistant proteins (MRPs) membrane of ABC superfamily (Lu et al. 1997; Tommasini et al. 1998). Inside the cells, the metalloids/metals ions are translocated to final destination for storage and chelation involving membrane metal transporters identified such as ATP-binding cassette (ABC) (Song et al. 2003; Vande Mortel et al. 2006), cation diffusion facilitators (CDP) (Peiter et al. 2007), zinc transporter of *Arabidopsis thaliana* (HMA, ZAT renamed as AtMTP1) (Becher et al. 2004; Willems et al. 2007), and Ca2+/cation antiporter (CaCA/CAX) superfamily MHX (Elbaz et al. 2006).

Another metal/metalloid chelating agents are metallothionins that also play role in detoxification of arsenic species. The production of metallothionins is upregulated when metallic concentration was increased (Guo et al. 2008a, b); its size is about ~3.5–14 kDa that is cysteine-rich metal binding proteins almost found in all plant species (Cobbett and Goldsbrough 2000). Some metal chaperons are also involved in intracellular transport of nonessential metals and metalloids that bring nonessential element at specific site in the cell where the elements can create least damage to vital cellular processes (Roosens et al. 2004). Metal chaperons have specific transporters such as ZAT1, aCDF-type transporter (Verbruggen et al. 2009). Reports also studied that in some of the plant, arsenic bioaccumulation is induced by oxidative stress that generates different reactive oxygen species (ROS), i.e. hydroxyl radicals (H_2O_2 and OH^-), sulfur oxide anions (O_2^-) (Hartley-Whitakar et al. 2001), whereas oxidative stress generally affected adversely and damaged DNA, lipids, proteins, and other plants biomolecules (Singh and Ma 2006). It also interferes with electron transport system in the thylakoid membrane, photosynthesis, metabolic processes, membrane permeability, and enzymatic processes that leads to leaf chlorosis and necrosis (Tu and Ma 2005; Karabal et al. 2003; Nguyen et al. 2003). In those methods, plant uses there antioxidant molecules and antioxidant enzyme for detoxifying of different ROS. It has strategy of binding nonessential element such as arsenic species to plant cell wall (Bringezu et al. 1999) or chelating metals in the cytosol by peptides (Schmoger et al. 2000). *Pteris vittata* has been described as applying the strategies to detoxifying As(III) (Verbruggen et al. 2009).

14.2.2 Differential Gene Expression Modulation During As(III) Accumulation

The genome expression has been studied in different types of plant species under As (III) stress (Pandey et al. 2020; Abbas et al. 2018; Kumar et al. 2015a, b, c; Tripathi et al. 2012a, b). During As(III) exposure in rice, different types of transporters like glutathione *S*-transferase (GST), glutaredoxins, heat shock proteins, metallothioneins, multidrug resistance proteins, helix-turn-helix protein, and sulfate

transporters were upregulated. While only one downregulated protein is aquaporin gene in AS(III) stress, whereas zinc-finger C3HC4-type protein is both up- and downregulated in As(III) stress. The large number of heat shock proteins here upregulated expression during As(III) stress (Chakrabarty et al. 2009).

Another observation of As(III) stress on *A. thaliana* and *Oryza sativa* revealed catalases, acid phosphatases, cationic peroxidase, zinc-finger protein, xyloglucan endotransglucosylase/hydrolases. Serine/threonine protein kinase, patatins, integral membrane family protein, hydrolases, glycosyl hydrolase family 17 proteins, and ferritins were always downregulated in both *A. thaliana* and *O. sativa*, while peptidyl-prolyl-*cis-trans* isomerase and metallothionein-like protein1 are upregulated in both plants. NAC domain-containing proteins, lipoxygenases, glycosyl hydrolase family 1 proteins, and glutathione *S*-transferases gene show both up- and downregulated during As(III) exposure in *O. sativa*, whereas peroxidases and glutathione *S*-transferases both up- and downregulated in *A. thaliana*. Germin-like proteins only show upregulation in *O. sativa* and glycosyl hydrolase family1 and ferredoxin chloroplast show upregulated expressions in *A. thaliana*. Cytochrome P4583B1, germin-like proteins, lipoxygenases, and NAC domain-containing proteins show downregulation in *A. thaliana* (Chakrabarty et al. 2009; Abercrombie et al. 2008; Tripathi et al. 2012a, b).

Expression patterns of proteins during arsenic accumulation in Maize have been described that 10% of detectable proteins in their root were differentially regulated by arsenic species (Requejo and Tena 2005, 2006). Root proteins of *Zea mays* plants show upregulation of antioxidant enzymes related protein like as SODs, GPXs, and peroxiredoxin (prex) during arsenic stress, while succinyl-CoA synthetase, ATP synthase, cytochrome P45, and guanine nucleotide-binding protein are responsible for oxidative stress, a major process underlying arsenic toxicity in plants (Tripathi et al. 2012a, b). In shoot protein of *Z. mays* such as guanine nucleotide-binding protein, protein kinase C inhibitor, Tn10 transposase-like protein, malate dehydrogenase, CS, ATP synthase and elF-SA are reported as downregulated during arsenic stress (requejo and Tena 2006). In *P. Vittata*, enolase, phosphoglycerate kinase and glyceraldehyde-3-phosphate proteins were upregulated during arsenic accumulation and may play a central role in arsenic metabolism (Bona et al. 2010).

14.2.3 Expression Modulation of miRNAs During Arsenic Accumulation

Function of miRNAs play a responsive and an important role during arsenic bioaccumulation by plants from roots. From the last decades, several studies state that 69 miRNAs from *Brassica juncea* belonging to 18 plant miRNA families respond to arsenic accumulation or stress (Srivastava et al. 2012). In addition to this miRNA from Indica rice belonging to miR827, miR528, miR444, miR408, miR397, miR393 and miR319 were upregulated expression during As(III) bioaccumulation or stress, whereas miR3979, miR2121, miR1432, miR1427, miR1318, miR819, miR818, miR815, miR812, miR810, miR396, miR390,

miR172, miR171, miR169, miR167, miR166, and miR164 were downregulated during As(III) exposure (Liu and Zhang 2012). Accepted target prediction for these miRNAs in *B. juncea* identified a number of genes related to signal transduction, photosynthesis, plant development, sulfur uptake, metabolism, assimilation of hormonal biosynthesis, and transport (Srivastava et al. 2012; Liu and Zhang 2012).

14.2.4 Recombinant DNA Technology to Modulate Arsenic Bioaccumulation

Application of plant species known as bioaccumulator of arsenic with native genes has limited success to decontaminate arsenic species from affected sites. To improve their efficiency, origins of microbial genes are a wide source to develop genetically modified plant species to sequestration of arsenic species more effectively (Vasupalli et al. 2020). This term is also known as genoremediation that involves the genetic transformation of plants with genes regulating metals or metalloids transport and homeostasis response to oxidative stress or detoxification (Mani and Kumar 2014). Genoremediation is the most important technique for accumulation of toxic element in plants. Similarly, gene engaged in glutathione and other phytochelatin biosynthesis is also being widely utilized (Li et al. 2004).

As(III) uptake enhancement using transgenic technology has been successfully implemented by the overexpression of PvACR3 transporter from *P. vittata* in *A. thaliana* (Indriolo et al. 2010). This transporter helps in the translocation and storage of As(III) into vacuolar system in *P. vittata*. *A. thaliana* overexpression plants show a considerable increase of As(III) export from root to shoot and increased of arsenic tolerance. The strong expression of this transporter makes it to localize in the plasma membrane of the transgenic plants which increased As(III) extrusion to the external medium. This technology enhanced translocation of As(III) in aerial parts has been reported (Wang et al. 2018). Thus, it appears useful to constitutively express PvACR3 transporter in vigorous crops for facilitation of translocation from root to shoot.

Dhankher et al. (2012) demonstrated that utilization of two bacterial genes *γ-glutamyl cysteine synthetase*, As(V) reductase (*arsC*), and their expression showed enhanced arsenic bioaccumulation in transgenic line of *A. thaliana*. This mechanism to develop arsenic removal plant with increased accumulation of arsenic via gene pyramiding of *arsC* and *γ-ECS* may be helpful in arsenic remediation. Another study reported that transgenic lines harboring cdPCS1 isolated from phytochelatin synthase gene from *Ceratophyllum demersum* (cdPCS1) was expressed in transgenic *A. thaliana* and *Nicotiana tabacum* showed enhancement of PC content with enhanced heavy metals bioaccumulation without any impediment in plant growth (Shukla et al. 2012, 2013). Expression of *A. thaliana* metallothionein gene, *AtMT2b* in *N. tabacum* observed significant decreased accumulation of arsenic in shoots where arsenic uptake by plants remains unchanged (Grispen et al. 2009). Besides this, greater accumulation potential of As and Cd has been reported by

overexpression of genes encoding for gamma-glutamyl cysteine synthase and glutathione synthase in *B. juncea,* respectively (Navaza et al. 2006).

Some reports also state that enhancement of bioaccumulation of different heavy metals including arsenic species takes place by modulation of phytochelatin (PC)-Cd-transporter, SpHMT1 of *Schizosaccharomyces pombe* in *A. thaliana* (Huang et al. 2012). Other transgenic lines such as overexpression of As PCS1 and GSH1 derived from garlic and baker's yeast in *Arabidopsis* also showed enhanced tolerance and accumulation arsenic along with cadmium (Guo et al. 2008a, b).

To regulate the As(III) accumulation in plant species, transcriptional regulation also is significant in the regulation of the capacity of plants to bioaccumulate arsenic (Clemens 2001). Recent studies show that *OsARM1*, a MYB transcription factor, has been identified in rice. This gene, strongly induced by As(III) adversely regulates arsenic associated transporter genes, namely *OsLsi1*, *OsLsi2*, and *OsLsi6* which play an important role in the transcriptional regulation of arsenic response in rice (Wang et al. 2017). The discovery of such transcription factors is fundamental for the development of genetically modified crop for As(III) removal.

14.2.5 Hyperaccumulator Plants

Plants species which have capacity to bioaccumulate arsenic more than 1000 μg g^{-1} of dry weight is considered as hyperaccumulator plants (Reeves et al. 2018; Van der Ent et al. 2013). Metal/metalloid hyperaccumulation is not common in terrestrial higher plants. At least 400 plant species have been established as hyperaccumulators of arsenic and heavy metals. Due to this unique behavior, these are used as bioaccumulator of arsenic species from contaminated sites (Kumar et al. 2014, 2015a, b, c, 2017). A Chinese brake fern (*P. vittata*) was first established as arsenic hyperaccumulator (Ma et al. 2001). This plant can uptake up to 22,630 mg As kg^{-1} in the ground by dry weight from standard experimental condition (Ma et al. 2001). After this finding many Pteridophytic and angiospermic plants have been reported as As(III) hyperaccumulator. As hyperaccumulation mechanism in *P. vittata* takes place through As accumulation and detoxification by cellular compartmentalization into different tissues including minor veins (Bondada and Ma 2003). A number of fern, angiosperm, and aquatic plant species are also known to hyperaccumulate huge amount of arsenic and perform their tolerance (Sridokchan et al. 2005). Some recent established As(III) hyperaccumulator plants are listed in Table 14.1.

14.2.6 Role and Prospects of CRISPR/Cas9 in Arsenic Bioaccumulation

Recently, the next-generation gene editing technology, clustered regularly interspaced short palindromic repeats (CRISPR) Cas (CRISPR associated protein) system is nowadays an emerging tool for phytoremediating plants (Jaganathan et al. 2018). This application is selective and allows targeting multiple genes in the

Table 14.1 List of As(III) hyperaccumulator plants

S. no.	Plant species	References
1	*Pteris cretica*	Zhao et al. (2002)
2	*Pteris umbrosa*	Zhao et al. (2002)
3	*Pteris vittata*	Ma et al. (2001)
4	*Salvinia species*	Rahman and Hasegawa (2011)
5	*Cymbopogon flexuosus*	Jha and Kumar (2017)
6	*Azolla filiculoides*	Rahman and Hasegawa (2011)
7	*Azolla microphylla*	Jha et al. (2015)
8	*Silene vulgaris*	Schmidt et al. (2004)
9	*Azolla pinnata*	Rahman and Hasegawa (2011)
10	*Isatis cappadocica*	Souri et al. (2017)
11	*Eichhornia crassipes*	Jha et al. (2015)
12	*Cyperus difformis*	Tripathi et al. (2012a, b)
13	*Portulaca oleracea*	Tiwari et al. (2008)
14	*Vetiveria zizanioides*	Gunwal et al. (2014)
15	*Chrysopogon zizanioides*	Gautam et al. (2017)

genome with increased efficiency and specificity. Thereby, this system explores possibilities to obtain precisely edited plants with greater arsenic extraction and accumulation. Recent studies have been done on engineering the aquatic plant *Lemna minor* with CRISPR/Cas9 for point mutations in the As(V)/phosphate transporters and As(III)-PCs vacuolar transporters at the same time may be a suitable option for removal of arsenic from water resources (Mateo et al. 2019). In addition to this, several studies suggested involvement of plant glutathione *S*-transferase (GST) gene family in As response due to the requirement of sulfur and GSH in the decontamination of As(III). Using CRISPR-Cas9 in human and mice cells, genome-wide, targeted loss of function pooled screens has been studied which provided information regarding the inactivated genomic loci and strategies to modulate transcriptional activities (Sharma et al. 2014). Apart from other genes, *glutathione S-transferase Mu class* gene (*GSTM1*) from the human genome has been edited using CRISPR-Cas9 system (Sanjana et al. 2014).

In this perspective, it becomes essential to know how CRISPR-Cas9 system can be helpful in the improvement of crops by harnessing the precision of genome editing of GSTs in different plant species. Hence, thorough study is required to unravel multifactorial role in GSTs in plant stress and development (Kumar and Trivedi 2018). Another recent report established that site-specific mutagenesis of OsNramp5 is induced by CRISPR/Cas9 system in indica rice with low Cd accumulation capacity without compromising their yield. This mechanism may be applicable in case of arsenic accumulation to regulate their effect by plants (Tang et al. 2017).

14.2.7 Statistical Factor of Bioaccumulation

The relationship between arsenic species accumulated by plants and those in soil or aqueous medium can be recognized and calculated by bioaccumulation factor (BAF) and bioconcentration factor (BCF).

$$\mathrm{BAF} = \frac{\text{As in plant biomass } \left(\frac{\mathrm{mg}}{\mathrm{kg}}\right)}{\text{Total As in soil or aqueous medium } \left(\frac{\mathrm{mg}}{\mathrm{kg}}\right)} \tag{14.1}$$

$$\mathrm{BCF} = \frac{\text{As in plant biomass } \left(\frac{\mathrm{mg}}{\mathrm{kg}}\right)}{\text{Soluble (Extractable) As in soil}} \tag{14.2}$$

The rate of translocation of As from root to upper aerial parts (shoot and leaf) is examined by translocation factor (TF) which is given below

$$\mathrm{TF} = \frac{\text{As in shoots}}{\text{As in roots}} \tag{14.3}$$

In arsenic contaminated area, for processing of plant sample during phytoremediation, the element enrichment factor (EF) was calculated as follows:

$$\mathrm{EF} = C_{\text{polluted}} / C_{\text{control}} \tag{14.4}$$

where C_{polluted} are the arsenic concentration (mg/kg) in plant biomass (leaves, shoots, and roots) collected from As contaminated sites. C_{control} are the As concentration (mg/kg) in plant biomass collected from control site (uncontaminated area).

Pollution indices (PI) of As and other metallic contaminant are also an important factor in bioaccumulation techniques which also reveal the interaction between metals in soil and plants. The PI is the ratio of As concentration in an abiotic or biotic medium to that of the regulatory standard of international bodies such as World Health Organization (WHO), United States Environmental Protection Agency (USEDA), Federal Environmental Protection Agency (FEPA) of Nigeria, etc. (Jamali et al. 2007). PI indicates the contamination of soil or plant. If it is less than unity, it shows that soil and plants are not contaminated. If PI is greater than unity, it shows pollution. If PI is equal to one, it indicates a critical state making the involved plant helpful in environment monitoring (Chukwuma 1994). Mathematically PI is explained as

$$\mathrm{PI} = C_{\text{soil or plants}} / C_{\text{USEPA-Standard}} \tag{14.5}$$

Let PI be the individual pollution index of study material. $C_{\text{soil or plants}}$ be the concentration of the metal or metalloid in soil or plants. $C_{\text{USEPA-Standard}}$ be the value of the regulatory limit of heavy metals by USEPA.

14.3 Biosorption

Waste plant materials or dead biomass are such type of substances that can be able to remove/bind metallic ions or desired substances from aqueous solution. This process takes place without supplement of any external energy and takes place through intraparticle interaction in which chemical and physical mechanisms of molecules and compounds are involved (Michalak et al. 2013). Naturally abundant plant waste biomass has been reported as biosorbent of As(III) (Volesky 1990). Several researches have been carried out to develop effective, relatively cheap, and easy to use biosorbent that has capacity to remove significant amount of arsenic from aqueous medium. The application of low-cost biosorbent for arsenic biosorption has gained significance (Maind et al. 2012, 2013). As any application of biosorption does not require or involve any type of metabolism.

The adsorbate per unit mass of adsorbent has been calculated by the equation given below.

$$q_t = (C_0 - C_t)\, V/W \tag{14.6}$$

where

q_t (mg/g) is the amount of As (III) adsorbed after time t in minutes. C_0 represents initial concentration and C_t final concentration. V is the volume of As(III) in solution (ml) and W is the weight of biosorbent (g).

The removal percentage (%) of As(III) ions from aqueous solution after biosorption was calculated by applying the following equation:

$$\text{Removal}\ (\%) = (C_0 - C_t)/C_t \times 100 \tag{14.7}$$

where

C_0 and C_t were the initial and final concentration of As(III) after the biosorption process.

A variety of plant biomass based biosorbent for As(III) ions were reported for removal, e.g. mango leaf powder, rice husk, *Psidium guajava* leaf (Roy et al. 2017), *Azadirachta indica* bark powder (Ahalya et al. 2005), leaves of *Acacia auriculiformis* (Al-Mamuna et al. 2013), leaves of *Bambusa vulgaris* (Srivastava and Dwivedi 2016) have been reported. These are some recent researches that reported different plant biomass as remover of arsenic contamination from aqueous medium. Many other plant species are also under continuous investigation for remediation in different parts of the world.

14.3.1 Biosorption Mechanism

The biosorption of As(III) includes $As(OH)_3$, $As(OH)_4^-$, $AsO_2OH_2^-$, and AsO_3^{3-} using plant material that complexes with these ions using their functional group presented on biomass surface. This mechanism takes into account a solid phase

(biosorbent) and dissolved adsorbate in water (arsenic ion) (Sahmoune 2016). Plant biomass involves the binding of arsenic ions by electrostatic interaction on Vander walls forces, precipitation, ion exchange, complexation, and chemical adsorption including chelation, reduction, and ion exchange or proton binding (Kanamarlapudi et al. 2018).

The key factor in removing As(III) by plant biosorbents is different complex organic compounds that contain amide, amine, thioether, imidazole, carboxyl, sulfonate, sulfhydral, phenolic imine, phosphodiester, and phosphate groups that can attract and scavenge metal ions (Park et al. 2010; Tsezos et al. 2006). Besides this, the stereochemical, chemical, and coordination characteristics such as molecular weight, oxidation state, and ionic radius of targeted arsenic species are also important. Other factors such as initial concentration of arsenic ions in solution, effect of contact time of biosorbent and sorbate, effect of pH, temperature, and other competing metal ions present in solution combinedly influence the rate of biosorption (Park et al. 2010; Tsezos et al. 2006).

14.3.1.1 Chelation

During interaction of arsenic ions present in solution with plant biosorbent, chelating agents present on biosorbent surface bind to the arsenic ions to form a complex known as chelates. Polydentate ligands have different donor atoms to bind and as a result stability of the complex is increased. Chelates formed from polydentate ligands are more stable than other complexes (Witek-Krowiak and Reddy 2013).

14.3.1.2 Coordination

In biosorption phenomenon the arsenic and other heavy metals in the complex are bound to its neighbors with covalent bond by accepting long pair of electrons from the donor atom. Here nonmetal acts as donor atom of a ligand and the central atom is known as acceptor. A co-ordinate bond is thus formed between central metal and ligand. Some examples of coordinating groups are, e.g. $–NH_2$, =O, –N=, –NH, –S–, –OH, =NOH, and –O–R (Kanamarlapudi et al. 2018).

14.3.1.3 Ion Exchange

Removal of arsenic and heavy metals by minerals takes place both by adsorption and ion exchange. Ion exchange process also takes place partly in biosorption where adsorbate ion exchanges with the ions present on the surface of biosorbent. The main exchangers in biosorption are carboxyl group, amino and imidazole groups present on the surface of biosorbent. Phosphate hydroxyl groups have also been identified as exchangers (Ding et al. 2012; Chojnacka et al. 2005; Liu et al. 2012).

14.3.1.4 Reduction

Reduction is the important property of biosorption in which sorbed metal ions interact with surface functional group such as carboxyl, get reduced, and leads to the growth of crystals. The metallic ions get reduced once it is attached to the biosorbent at discrete places (Park et al. 2010, 2005, b). The mechanism of biosorption involves the functional groups on the surface of adsorbents and ion

exchange properties (Michalak and Chojnacka 2010). Nature of the bonds present in the functional group present in the adsorbent is determined by Fourier transform infrared spectrometry (FTIR). FTIR peaks explain the presence of carboxyl, amino, amide, hydroxyl, ether, and ester groups (Pistorius et al. 2009). Scanning electron microscopy (SEM) explains the morphological changes before and after adsorption. This has emerged as an important technique to determine the extent of biosorption. Energy dispersive X-ray (EDX) provides the information of extent of arsenic adsorption which can clearly be visualized in the peaks. X-ray photoelectric spectroscopy (XPS) is also a modern technique which helps in quantitative state and empirical formula of elements present and oxidative states of adsorbate are also confirmed by XPS (Michalak and Chojnacka 2010).

14.3.1.5 Complexation

Complexation is a phenomenon of biosorption in which complex is formed by the association of two or more ions and compound. Mononuclear complexes are formed when monodentate ligands co-ordinate the central metal ion. Polydentate complexes are formed by the donation of electrons from multidentate ligands to central atom. Ligands may be negative or neutral having lone pair of electrons so that electron pair might be donated to the central metal ions. The complexes with monodentate ligands are preferable to multidentate ligands due to stability and stability constants. Thus it has become crystal clear that metal ions form bonds with ligands by co-ordinate bond and this complexion facilitates biosorption (Wu et al. 2012; Hu et al. 2012).

14.3.2 Biosorption Isotherm

Adsorption isotherm models describe an empirical relation between solute concentrations with adsorbent surface. The applicability of different isotherms is analyzed by linear regression coefficient (R^2) by using their linear plots. Most widely applicable isotherm in arsenic biosorption was linear form of Langmuir and Freundlich isotherm (Ayawei et al. 2017). Langmuir isotherm depends on the basic assumption that biosorption materializes at specific homogenous site with the biosorbent. Freundlich model supports the heterogeneous surface energies and gives the experimental diffusion of active site (Gaur et al. 2018). Some of the most studied isotherm in arsenic biosorption are Elovich isotherm, Temkin isotherm, Halsey isotherm, Harkin–Jura isotherm and Dubinin–Radushkevich isotherm (Ayawei et al. 2017).

The Elovich isotherm system has also been used for aqueous media to evaluate adsorption mechanism. The basic mechanisms of linear Elovich model theory describe application of the absolute rate theory to adsorption on an energetically heterogeneous surface along with rectangular scattering of activation energies for biosorption. It describes the adsorption isotherm which implies that adsorption process is at quasi-equilibrium, takes place in a stepwise fashion, and the activation energy increases linearly with surface coverage (Wu et al. 2009).

As far as Temkin isotherm is concerned, indirect adsorbate interaction has been considered as the basic assumption. The heat of adsorption (ΔH_{ads}) of the molecules in the layer decreases with increase in surface coverage area (Ringot et al. 2007). Halsey isotherm has also been used to know multilayer adsorption on the surface (Ayawei et al. 2015). Harkin–Jura isotherm also considers multilayer adsorption with heterogenous pore distribution (Foo and Hameed 2010).

Dublin–Radushkevich isotherm model (Travis and Etnier 1981) is expressed by an empirical relation which is applicable to adsorption mechanism with Gaussian energy distribution onto heterogenous surface (Celebi et al. 2007). This model is applicable to intermediate range of adsorbate concentrations because it exhibits unrealistic asymptotic behavior and does not predict Henry's low at low pressure (Theivarasu and Mylsamy 2011). The semiempirical equation of this model explains pore filling mechanism. This adsorption is multilayer applicable to physisorption and this fundamental equation explaining the adsorption of gases on micropores of sorbent (Israel and Eduok 2012). It makes difference between physisorption and chemical adsorption (Vijayaraghavan et al. 2006). A distinguishing feature of the Dublin-Radushkevich isotherm is the fact that it is temperature dependent. In this, log of amount adsorbed at different temperatures is plotted against square of potential energy. A fit for suitable isotherm is thus determined by analysis of all useful models (Gunay et al. 2007).

The expression of linear equation with their linear plot of all above mentioned isotherm models has been classified in Table 14.2.

14.3.3 Kinetic Model of Biosorption

Kinetic analysis is very essential in arsenic and other metallic biosorption batch studies. The rate of arsenic biosorption by biosorbent was analyzed using different kinetic models (Nayak and Pal 2017). Kinetic study of biosorption has gained importance in view of optimization of contact time (Kongarapu et al. 2018).

In most arsenic biosorption studies pseudo-first order (Barrett et al. 1951) and pseudo-second order kinetics model were applied (Ho and McKay 2000). Some other kinetic models that are important into understand the mechanism of biosorption are intraparticle diffusion (Weber Jr. and Morris 1963), Elovich (Wu et al. 2009), Bangham model (Aharoni and Ungarish 1977), and Modified-Freundlich model (Kuo and Lotse 1973) whose linear equation are mentioned below, respectively.

$$\ln\,(q_e - q_t) = \ln(q_e) - K_1 t \tag{14.8}$$

$$t/qt = 1/K_2 q_2 + t/q_e \tag{14.9}$$

$$q_t = K_{int} t^{0.5} + C \tag{14.10}$$

Table 14.2 Linear equation of different isotherm models with their linear plot's equation

S. no.	Isotherm model	Linear equation	Linear plot	References
1	Freundlich isotherm	$\log\ q_t = \log\ K_F + \frac{1}{n} \log\ C_t$	Log q_t versus log C_t	Freundlich (1906)
2	Langmuir isotherm	$\frac{1}{q_t} = \frac{1}{K_L q_m}\left(\frac{1}{C_t}\right) + \frac{1}{q_m}$	$\frac{1}{q_t}$ versus $\frac{1}{C_t}$	Langmuir (1961)
3	Elovich isotherm	$\ln\ \left(\frac{q_t}{C_t}\right) = \ln\ K_e q_m - \frac{q_t}{q_m}$	Ln $\left(\frac{q_t}{C_t}\right)$ versus q_t	Elovich (1959)
4	Temkin isotherm	$q_e = \frac{Rt}{b} \ln\ Kt + \frac{Rt}{b} \ln\ C_e$	q_e versus C_e	Shahbeig et al. (2013)
5	Halsey isotherm	$q_e = (1/n_H)\ \ln\ K_H - (1/n_H)\ \ln\ C_{qe}$	Ln q_e versus ln C_e	Fowler and Guggenheim (1939)
6	Harkin–Jura isotherm	$1/q_e{}^2 = (B/A) - (1/A)\ \log\ C_e$	$1/q_e{}^2$ versus log C_e	Foo and Hameed (2010)
7	Dubinin–Radushkevich isotherm	$\ln\ q_e = \ln\ q_m - \beta E^2$	q_e versus q_m	Travis and Etnier (1981)

$$qt = 1/\beta\ \ln(\alpha\beta) + 1/\beta\ \ln(t) \tag{14.11}$$

$$\ln\ [\ln\{C_0/(C_0\text{-}q_{tm})\}] = \ln\ [K_{0m}/V] + \alpha\ \ln\ (t) \tag{14.12}$$

$$\ln\ (q_t) = \ln\ (K_{MF}C_0) + 1/M_1 \ln(t) \tag{14.13}$$

In Eq. (14.8) q_e and q_t (mg/g) are the amount of ions adsorbed by biosorbent at equilibrium and time t (min.), respectively. K_1 (1/min) is the pseudo-first order rate constant; In Eq. (14.9) K_2 [g/(mg min)] is pseudo-second order rate constant; in Eq. (14.10), K_{int} [mg(g $\text{min}^{0.5}$)] is the rate constant of intraparticle diffusion, C is the diffusion constant; in Eq. (14.11), α [mg/(g min)] and β (g/mg) are the Elovich constant related to initial rate of adsorption and extent of surface coverage for chemosorption, respectively; in Eq. (14.12), C_0 (mg/L) is the initial metallic ion concentration dissolved in the aqueous solution. V (mL) refers to the volume of medium or solution, m (g/L) is the weight of the adsorbent employed, α_0 (<1) and K_0 [mL/(g/L)] are related to the Bangham constant; and in Eq. (14.13), K_{MF} (L/g min) is apparent adsorption rate constant and M_1 is the Kuo–Lotse constant. These frameworks of all the kinetic models were calculated by linear regression plots by using origin pro software or MS Excel word.

14.3.4 Role of Thermodynamics in Biosorption

It has been reported that the temperature is widely affected by the rate of biosorption. Therefore thermodynamic parameters such as ΔG, ΔH, and ΔS usually evaluated because it influences the adsorption potential and explores the nature of adsorption (Maji et al. 2007). These thermodynamic parameters have been calculated using these equation mentioned below (Aydin et al. 2008; El-Sayed et al. 2011).

$$K_e = (C_0 - C_e)/C_e \tag{14.14}$$

$$\ln K_e = \frac{\Delta S}{R} - \frac{\Delta H}{RT} \tag{14.15}$$

$$\Delta G = -RT \ln K_e \tag{14.16}$$

where K_e is the equilibrium constant, C_0 is the initial ion concentration, C_e is the concentration of ions in solution after equilibrium, ΔS is the entropy change, ΔH is the enthalpy change, and ΔG is the Gibb's free energy. R is the universal gas constant (8.314 JK^{-1} mol^{-1}), T is the temperature (K).

ΔS and ΔH are calculated by slope and intercept of the Van't Hoff plot (ln K_e versus $1/T$). Negative value of Gibbs free energy change (ΔG) and positive value of entropy change (ΔS) show the spontaneity of the reaction, i.e. surface of adsorbent accumulates metallic ions. So the favorable thermodynamic condition for adsorption is the negative value of ΔG and positive value of ΔS (Aydin et al. 2008). If ΔH is positive, biosorption process is endothermic in nature (Rajic et al. 2010).

14.3.5 Biosorption by Hairy Root Biomass

In recent years production of hairy root biomass through tissue culture techniques has been exploited as a potential approach for biosorption through different plant species to adsorb organic and inorganic contaminants including metals and metalloids from environment (Agostini et al. 2013). The hairy root originates from infection of explants with *Agrobacterium rhizogenes* strains that is gram negative soil bacteria during the operation of genetic transformation by tissue culture techniques. T-DNA of *A. rhizogenes* transfers to targeted explants. It comprise the loci in between T_R and T_L region of the Ri (root inducing) plasmid into the plant genome. A number of genes of pRi, e.g. *vir*, chromosomal virulent genes (*ehv*) are instrumental in transformation. T-DNA also belongs to this class of genes. In particular, *rol* genes present in T-DNA promote rhizogenic growth with the massive adventitious roots and abundant root hairs (Singh et al. 2020).

Among several available plants for phytoremediation/bioremediation, hairy roots (HRs) emerged as an important option of detoxification of environmental pollution such as organic and inorganic hazards including arsenic and other heavy metals without interference of soil microbes (Agostini et al. 2013). Hairy root does not require any additional growth hormone and their undifferentiated growth properties

suitable for arsenic removal. Some reports have been published on application of HRs in removal of environmental pollutants. Development of HRs in *B. juncea* and their application in removal of textile dyes have been successfully experimented (Telke et al. 2011). In addition this hairy root of tobacco has potential to decolorize malachite green, a complex organic dye from aqueous medium (Escudero et al. 2017). Arsenic and different heavy metals including radionuclides, e.g. Cs, P and U which occur naturally may be removed by hairy root from aqueous medium (Malik et al. 2017; Escudero et al. 2017). Hairy roots biomass should be considered as effective and optimal model system may potentially lead to detoxification of arsenic and other organic and inorganic pollutants from water resources. It will be a cost effective and an ecofriendly approach that leads to definite trends of results of phytoremediation because a vast data is available related to genes and enzymes (Malik et al. 2017).

14.3.6 Chemically Modified Biosorbent

Nowadays, some chemically modified biosorbents have been developed to enhance the As(III) removal potential of plant biosorbents. Chemical modification procedures enhance complexion. Common chemicals used in pretreatment of plant biomass are as acid, alkaline, acetone, and ethanol (Vijayaraghavan and Yun 2007; Göksungur et al. 2005). The modified biosorbents treated from suitable chemicals have proved to be suitable for effective biosorption. Pretreatment of the biosorbents depends mainly on the cellular structure of the biomass. In some cases acid treatment has been preferred to device best result of removal of arsenic. Modification of the biosorbents increases the binding capacity of the sites available for adsorption. Amides, carboxyl, phosphate, hydroxyl, and sulfonate groups on the surface of biosorbents have already been established as binder of adsorbates. The binding capacity of these functional groups is enhanced by modification or treatment with suitable chemicals, e.g. ferric hydroxide and several nanoparticles. In addition of this chloroacetic acid is used to initiate carboxyl in the place of hydroxyl group (Jeon and Höll 2003). The carboxylated biomass was then chemically treated with ethylenediamide and carbodiimide to give an aminated biomass. Such treatment of amine group enhanced the removal of Hg (Li et al. 2007).

Functional groups onto the biomass surface can also be introduced by grafting of long polymer chains onto the biomass. There may be direct grafting or polymerization for this. Deng and Ting (2005a, b, c, 2007) worked extensively with polyethylemide, composed of a large number of primary and secondary amine groups, which on cross-linking with biomass showed good biosorption abilities for arsenic and other heavy metals. Deng and Ting (2005a, b, c) showed that copolymerization of acrylic acid on biomass surface enhanced the activity of carboxyl groups manifold for uptake of copper and cadmium.

Studies on plant biosorbent prepared from spruce (Picea abies) (Saw dust) after modification with Fe(III) oxyhydroxide exhibit high removal efficiency of arsenic with respect to untreated control (Urík et al. 2009). Natural watermelon rind (WMR)

treated with citric acid shows excellent potential to sorb As(III). This study shows that citric acid modification enhanced the efficiency of functional group such as –OH, –COOH, C=S, S = 0, and S–S which were involved in As(III) sequestration (Shakoor et al. 2018).

Cellular fiber chemically modified by hyperbranched polyethylenimide (HPE1) prepared from microwave (MW) irradiation shows the high adsorption capacity to remove arsenic from aqueous medium with respect to general cellular fiber. This report presents MW irradiation method to treat biosorbent and has great potential in dealing with arsenic species present in wastewater (Deng et al. 2016).

14.4 Conclusion

It has been established that biotechnological interventions enhance the rate of bioaccumulation of As(III) by plants. During exposure of plants to As(III), several enzymatic activities and gene expressions change including the expression of transcription factors, different types of transporters, and miRNAs that possibly confer metallic tolerant properties in plants. Several plants species such as *Azolla*, *Eicchornea,* and *Cymbopogon flexuous* have been found as potential biosorbent of arsenic from aqueous medium as well as soil. Hairy root biomass through tissue culture techniques has also proved to be a success in removal of different metallic contaminant, so it may be applicable to use as an As(III) remover. Though a number of adsorption isotherms are known, Freundlich and Langmuir adsorption isotherms are employed frequently during biosorption studies. Thermodynamic studies such as entropy change, Gibbs free energy change, and enthalpy change control the reaction processes. Biosorption mechanism includes complexation, ion exchange, reduction, and transportation. SEM, EDX, and FTIR take part in deciding the extent of adsorption by researchers. Biosorbent when modified chemically becomes more effective towards removal of As(III). There is good prospect of developing low-cost, eco-friendly, and novel methods of remediation of arsenic from aqueous medium and soil, and the use of plants could be comparatively better option.

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Genes and Biochemical Pathways Involved in Microbial Transformation of Arsenic

15

Hareem Mohsin, Maria Shafique, and Yasir Rehman

Abstract

Arsenic exists as a ubiquitous toxic metalloid in both organic and inorganic forms. Most predominant forms are arsenate [As(V)] and arsenite [As(III)]. Both natural processes and anthropogenic activities play part in arsenic entry in the environment and the water bodies. Environmental arsenic is biologically cycled by many microbial species. These microbial species possess certain genes and corresponding proteins to ensure survival in metal contaminated sites. Microbial resistance to arsenic can accompany with oxidation, reduction, or methylation of arsenic. The relevant genes are often plasmid borne but can also be found in the chromosome of the bacteria. Various operons, gene products, and biochemical pathways are involved in biotransformation of arsenic. Arsenic also serves as electron acceptor for many bacterial species under anaerobic conditions. All these processes take place in coordination within a bacterial cell depending upon the valence state of arsenic and types of genes and proteins present in the bacteria. The current chapter highlights the microbial genes, proteins, and the biochemical pathways involved in microbial transformation of arsenic. These processes not only play important roles in maintaining the environment, but also have the potential for biotechnological interventions.

H. Mohsin
Department of Allied health Sciences, Superior University, Lahore, Pakistan

M. Shafique
Department of Microbiology and Molecular Genetics, University of the Punjab, Lahore, Pakistan

Y. Rehman (✉)
Department of Life Sciences, School of Science, University of Management and Technology, Lahore, Pakistan
e-mail: Yasir.rehman@umt.edu.pk

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15.1 Introduction to Arsenic

15.1.1 Sources/Origin of Arsenic

Arsenic (As) is a metalloid present ubiquitously with a molecular weight of 75 and atomic number of 33. The dominant forms are arsenate and arsenite with valence states of +5 and +3, respectively (Garland 2018). It is found in Earth's crust with a relative abundance of 54 and is a part of almost 245 minerals in association with copper, lead, gold, sulfur, zinc, and other elements. Many areas in the world have high concentration of arsenic owing to the processes of natural mineralization (Cullen 2008). Arsenopyrite (FeAsS) is the most commonly found mineral comprised of iron, arsenic, and sulfur (Corkhill and Vaughan 2009). Literature reports that the average arsenic concentration in earth's crust is approximately 5 ppm (ug/g) (Garelick et al. 2008).

It is known that one-third of arsenic flux in the environment is of natural origin (Chatterjee et al. 2017). Major sources that release arsenic in the environment are volcanic eruptions and hydrothermal vents followed by the volatilization process taking place at low temperatures. Anthropogenic activities such as mining, smelting, and combusting processes also release arsenic in the environment. Moreover, use of arsenic-containing herbicides and pesticides (e.g., monomethyl arsenate (MMA) and dimethyl arsenate (DMA), preservatives for wood, animal feed, paints, dyes, and semi-conductors (Bhattacharjee and Rosen 2007; Shen et al. 2013) also act as source of arsenic contamination in the environment.

Arsenic naturally forms organic and inorganic compounds which are mobile and cannot be eliminated (Chung et al. 2014). The inorganic form is usually found in combination with chlorine, oxygen, and sulfur in igneous and sedimentary rocks while the organic forms of arsenic are widely present in combination with hydrogen and carbon. The inorganic form is prevalent in groundwater. Likewise, the drinking water of many countries such as Bangladesh, India, and Taiwan has high arsenic concentration. This inorganic form also enters the food web via the agricultural practices where contaminated water is used. The crops having arsenic is then used in further food preparation and thus, arsenic travels to the higher trophic levels (Sharma et al. 2016). Organic form of arsenic can be chiefly found in many aquatic animals, meat, poultry, and dairy products. However, arsenic concentration in food products is lower as compared to its concentration in groundwater (Upadhyay et al. 2019; Awasthi et al. 2020).

15.1.2 Arsenic Toxicity

Arsenic is categorized as a carcinogen by Environmental Protection Agency (EPA) and International Agency for Research on Cancer (IARC) (Chen et al. 2011). Strong relatedness of arsenic and prevalent cancers (Smith et al. 2009) has been observed which includes lung and skin cancers. Arsenic is ranked number 1 by The United

States Agency for Toxic Substances and Disease Registry (ASTDR) in the ASTDR Substance Priority List (https://www.atsdr.cdc.gov/SPL/index.html#2019spl).

Humans Arsenic has been known to people for centuries. During war times in the past, it had been used to preserve dead bodies (Konefes and Mc Gee 2001). In the 1930s–40s, arsenic was most commonly used as a pesticide for apple trees (Murphy and Aucott 1998). Long ago people were of the view that depending on the dose, arsenic can either be used for treatment of various illnesses like syphilis (Vrotsos et al. 2014) or it can be a poisonous that may lead to death (Cullen and Reimer 2017).

Arsenic is notorious for being the largest potential threat towards living organisms, microorganisms, and environment as well. Arsenic contamination leads to arsenicosis (Yu et al. 2007; Mohsin et al. 2019). In case of humans, it is responsible for being one of the major risks of cancer and other related diseases in more than 100 million people globally (Jain and Ali 2000). Research based on epidemiology has revealed that populace is mostly affected with arsenic by drinking groundwater especially in places like Taiwan (Chen et al. 2016), Argentina (Steinmaus et al. 2010), Chile (Shen et al. 2013), and China (Mo et al. 2006). As reported in literature, the lethal dose of arsenic trioxide upon ingestion is 70 mg to 300 mg. Ingestion of lethal dose results in death within 12–24 h. This toxicity induced by arsenic includes stress by reactive oxygen species, apoptosis, thiamine deficiency, and reduced activity of acetyl cholinesterase (Mochizuki 2019). Further, arsenic is also reported to cause neurotoxic effects on the brain cells (Yoshinaga-Sakurai et al. 2020).

Plants Plants gain no health benefits from arsenic. It has been reported that the phosphate fertilizers, when used in excess, can lead towards arsenic toxicity by the release of retained arsenic from the soil. These two anions have more compatibility with the soil components and are highly mobilized as compared to other ions, thus resulting in arsenic uptake by plants (Moreno-Jiménez et al. 2012). Uptake of arsenic by plant can lead to its entry into the apoplastic phase of the plant from where transpiration process takes the metal towards the foliar regions of the plant. In lesser concentrations, arsenic is transported to short distances in the plant. However, in high concentrations, arsenic affects the membranes and cause degradation (Zhao et al. 2009; Wang et al. 2011b; Abbas et al. 2018). These uptake mechanisms by plants become a potential reason of entry of arsenic into the human diet and ultimately the food web.

Microorganisms Arsenic equally effects the microorganisms and their metabolic processes. Microorganisms interact with environmental arsenic via a number of mechanisms such as absorption, adsorption, mobilization, precipitation, redox reactions, methylation, and the metal efflux outside the cell (Mohsin et al. 2019). These microbial processes can cause biotransformation of arsenic and thus can affect its fate in the environment.

15.1.3 Biogeochemical Cycling

There is a directional flow of energy in an ecosystem. Starting from the entry of sunlight as the primary energy source, it is released as heat during energy transformation processes between various trophic levels. However, the energy does not escape from the ecosystem, but is recycled and conserved. Major elements in the earth's crust include carbon, hydrogen, oxygen, nitrogen, sulfur, and phosphorus. These elements are recycled during the geological processes like weathering, mineralization, erosion, etc. and when this recycling occurs between living and non-living environment, this is termed as biogeochemical cycling (Johnson and Van Hook 2012).

15.1.4 Environmental Arsenic and Microorganisms

Microbial life forms play a very vital role in biogeochemical cycling of ubiquitous elements and minerals by fundamentally affecting the environment with the processes of electron and elemental transfer in the ecosystem (Tamaki and Frankenberger 1992; Huang 2014).

Microbes play a chief role in the fate of environmental arsenic where they are capable of converting arsenic into two predominant valence forms, i.e. pentavalent arsenate (+5) and trivalent arsenite (+3) (Bhattacharjee and Rosen 2007). The relation of microbial diversity with the prevalence of arsenic in the environment has been deeply studied. Studies regarding geochemistry in relation to microbiology and molecular ecology have played an important role in comprehending the microbial association with geochemistry. Islam et al. (2005) reported that arsenic was released from the environmental samples of West Bengal where arsenic and iron were in combination. Arsenate reduction was carried out by *Clostridium* species while iron (III) reduction was carried out by *Geobacter* species. Arsenic methylation was also studied to be microbially assisted by Jia et al. (2013). Research on geochemistry and microbial activities was done by Demergasso et al. (2007) where the role of microorganisms in arsenic precipitation from arsenic-sulfur minerals was studied. All such studies clearly state that microorganisms play a critical role in the arsenic cycling (Huang 2014).

Oxidation Arsenite oxidation is a detoxification process where microorganisms become capable enough to tolerate arsenite toxicity and convert arsenite to arsenate. This results in lower mobility rate of arsenic as arsenate is more compatible with minerals compared to arsenite (Wang and Zhao 2009; Huang et al. 2011b). Several microorganisms are involved in this process which includes *Alcaligenes faecalis, Hydrogenophaga* sp., *Alcaligenes ferrooxidans, T. aquaticus,* and *T. thermophilus*. This method is also considered as a potential process for bioremediation of arsenic (Ito et al. 2012).

Reduction Reduction of arsenate results in the formation of arsenite which enhances the mobility of environmental arsenic. Many microbial species also exhibit arsenate reduction via the detoxification process (Stolz et al. 2006). Several microbes perform this mechanism which includes *E. coli, Staphylococcus aureus,* and *Staphylococcus xylosus*. The detoxification process usually occurs in aerobic conditions. Corsini et al. (2010) conducted a research that showed *Bacillus* and *Pseudomonas* species to detoxify arsenate into arsenite in the soil under aerobic conditions (Huang et al. 2011b).

Many microorganisms can also carry out respiratory reduction of arsenic under anaerobic conditions where arsenate acts as an electron acceptor in the electron transport chain of many bacteria such as *Rhodopseudomonas* sp., *Rhodobacter* sp. (Mohsin et al. 2019), *Sulfurospirillum barnesii, Bacillus arsenicoselenatis, Bacillus selenitreducens, Sulfurospirillum arsenophilum, Chrysiogenes arsenatis,* and *Desulfomicrobium* sp. It is evident that arsenic present in the environment is bounded or adsorbed with a wide range of minerals in which sulfur and iron-based minerals are predominant. According to the research conducted by Zobrist et al. (2000), the rate of arsenic reduction is also influenced by the extent of binding and adsorption. The microbially assisted reduction rate is fastest in dissolved form of arsenate. It then reduces with the passage of time when bounded or adsorbed on an iron-containing mineral. *Shewanella* sp. strain ANA-3 has been reported by Malasarn et al. (2008) to carry out arsenate reduction by the help of an enzyme arsenate respiratory reductase and release the reduced form, i.e. arsenite, in the environment. Newman et al. (1997) reported the arsenate reduction bounded with sulfate by microorganism *D. auripigmentum*, but this microbe preferred to act on sulfate part of the minerals (Huang 2014).

Methylation Both aerobic and anaerobic microbes are involved in arsenic methylation. The methylation process results in the transformation of solid or aqueous inorganic arsenic compounds into a variety of gaseous arsines which escape and is considered as a detoxification mechanism (Huang 2014). There is production of monomethyl arsonic acid (MMAA), dimethyl arsenic acid (DMAA), and trimethyl arsine oxide (TMAO), while demethylation results in the reconversion of methylated forms into inorganic forms. Microbes further act on the methylated arsenic products by producing methylarsine (MMA), dimethylarsine (DMA), and trimethylarsine (TMA) (Dhuldhaj et al. 2012). The arsines formed are mobile as compared to the solid or aqueous forms of arsenic, thus travelling across long distances in the environment. This increased mobility of methylated arsenic owes to the limited adsorption of arsenic. The production and mobilization of methylated arsenic is highly supported by reducing environment, i.e. lower redox potentials (Frohne et al. 2011). Such reducing conditions, converting As^{+5} to As^{+3}, can enhance the dissolved arsenic levels in the environment (Bennett et al. 2012), thus increasing arsenic microbial methylation. Cullen et al. (1994) reported that *Apiotrichum humicola* and *Scopulariopsis brevicaulis* are able to perform arsenic methylation. The pathways include the conversion of inorganic arsenic to MMAA followed by the formation of DMAA and then TMAO. MMAA was subjected to internal

metabolic process of microbes having lower permeability while DMAA easily crossed the microbial membranes easily. This proved the presence of DMMA in higher concentrations in natural environments as compared to MMAA which was found to be in lower concentrations (Fauser et al. 2013; Huang 2014). The production of MMAA and DMAA is found in a number of environmental samples and reported to be intermediate products during the Challenger's Pathway of arsenic methylation (Huang et al. 2011a). Literature also reports the As^{+5} methylation intracellularly by *Trichoderma asperellum, Penicillium janthinellum*, and *Fusarium oxysporum*. Metabolic processes in these microbes lead to the production of As^{+3}, MMAA, and DMAA (Su et al. 2012). The methyl arsines MMA, DMA, and TMA are produced via the microbial action on aqueous methyl arsenic. Microorganisms involved include *Methanobacterium bryantii, Methanobacterium formicium, Clostridium collagenovorans, Desulfovibrio gigas,* and *Desulfovibrio vulgaris* (Michalke et al. 2000). Most reported is the arsenite S-adenosyl-methionine methyltransferase enzyme which is involved in the methylation process converting the inorganic arsenic into various arsines. Several other enzymes have been reported which are involved in microbial methylation like arsenate reductase, MMAA reductase, arsenite methyltransferase, and monomethyl arsonous acid methyltransferase (Wu 2005).

Demethylation Demethylation of arsenic refers to the methylated arsenic degradation. The arsines that are produced are subjected to photooxidative degradation (Mestrot et al. 2013). Yoshinaga et al. (2011) conducted a study which revealed that *Burkholderia* sp. and *Streptomyces* sp. are involved in the monomethylarsonic acid reduction and monomethylarsonous acid demethylation. The study also concluded that *Mycobacterium neoaurum* has the ability to perform demethylation on MMAA and monomethylarsonous acid (Lehr et al. 2003). However, demethylation of arsenic via the microbial involvement still needs to be deeply studied (Huang 2014).

15.2 Microbial Transformation of Arsenic

In the continuous exposure of toxic metals and metalloids in the microenvironment, microbes acquire resistance genes which provide a selective advantage for survival and propagation. A wide range of microbes have developed resistance against arsenic that can involve reduction, respiratory reduction, oxidation, and methylation. Following is the detailed description of the genes and gene products which confer arsenic resistance via different mechanisms.

15.2.1 Genes Involved in Resistance

The genetic makeup of microorganisms is ever evolving, and with the increasing arsenic concentration in the environment, the resistance genes have developed

against it. The resistance system against arsenic toxicity includes the *ars* operons which are extensively present in bacterial and archaeal species. It has been reported in literature that *ars* operons are present in prokaryotes more commonly as compared to the genes responsible for tryptophan synthesis (Silver and Phung 2005a). This evolution and development of arsenic resistance genes reflects the presence of arsenic in the environment ubiquitously (Yang and Rosen 2016; Ben Fekih et al. 2018).

Arsenic resistance genes were identified 50 years back during the research of resistance genes against antibiotics in clinical isolates (Novick and Roth 1968). A plasmid pI258 isolated from *Staphylococcus aureus* was found to confer resistance against antibiotics, As (V), As (III), and other heavy metals and metalloids. Another plasmid named R773 was also identified from *E. coli* that had arsenic resistance genes (Hedges and Baumberg 1973). According to literature, a collaborated research project was conducted which was based on exploring and isolating the plasmids exhibiting arsenic resistance in gram-positive and gram-negative bacteria. Energy-dependent efflux system was discovered, first in case of antibiotics (McMurry et al. 1980) and shortly afterwards, for arsenite efflux from the cell (Mobley and Rosen 1982; Silver and Keach 1982). *arsRDABC* operon was identified from R773 plasmid isolated from *E. coli.* The plasmids, i.e. pI258 and pSX267 from *Staphylococcus aureus* revealed the presence of *arsRBC* operons that code for the arsenic resistance genes having homology with R773 genes (Ben Fekih et al. 2018). Other microorganisms which comprise of arsenic-resistant genes residing plasmids include *Yersinia* sp., *Acidiphilum multivorans* AIU 301, *Serratia marcescens,* archaea *Halobacterium* sp. NRC-1, and *Sinorhizobium* sp. M14 (Ben Fekih et al. 2018).

arsR gene codes for ArsR protein that belongs to SmtB/ArsR family. ArsR protein binds to the promoter region of *ars* operon and acts as a transcriptional repressor protein, thus acting as a regulator (Zhu et al. 2014). The interaction of this protein with arsenite allows the transcription of this operon.

The ArsA is a protein which works in interaction with ArsB. This combination works as a system for arsenite efflux which gets the energy via ATP hydrolysis (Yang et al. 2015). Along with the interaction of ArsB, ArsA ATPase leads to the formation of arsenite transporters associated with membrane embedded proteins (Castillo and Saier 2010).

ArsB alone is an important protein in the membrane which removes arsenite from the cytoplasm. This helps in reduction in arsenite accumulation.

ArsC is another protein that was identified from pI258 and R773. It works as arsenate reductase enzyme resulting in the conversion of arsenate into arsenite before the removal of arsenite oxyanion from the cell cytoplasm (Zhu et al. 2014).

Another protein is ArsD that acts as a weak repressor of *ars* operon which is inducer independent. Its major function is the binding of arsenite followed by its transfer to ArsA ATPase before it is expelled from the ArsB protein pump (Yang and Rosen 2016).

Variants of *ars* genes have also been identified in several microbial species which include *Acidithiobacillus ferrooxidans*, *Pseudomonas fluorescens* MSP3, *Synechocystis* sp. PCC 6803, *Shewanella oneidensis* ANA-3 a gamma

proteobacterium, and *Campylobacter jejuni* (Ben Fekih et al. 2018). Archaeal specie *Ferroplasma acidarmanus* has the ability to resist arsenic because of the chromosomal *ars* operons (Lin et al. 2006).

Silver and Phung (2005b) were the first ones to report arsenic gene islands in microbial specie *Alcaligenes faecalis* playing a role in metabolism and resistance against arsenic. pSinA plasmid isolated from *Sinorhizobium* also contained arsenic-resistant gene islands that might be acquired by horizontal gene transfer mechanisms.

arsRB operon evolved conferring arsenic resistance encoding the regulator protein ArsR and the arsenite efflux pump protein ArsB. This *arsRB* operon evolved to form *arsRBC* encoding for ArsC enzymes. ArsA ATPase and ArsD developed with the evolution of a complex called as *arsRDABC* after the operon *arsRBC,* thus providing resistance to increased levels of environmental arsenic and having a much tighter regulatory effect. *arsD* and *arsA* are the genes placed adjacent to each other in *ars* operon which reflects that both genes act in combination. *arsBC* comprise of genes *arsB* and *ars C* leading to the formation of protein product ArsB and ArsC, respectively. Plasmids bearing these genes in combinations lack *arsA* gene and are usually found in gram-negative bacteria. However, literature reports that it is not necessary for ArsB and ArsC to work in combination as reported in *P. aeruginosa* and *Neisseria gonorrhoeae*, while the proteins ArsR and ArsC have been identified coordinating with each other in *arsRBC* operons in species like *L. ferriphilum* and *Sinorhizobium*. Such functioning of ArsC provides the evidence of its working as fusion proteins because of having a relatively smaller molecular weight of 130–140 amino acid residues (Wu et al. 2017). This ultimately provides advantage to the bacterial cell in terms of sensing and detoxifying arsenite (Ben Fekih et al. 2018). The *ars genes* are also reported to be present in prokaryotic genetic makeup in redundant manner, via gene duplication or horizontal gene transfer mechanism, more frequently owing to the increased arsenic levels in the environment (Li et al. 2014). Some species like *Bacillus* CDB3 strain possess simple repeating *ars* genes while *P. putida* possess two *ars* operons together. The function is not symbiotic against arsenic resistance but depends on the bacterial growth and external environment temperature. Moreover, industrially important microbial strains also possess multiple genes which include *Corynebacterium glutamicum* ATCC 13032, anaerobic *Rhodopseudomonas palustris* CGA009, and *Ochrobactrum tritici* SCII24. *R. palustris* resist different levels of arsenite according to the concentrations in harsh environments owing to the presence of redundant *ars* genes (Zhao et al. 2009).

Other resistance genes have also been reported that encode for the proteins conferring arsenic resistance.

acr3 gene has been identified in many strains like *Microbacterium* sp., *R. palustris, C. jejuni,* etc. that confers arsenic resistance to the microbe. The protein product Acr3 (also called as ArsY) transporter is also reported to work in coordination with AcrC as a fusion protein in *M. tuberculosis*. This fused transporter complex functions as an efflux pump against arsenite limiting the arsenic accumulation in the bacterial cell (Achour-Rokbani et al. 2010). Achour-Rokbani et al. (2010) have reported the prevalence of *arsB* genes in gamma proteobacteria as well. Both

genes can be present in symbiotic relation within an organism but genes coexisting in a same operon have not yet been discovered (Yang et al. 2015; Ben Fekih et al. 2018). Yang et al. (2015) have reported the presence of ArsB proteins only in prokaryotes while the protein Acr3 is reported in bacteria, archaea, fungi, and plants as well (Ben Fekih et al. 2018). *ars* operons also comprise of genes that encode for aquaglyceroporin product, i.e. AqpS performing the function of an arsenite efflux pump that is used as a substitute for transporter ArsB. AqpS also has the ability to sensitize the arsenite in the external environment after which ArsC protein will reduce arsenate in internal environment. Two genes *gapdh* and *arsJ* are located in *ars* operon conferring resistance against arsenic encoding for enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and MFS transporter ArsJ, respectively. The enzyme GADPH catalyzes the reaction for the formation of arsenate phosphoglycerate followed by its expulsion via the ArsJ transporter after the disassociation of arsenate from the complex resulting in detoxification of arsenic. *arsN* gene has also been identified via metagenomic studies by Chauhan et al. (2009) which is associated with *ars* operon. In some cases, it functions in fusion with *arsC* and *arsD*, thus playing a role in arsenic resistance. However, the functioning of *arsN* genes has not been completely studied (Ben Fekih et al. 2018).

15.2.2 Genes Involved in Dissimilatory Reduction (Anaerobic)

Bacterial species perform reduction of heavy metals and metalloids to prevent the metal accumulation in the cells. In the same way, a wide range of bacterial species have developed mechanisms to succor arsenate reduction into arsenite in anaerobic environment. Species like *Chrysiogenes arsenatis* (Krafft and Macy 1998), *Shewanella* sp. strain ANA-3 (Malasarn et al. 2008), and *B. selenitireducens* (Afkar et al. 2003) have the ability to reduce arsenate into arsenite by using arsenate as a terminal electron acceptor. The genes in bacterial genomes are responsible for encoding of respiratory arsenate reductase (Arr) which is composed of two further subunits named as ArrA and ArrB (Duval et al. 2008). *Shewanella* sp. strain ANA-3 has been studied where the expression of *arrA* gene was observed only under anaerobic conditions when other electron acceptors like oxygen, nitrate, and fumarate were not used. The gene *arrA* has been identified from *Geobacter* sp. from a variety of sites which include Bengal delta (Héry et al. 2010), Mekong Delta (Ying et al. 2015), Cambodia (Lear et al. 2007), and China paddy soils (Qiao et al. 2018). Mirza et al. (2017) have recovered almost 62,056 *arrA* genes out of which 16% sequences of 16S gene were identified as *Geobacter* sp. It has also been reported that *Geobacter* sp. OR-1 also possess arsenic islands (Ehara et al. 2015) which is having *arrB* genes as well. These genes are flanked by *ars* operons and they play a pivotal role in utilization of arsenic ferrihydrite as an electron acceptor. These genes thus play a role in arsenic respiration by which electron transport chain in bacteria is driven by using arsenic as an electron acceptor. After this, the reduced arsenite is transferred outside the cells via the transporter proteins and chaperons which are encoded by *ars* operons (Tsuchiya et al. 2019) as described in the previous section.

15.2.3 Genes Involved in Arsenic Oxidation

Microorganisms are also involved in arsenite oxidation in natural environments contaminated with arsenic. Several microbial species carry out arsenite oxidation for arsenic detoxification converting more toxic arsenite into less toxic arsenate. However, in this detoxification process, microorganisms are also capable of respiring arsenite as a source of electron. *aioA* refers to arsenite oxidation in aerobic environment and is the recently accepted nomenclature (McDermott et al. 2020) for the previously identified arsenite oxidation genes, i.e. *aoxB, asoA, and aroA*. A new gene family has also been identified as arxA that supports growth mechanism of chemoautotrophy using arsenite (Escudero et al. 2013). Examples include *Herminiimonas arsenicoxydans, Thiomonas* sp., and *Rhizobium* sp. strain NT26 (Heinrich-Salmeron et al. 2011). This oxidation of arsenite is catalyzed by arsenite oxidase and encodes a small and large subunit. Small subunit comprises of genes *aoxA/aroB/asoB* and the large subunit comprises of genes *aoxB/aroA/asoA* (Cai et al. 2009).

Another system has also been reported for arsenite oxidation. The system is of *arx* genes that work in the anaerobic conditions (Zargar et al. 2010). The anoxic oxidation process of arsenite is coupled either with the nitrate respiration process or the anoxygenic photosynthesis electron transport chain (Zargar et al. 2012). *Alkalilimnicola ehrlichii* MLHE-1 from the family of gammaproteobacterial has been identified as the first organism comprising of this oxidation system by Zargar et al. (2010). The homologs for arx system were further identified via comparative genomics techniques in other microbial species which include *Ectothiorhodospira* sp. PHS-1 and *Halorhodospira halophila* SL1 (Andres and Bertin 2016). Watanabe et al. (2014) also identified *arxA* present in this oxidation system from the bacterial species isolated from arsenic-contaminated environments (Andres and Bertin 2016).

15.2.4 Genes Involved in Arsenic Methylation

As microorganisms are involved in arsenic metabolism, methylation and demethylation are also important mechanisms by which toxicity of arsenic is reduced. Two genes *arsM* and *arsI* are involved in this process where they encode for arsenite methyltransferase enzyme and Cas lyase enzyme, respectively. The erstwhile is involved in the methylation process starting from arsenite (Rahman and Hassler 2014) while the latter enzymes regulate the demethylation process of methylarsonous acid (Yoshinaga and Rosen 2014). These are the processes that confer resistance against arsenic and make microbes capable enough to tolerate this toxic metal. However, it is also considered simply as the detoxification process (Andres and Bertin 2016). Literature reports that *arsM* genes are prevalent in bacteria and archaea while *arsI* genes and their orthologs are restricted only to bacterial species (Yoshinaga and Rosen 2014).

15.3 Biochemistry of Microbial Arsenic Transformation

Metals are required by the microbes in small quantities thus function as micronutrients. Many other metals are nonessential for microbes and have no biological role thus posing toxic effect. Biotransformation of these metals is carried out either for redox reactions resulting in the stability of molecules or turning inorganic form to organic or vice versa. When microbes interact with metals, it leads to cell membrane damage, alteration in enzyme function, genetic material impairment particularly when exposed to high levels of nonessential as well as essential metals (Dey et al. 2016). Many arsenic compounds are readily solubilized in water followed by microbial uptake, thus exhibiting increased levels of bioavailability, depending on the physical and chemical environmental conditions. The ubiquity of arsenic (Williams and Silver 1984) results in the development of multiple strategies for microorganisms to grow in metal contaminated environment. Biotransformation readily occurs due to various metabolic functions such as detoxification, oxidation, anaerobic respiration, and methylation (Satyapal et al. 2016). The speciation and mobility of arsenic can be influenced by microbes via redox reactions along with arsenate resistance and respiration. Two different arsenate reductases are encoded by *arr* and *ars* genes which are linked to cellular respiration and detoxification mechanisms, respectively. On the other hand, arsenite oxidase is encoded by *aox* and *aso* genes responsible for oxidation to gain energy (Gupta 2015). Various mechanisms help microbes to interact with arsenic like chelation, compartmentation, exclusion, and immobilization (Zhu et al. 2017). These microbes either increase the arsenic bioavailability and toxicity or immobilize arsenic for toxicity reduction. Biotransformation plays significant part in biogeochemical cycles which is utilized for bioremediation of contaminated environmental sites (Lloyd and Lovley 2001). Microorganisms evolved a number of strategies to combat arsenic toxicity (Plewniak et al. 2018).

(a) Active exclusion of arsenic
(b) Intercellular chelation by several metal binding peptides such as glutathione (GSH), metallothioneins (MTs), or phytochealtins (PCs)
(c) Transformation of arsenic to other less harmful organic forms
(d) Extracellular sequestration

15.3.1 Biochemical Pathways Involved in Resistance

Microorganisms mitigate different forms of arsenic through oxidation, reduction, methylation and intracellular bioaccumulation. Two distinct mechanisms are found in *Escherichia coli* for arsenic resistance; chromosomal and plasmid encoded systems (Tamaki and Frankenberger 1992). Resistances conferred by plasmids is the result of accelerated extrusion of arsenate from the cell. It is wide spread among various bacterial species resulting in stimulation of an anion for translocation of ATPase with improved arsenate and arsenite selectivity. Arsenate and arsenite but

not phosphate exported out of the cell by highly specific membrane associated pumps. Three genes *ArsA, ArsB,* and *ArsC* mainly responsible for the arsenate export were revealed via molecular analysis of plasmid encoding resistance. *ArsA* and *ArsB* export arsenite while *ArsC* conferred arsenate resistance. The oxyanion pump comprises of ArsA and ArsB protein. ArsA protein is mostly cytosolic but a part is embedded in cell membrane which forms a complex with ArsB. ArsB is present in the inner membrane of *E. coli*. It is reported to be the part of pump responsible for the anions transport from the cell. ArsC polypeptide transforms ArsB-ArsB complex, thus allowing the arsenate pumping. ArsC is not necessary for the efflux of arsenite. It is highly selective in inhibiting the phosphate transport out of the bacterial cell (Tamaki and Frankenberger 1992).

Arsenic has molecular similarity with various membrane transporter proteins thus allowing the uptake of arsenic. Arsenate has structural similarities with phosphates and is taken up by the cell via membrane phosphate transporter proteins (Pandey et al. 2015). The well-defined bacterial resistance mechanism involves the reduction process from arsenate to arsenite. This process is either exuded from the cells or seized in intracellular compartments. Chromosomally encoded resistance is conferred by triggering of pumps for phosphate uptake because of structural similarities between arsenate and phosphate. Arsenate is transported via the phosphate pumps. As(V) gains entry via the PhoE protein (outer membrane porin), followed by transportation into the cytoplasm through inorganic Pi transport (Pit) and phosphate-specific transport (Pst) (Willsky and Malamy 1980). Pit system is expressed constitutively and does not differentiate between phosphate and arsenate (Jackson et al. 2008). Under phosphate rich conditions, Pit system achieves the cell's requirement regarding phosphate and results in arsenate accumulation. However, in the case of phosphate deficiency, particular Pst system is activated resulting in the higher level of arsenate resistance due to reduced uptake of arsenate. *S. cerevisiae* codes phosphate transporter which is comparable to the low-affinity transporter of the prokaryotes and the expression is controlled through a feedback mechanism. In case of increased phosphate concentrations, Pit transporters, belonging to the category of permease channel transporters, are expressed exhibiting low affinity. Pst exhibits 100 times more efficiency in differentiating between phosphate and arsenate as compared to Pit (Saona et al. 2019). Inactivating Pit system by pit mutation is a method that adopts arsenate stress. It leads to moderate tolerance of arsenate owing to discrimination between phosphate and arsenate by Pst system (Hudek et al. 2016).

Arsenic exclusion is done via two mechanisms by microbes. One is the arsenite efflux through an arsenite carrier protein, where energy is derived from the membrane potential. Second is the arsenic exclusion by an arsenite-translocating ATPase. The three-gene operon *arsRBC* has the capability to expel arsenite by *ArsB* alone whereas the five-gene operon, *arsRDABC,* expels arsenite by ArsAB pump. An ArsAB complex forms when *ArsA* is co-expressed with *ArsB*. *E. coli* is capable of producing ArsA protein from plasmid R773. *arsRDABC* operon confers increased resistance to arsenite as ArsAB ATPase can remove arsenite more effectively in complex form than alone (Slyemi and Bonnefoy 2012).

Arsenite occurs as $As(OH)_3$ in aqueous solution which is structurally similar to the glycerol thus is taken via the membrane proteins like glyceroporin membrane proteins, transporters like hexose transporters or glucose permease (Yang et al. 2012). $As(OH)_3$ is transported by aquaglyceroporins (AQP) into cells at neutral pH in bacteria, yeast, and mammals. $As(OH)_3$ is similar to a polyol, GlpF, which results in the capability of the glycerol transporters to carry arsenite (Meng et al. 2004). These transporters are responsible for the osmoregulation. It appears that arsenic oxyanion also acts as a GlpF substrate. High osmolality shuts down Fps1p channel thus providing resistance against As(III). The *aqpS* gene of *Sinorhizobium meliloti* was mutated to study the role of AQP in arsenic resistance. It resulted in higher tolerance to arsenite specifying that AqpS assists the arsenite uptake (Meng et al. 2004; Yang et al. 2005).

15.3.2 Biochemical Pathways Involved in Reduction

Arsenate reduction by microbes mobilizes the arsenite which is a more toxic form as compared to arsenate thus contaminating the groundwater. The reduction of arsenate to arsenite in the course of detoxification appears counterproductive. Arsenite resistance mechanisms first developed under anoxic atmosphere when nearly no arsenate was present. The development of oxygenic conditions results in the evolution of arsenate reductases in presence of increase arsenate content. Arsenite allows easy recognition as compared to the arsenate probably playing a role in the evolution of these pathways (Chen et al. 2020). Microbes take up the arsenate followed by the reduction of arsenite which is carried out either at periplasmic or cytosolic site. ArrA is a periplasmic respiratory arsenate reductase enzyme associated with cellular respiration. Arsenate uptake via Pit or Pst is followed by reduction of arsenate to arsenite occurs by the enzymatic reaction of arsenate reductase enzyme, ArsC leading to extrusion of arsenite via ArsAB pump (Silver and Phung 2005b; Rensing and Rosen 2009). In cytoplasmic reduction arsenate first binds to the anion site in the ArsC leading to the formation of an arsenate thioester intermediate. This intermediate is reduced in two phases by glutaredoxin and glutathione, leading to the formation of an intermediate Cystic2-S-As(III). This intermediate results in the release of arsenite upon hydrolysis. The reduced arsenite is released from the cell or sequestered in the intracellular compartments, either in conjugation with glutathione or other thiols or as free arsenite (Satyapal et al. 2016).

15.3.3 Biochemical Pathways Involved in Anaerobic Reduction

Arsenate reducing organisms are found in diverse environments like freshwater, sediments, soda lake, hot springs, estuaries, and gold mining areas. Arsenate reducing bacteria are also inhabiting gastrointestinal tract of animals along with subsurface aquifer materials show the occurrence of arsenate reducing bacteria. Dissimilatory arsenate respiring prokaryotes (DARPs) are the group of

microorganisms that can oxidize various organic or inorganic electron donors. Heterotrophic DARPs reduce arsenate to arsenite anaerobically. In anaerobic conditions, dissimilatory arsenate reducing bacteria perform respiratory oxidation by the utilization of arsenate. Arsenate resistance microorganisms (ARMs) reduce arsenate (used as electron acceptor) to arsenite or expel the metal out of the cell via precipitation under anaerobic conditions. Arsenic mobilization from solid to soluble phase takes place by the process of microbial arsenate respiration in various habitats worldwide. In particular, microbial respiratory reduction of As(V) to As(III) prevents the re-adsorption of arsenic once it is taken away from environments rich in iron (Cavalca et al. 2013).

DARPs belong to groups such as Gram positives, β-, γ-, and ε Proteobacteria, thermophilic Eubacteria, *Chrysiogenes arsenatis, Crenarchaeota*, Epsilon proteobacteria, Firmicutes, Aquificae, Deferribacteres. These are metabolically diverse groups and can use wide range of inorganic compounds as electron donors such as H_2 to small organic acids and sugars to complex aromatic substrates like benzoate and toluene.

Ahmann et al. (1994) reported the first arsenate respiring bacterium as *Geospirillum arsenophilus* strain MIT-13. The bacterial specie was isolated from anoxic sediments which was characterized with the presence of arsenite owing to the removal of lactate and arsenate. DARPs can also use other terminal electron acceptors such as nitrate, various sulfur compounds, selenate, Fe(III), or fumarate except strain MLMS-1 isolated from Mono Lake rely obligatory on arsenate reduction combined to sulfide oxidation (Hoeft et al. 2002).

DARPs can utilize arsenate as terminal electron acceptors in anoxic arsenate respiration and can deliver energy needed for the microbial growth (Cavalca et al. 2013). Membrane associated enzymes from *Bacillus selenitireducens* and *Chrysiogenes arsenatis* were found in periplasm and are different from the non-respiratory arsenate reductases of *E. coli* and *S. aureus* (Afkar et al. 2003). Ars detoxification system of *E. coli* plasmid R773 is beneficial but is not required for respiratory arsenate reduction mediated by *arr* operon. ArrA has the ability to reduce arsenate into arsenite, whereas ArrB channels the electrons from c-type cytochromes in the respiratory chain. It is proposed that arsenic may hinder diverse ecologically important anaerobic respiratory processes (Saltikov et al. 2003) as arsenic was revealed to obstruct denitrification in subsurface aquifer sediments. It is possible arsenic toxicity has limited the distribution among bacteria. However, little is known about dissimilation and the related regulatory genes.

15.3.4 Biochemical Pathways Involved in Oxidation

Arsenite oxidase was first studied in 1918, when 15 strains of heterotrophic arsenite oxidizing bacteria were isolated. Arsenite oxidizing microorganisms can be categorized as heterotrophic arsenite oxidizers (HAO) and chemolithoautotrophic arsenite oxidizers (CAO). Heterotrophic oxidation is also a detoxification process which results in arsenite conversion in outer membrane of the cell. This reaction in

oxic conditions, when combined with nitrate reduction, produces CO_2 from the organic matter. HAOs use organic carbon as an energy source for cell growth (Heinrich-Salmeron et al. 2011; Hassan et al. 2019).

Bacteria are more resistant to arsenate than arsenite and results in arsenite oxidation. Arsenite oxidase performs arsenite oxidation in periplasmic space of bacterial cell. *A. faecalis* isolated from sewage was able to oxidize arsenite. Respiratory inhibitors suppress further arsenite oxidation signifying the role of oxygen as terminal electron acceptor. In extreme environments like acid mine water, the concentration of arsenic is very high and main inorganic species is arsenite (Santini and vanden Hoven 2004; Hassan et al. 2019).

AoxS acts as a sensor kinase and detects the presence of arsenite resulting in the activation of AoxR involved in regulation. AoxR regulates the *aox* operon expression functioning simultaneously with RpoN. This RpoN is indispensable for activation of arsenite oxidase transcription in *A. tumefaciens*. AoxAB complex is produced after *aox* operon expression and is transported to the periplasmic space via a TAT (Twin-Arginine Translocation) export pathway. It carries out the oxidation of arsenite into arsenate in the periplasmic space (Santini and vanden Hoven 2004; Zargar et al. 2012).

15.3.5 Biochemical Pathways Involved in Anaerobic Oxidation

Oremland et al. (2002) reported an arsenite oxidizing bacterium *Alkalilimnicola ehrlichii* sp. strain MLHE-1 from anaerobic environment with high arsenic concentration. It was chemolithoautotrophic bacterium that has the capability to perform arsenite oxidation along nitrate reduction under anoxic conditions. *Ectothiorhodospira* sp. PHS1, a purple-sulfur bacterium isolated from red-pigmented biofilms in Mono Lake can utilize arsenite as the electron donor for anoxygenic photosynthesis and yields arsenate under continuous illumination. ArxAB was discovered in *A. ehrlichii* strain MLHE-1 and *Ectothiorhodospira* strain PHS-1 which is responsible for the arsenite oxidation in presence of nitrate in absence of oxygen. It was categorized under the DMSO reductase family but was distinct from AioAB. Hoeft et al. (2002) reported that Arx enzymes may have evolved in ancient times in the absence of oxygen where they would have played a part for arsenite oxidation in the presence of light and absence of oxygen (Zargar et al. 2012).

They have the capability to use arsenite as an energy donor for chemoautotrophic growth occurring simultaneously with oxygen reduction, e.g., *Rhizobium* strain NT-26 or *T. arsenivorans*. Chemoautotrophs can oxidize arsenite by nitrate and selenite dependent respiration, or phototrophy in environments lacking oxygen. These include *Alcaligenes, Agrobacterium/Rhizobium*, *Ectothiorhodospira*, *Pseudomonas,* and *Thermus*. Another strain, ML-SRAO, anaerobically oxidizes arsenite while reducing selenite. These findings suggest a possibility that microbial oxidation of arsenite led to the incomplete arsenic detoxification in the archaic anoxic world (Cavalca et al. 2013).

15.3.6 Biochemical Pathways Involved in Methylation

Various microorganisms methylate arsenic into volatile forms. Morphologically, methanogenic bacteria comprise diverse group containing cocci, bacilli and spiral forms but all produce methane as chief metabolic end product. Most of them thrive in anaerobic environments in large numbers like sewage, freshwater, and composts that involve the decomposition mechanism. Generally, methylation of arsenic is a detoxification process, although some compounds of the pathway are found to be more toxic to eukaryotic cells as compared to inorganic forms.

The methylation mechanism based on *S. brevicaulis* was first reported by Challenger (1945). It comprises arsenate reduction followed by oxidative addition of methyl groups producing gaseous arsines, monomethylarsonic acid (MMAA), dimethyl arsonic acid (DMAA), trimethylarsine oxide (TMAO), and final product trimethylarsine (TMA) (Cullen 2014). Thiol groups such as glutathione contributes in reduction, methyl group is given by is S-adenosyl methionine (SAM), and some anoxic microbes utilize methylcobalamin as the electron donor (Páez-Espino et al. 2009).

Higher eukaryotes and bacteria have been described to yield monomethylarsine and dimethylarsine, fungi produce trimethylarsine, and methanogens and aerobic bacteria lead to the production of methylated arsines. *Corynebacterium* sp., *Escherichia coli, Flavobacterium sp., Proteus sp.,* and *Pseudomonas sp.* function in the reduction of arsenate followed by the production of dimethylarsine. *Pseudomonas* sp. forms all the above-mentioned forms from arsenic-containing pesticides. *Nocardia* sp. was the only organism to produce methylarsines from arsenical herbicides. It is revealed that soil bacteria *Pseudomonas* sp. and *Alcaligenes* sp. produce arsine only in the presence of nitrate and nitrite where oxygen is not present (Bentley and Chasteen 2002).

An alternate pathway was suggested by Hayakawa et al. (2005) after studies of the human arsenic methyltransferase Cyt19 where arsenite glutathione conjugates are methylated without undergoing oxidation. The process of arsenic methylation has been described for aerobic and anaerobic bacteria as well as for photosynthetic organisms. For anaerobes, methylcobalamin is important, but a defined role remains unidentified (Hayakawa et al. 2005).

15.4 Future Perspective

A large information has been reported regarding arsenic metabolism, genes involved, and regulatory mechanism. The biosorbent, bioaccumulation, and genetically engineered bio-containers prove to be promising candidates for metal bioremediation processes (Satyapal et al. 2016). Microbially mediated metabolism adds on to the environmental pollution due to the release of arsenic in water bodies used by humans. It is speculated that anaerobic respiratory arsenate reductase releases underground arsenate into water that was previously immobilized. Arsenite oxidase along with precipitation can be harnessed for practical bioremediation of arsenic in

water. Through a variety of processes of detoxification and respiration, microorganisms influence the arsenic speciation acting as an important element in the arsenic cycling. Sustainable technologies need to be established for remediation of the arsenic- contaminated sites. For this purpose, extensive research is required to advance the biotransformation of arsenic, viz., improving bacterial strain and improving the process (Silver and Phung 2005b; Cavalca et al. 2019).

15.4.1 Strain Improvement

They are used for neutralizing arsenite inside the cells by the plants. Expression of such PCs in the bacterial host enhanced the arsenic accumulation by 50 times by arsenite sequestration with efflux machinery. Another approach for increasing arsenic buildup in microbial cells includes expression of arsenic-binding proteins with properties like metallothionein (MT). These low-molecular weight Cys-rich proteins bind with metal ions such as Zn, Cd, Cu, Hg, and Ag (Zhu et al. 2017).

The intracellular accumulation by bacteria is preferred. A bacterial strain B1-CDA cells accumulate different arsenic forms inside the cells, such as free forms, meta-arsenite, orthoarsenite, and arsenate. A mutant *C. glutamicum* strain was engineered for intracellular arsenic accumulation. The removal of ArsC increased the accumulation by 28–30 folds in the mutant strain than the control strain. Arsenite bio-containers were also engineered by the removal of arsenite efflux system. Overexpression of GlpF protein can result in enhanced arsenite uptake in *C. glutamicum* (Rahman 2016).

15.4.2 Process Improvement

Combination of physicochemical and biological arsenic remediation resulted in increased rate of arsenic removal with reduced consumption of energy (Lim et al. 2014). Biofilms are single or mixed and diversified bacterial populations which adhere to different biotic or abiotic surfaces. They are more resistant to a number of toxic heavy metals and metalloids. Exopolymer secretion is one of the main resistance strategies of cells, which results in immobilization of toxic metals via sequestration. Recently, *H. arsenicoxydans* and *Thiomonas* spp. are reported to produce high content of exopolysaccharides (EPS) in the presence of arsenic. These properties may be used to develop bioreactors (Plewniak et al. 2018).

Active or passive treatments can be applied for bioremediation purposes. Passive system comprises of wetlands or bioreactors and offer enhanced removal of metal with low energy consumption. This system is reported to perform sequestration of almost 99% of arsenic, zinc, and cadmium. Active system offers an efficient control with the possibility of heavy metal recovery, but demands high energy consumption (Baldwin et al. 2015). Arsenic immobilizing bacterial cultures are sustained in these bioreactors. The performance is analyzed and measured by the addition of particular nutrients along with electron acceptors or donors. In arsenic-contaminated soils, the

most common tool for bioremediation is phytoremediation. Plants accumulate arsenic resulting in arsenic removal from the soil. Wang et al. (2011a) conducted a research which revealed that *Populus deltoides* with arsenic-resistant *Agrobacterium* resulted in improved growth and arsenic uptake showing the potential of bioaugmentation by bacteria.

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