

A Critical Review on Arsenic Exposure and Its Toxicopathophysiology

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Abstract: All natural resources are contaminated with high concentration of arsenic which ultimately results major environmental and health problems in the affected areas. It has been observed that inorganic form of arsenic is most toxic both acute and chronic. We conducted the review of available literature focusing on the adverse effect on human body as well as treatments to remove the contamination from ground water; soil. Initially arsenic enters into the body through inhalation, ingestion and distributed in different parts of human body like liver, skin, lungs and kidney. It has been very difficult to detect arsenic toxicity in body parts because it has many similar symptoms in other diseases also. Nowadays a wide range of different technologies are available for the removal of high concentration of arsenic from drinking water like ion exchange method, oxidation, and coagulation and filtration methods. Many chelating agents nowadays have discovered against the toxic effect of arsenic on human bodies like DMSA has potential to treat the chronic arsenic toxicity effectively. As well as the Dithiol & monothiol agents (BAL) Penicillamine SMSA has been reported as a best chelating agent for the treatment of clinical manifestations and reducing subsequent-cancer risk.

Keywords: Arsenic, toxicopathophysiology, phytoremediation, chelating agent

1. Introduction

Heavy metals are naturally occurring components with high atomic weight and density [1]. Their persistence in the environment makes human resources and aquatic life more polluted. The high concentration of heavy metals can lead to poisoning and creates high risk to human health. Anthropogenic activities such as burning of fossil fuels, mining, smelting operations and other industrial productions contribute significantly to environmental contamination and global climate change [2-5]. There are many other sources which are responsible for the contamination of environment like metal corrosion, soil erosion of metal ions, extraction of heavy metals and desiccation of metals from water resources to soil and ground water [6].

It has been reported that industrial processes which include heavy metal for refineries processes, in textile, nuclear plants, in coal industries and paper processing plants [7-9].

Heavy metals also play a very important role in biological processes in plants and human beings. They serve as important cofactors for various oxidation reduction reactions [10]. It has been found that in biological systems heavy metals mainly affect the cellular organelles and on some enzymes which are involved in important metabolisms [11]. There are many metal ions among heavy metals are found to be more toxic and dangerous which directly attack on DNA and nuclear proteins which lead to carcinogenesis and cell modulation [12-14]. It has been concluded from many lab studies that reactive oxygen production and oxidative stress play a vital role in toxicity and carcinogenicity of some metals like Arsenic [15-17], cadmium [18], chromium [19-20], lead [21-22] and mercury [23-24] because these metals show high degree of toxicity and lead to fatal diseases. According to the most popular agency of U.S (U.S.EPA) and other International Agency for Research on Cancer, these heavy metals can be considered as human carcinogens based

on experimental studies which declaring the relation between introduction and cancer incidents in human and other animal species. The degree of toxicity and functionality make a difference between the heavy metals.

2. Arsenic Metal

Arsenic is spread alive in all environmental aspects like soil air and water. The chemical element Arsenic has symbol as and has a metallic grey appearance. In the periodic table, Arsenic lies as the third element of group five having atomic number 33 and atomic mass 74.92 g/mol. It is considered as a metalloid as its physical and chemical properties lies between a metal and non-metal. -3, 0, +3 and +5 are the defined four oxidation states in which arsenic exists [25]. The combined form of arsenic with metal ions, oxygen, sulphur and chloride is considered as "inorganic arsenic" whereas the combined form with carbon and hydrogen is known as "organic arsenic". Arsenic is the 53rd most abundant element on earth. 1.5ppm (0.00015%) of earth's crust is comprised of arsenic. Arsenic basically occurs as mineral compounds in earth like $MAsS$ and MAs_2 ($M = Fe, Ni, Co$) [26]. The English word Arsenic is taken from the Greek word *arsenicum* which was adopted in Latin and later in French it became *arsenic* [27]. Since ancient times the sulphides (orpiment, realgar) and oxides of arsenic were known and were being used [28]. It was frequently used for murder due to the chronic symptoms of arsenic poisoning. It has been called as the king of poisons [29].

Geochemistry of arsenic

Arsenic occurs naturally in its inorganic form but it may be found as the metal element or as a compound where it is combined with other element in a range of reduced metalloid of in organic compounds [30]. Convergence of arsenic is mainly dependent on pH change and redox conditions along with desorption, absorption and ion exchange reaction

[31].The redox equilibrium is established between different forms of arsenic are dependent on pH conditions and convergence of arsenic is strongly affected by redox potential [32].Under low oxygen condition the trivalent form of arsenic becomes more persistent [33].The trivalent form of arsenic is oxidised to pentavalent form when it is adsorbed on the surface of Mn or Fe-oxides [34].The interconversion of different forms of arsenic is also carried out by biological reactions. It involves the redox reactions between arsenate to arsenite, reduction of arsenic, formation of organic compounds and methylation process which can be done by different forms of organism ranging from bacteria to yeast and through catalytic action of algae and bacteria [35]. Methylation is a very common organic process carried out by different bacteria in which the hydroxyl groups of arsenic compounds are replaced by methyl group [36].

Pathophysiology of arsenic toxicity

Arsenic gets attached to the allosteric site of pyruvate dehydrogenase enzyme which inhibits it to catalyse the oxidation of pyruvate to acetyl-CoA, leading to disturbance in energy system which results in cellular apoptosis. The potassium channels are affected by the arsenic trioxide which results to low potassium levels in cells which causes dysfunction of cellular electrolytes, CNS dysfunction, disturbed heart rhythm (long QT interval), neurological disturbances, anaemia and even death [37-38].ATP production is also is also disrupted by arsenic compounds through several mechanisms. In the TCA cycle, arsenic competes with phosphate and inhibits pyruvate dehydrogenase, thus inhibiting mitochondrial respiration and ATP synthesis [39]. Production of hydrogen peroxide is stimulated in the cells by arsenic which produces hydroxyl radicals by reacting with metals like manganese and iron. It also forms reactive oxygen species and oxidative stress. Compiling all the metabolic interferences causes organ system failure and leads to death. The enzyme succinic dehydrogenase and the formation of acetyl-CoA are inhibited by arsenite. Phosphate is replaced by arsenate and forms Glucose-6-Arsenate and hence hexokinase is inhibited (reason for the muscle weakness in chronic arsenic poisoning) [40].

Arsenate attacks glyceraldehydes 3-phosphate dehydrogenase bound thioester and forms 1-arseno-3-phosphoglycerate which gets hydrolysed being unstable. In the mitochondria, arsenate is synthesized in place of succinate and Adenosine diphosphate-arsenate is formed from ADP. ATP formation and cellular respiration is impaired by arsenate through this variety of mechanisms [39].

Toxicopathophysiology of Arsenic

Arsenic compounds have been known since thousands of years ago at least the days of Ancient Rome and Greece. Arsenic was first sanctioned as an element by alchemists. The whole credit for this exploration goes to Albertus Magnus; 1193-1280.when he heated the orpiment which is a very common compound of Arsenic (As_2S_3), with soap then pure form of arsenic was formed in this process. Arsenic compounds have variety of properties which are useful for

mankind. The compounds of Arsenic were used by physicians to treat many diseases. As arsenic is a well known toxic compound but sometimes used as insecticides and rat poison. The compound most often used for both purposes was arsenic sulphide [41].

The most important use of Arsenic is the preservation of wood. Its chromate cooper arsenate form is added in the wood to build wooden structures and houses. This compound of arsenic is mainly used in U.S.A for manufacturing of wooden shelters. It has been found that arsenic has medical applications. One of the known compounds of arsenic named arsenic trioxide is very useful drug (Trisenox) which is given to adults intravenously. The Trisenox drug is FDA-approved prescription drug. Despite of its toxic property, it is an important element which is essential for our physiology. For the healthy growth of nervous system we require 0.00001% of arsenic is needed [43]. Human body do not easily ingest pure arsenic element itself .Moreover pure arsenic element is very less risky than trivalent arsenic compounds such as AsH_3 and As_2O_3 which are readily absorb and highly toxic and carcinogens. But long term disclosure to Arsenic and its compounds can directly cause fatal diseases like cancer. In case of low doses, it can produce vomiting, nausea and diarrhoea etc. The cancer cell can affect mainly the kidneys, liver, lungs and bladder under large doses of arsenic. The direct contact with arsenic compounds can cause skin disease like swelling and redness and small corns may start to grow on the palms of the hand and soles of the feet [43].

3. Removal of Arsenic metal

Plant helps to remove arsenic from contaminated soils:

Arsenic is the most considerable toxic metal for plants and animals. Although Arsenic is the part of some plants but its important significance is not known to us. Plants can easily absorb arsenic through air and soil. Arsenic is absorbed mostly from soil by roots and transported to all parts of the plant by vascular system. But leaves play vital role in case of absorption of arsenic from air. The toxicity of arsenic prevents the transformation of arsenic to various parts of plant [44]. Arsenic can easily accumulated in the roots of plants and the plants accumulate the large amount of arsenic without any harm to itself. These types of plants are called hyper accumulators [45].In aerobic soil; plants can mostly absorb Arsenic in its inorganic form "Arsenate". The biological availability of arsenic makes it possibly able to affect the organism health [46-48]. Arsenic is less available for plant uptake in aerobic soil because of its high affinity towards Fe and Al-hydroxides and oxides [49].Phosphate replaces Arsenate in both soils and roots as it is chemically similar to arsenate and compete with it for absorption sites in soil, reducing As uptake by plants naturally[50-52]. Plants mainly absorb As from soil by roots but considering exceptions some plants absorb As by leaves from air too. The vascular system of plant transport As from roots to other parts of plant. The toxicity of As to transporting cells prevents transformation to take place[53]. The transport of As to other parts of plant is prevented by the ability of plants to accumulate As to roots. Cellular injury is caused by As by peroxidation of membrane lipids, production of reactive oxygen species which damages the chloroplast membrane

and cell membrane [54]. The terrestrial plants absorb arsenic from the soil in low concentration as compared to aquatic plants. The aquatic plants mainly absorb arsenic by means of roots and shoots in high concentrations (200 $\mu\text{g/g}$) but it has been observed that the plants growing near the borderline of arsenic contaminated water show very little arsenic amount [55]. Even if the concentration of arsenic in polluted soil is high, the accumulation of arsenic in terrestrial plants is comparatively low [56-57]. The existence of arsenic in soil makes it toxic and result of its exposure to plants and animals is carcinogenic [58]. It has been reported that the fern "*Pteris vittata*" (brake fern) was the first hyper accumulator which worked efficiently in removing the arsenic from soil and translocating it into its above ground biomass. This species is found in Central Florida, growing on the land which is contaminated with chromated copper arsenate. It is used in the remediation of arsenic contaminated soil cheaply and helps in the detoxification of plants [59].

Water as a source of Arsenic

Arsenic is widely distributed in surface water, ground water and finished drinking water in different concentrations. Arsenic present in water can undergo various complex reactions which involve redox reactions, precipitations reactions, ligand exchange and some biotransformation reactions [60-62]. These reactions occur in aquatic environment mainly influenced by some factors like pH, temperature, salinity, iron concentration, metal sulfide and sulfide ion concentrations, organic matter concentration [63-65]. According to the report submitted by WHO 2001, the concentration of arsenic in water sources varies accordingly like in ground water concentration can be 3mg/L in volcanic areas and in open ocean sea water the limit can be 1-2 $\mu\text{g/L}$. Comparison to this the arsenic concentration is typically less in fresh water sources. Although its concentration can be literally high due to human activities such as burning of fossil fuels, mining, smelting operations and other industrial productions [66].

4. Removal of Arsenic from water

Arsenic and its compounds which are highly toxic are produced by waste by-products of dyes, pesticides and other chemical based industries which produce contaminated waste water. The aquatic system has been highly affected through arsenic poisoning which leads to mutagenic effects in all life forms. Nowadays a wide range of technologies has been developed for the removal of elevated concentrations of arsenic from drinking water. Some techniques are discussed below:

1) Oxidation Method:

Many treatment systems are available in the market which include oxidation step which convert the pentavalent form of arsenic As (V) to its trivalent form As (III). Arsenite As (III) form can be easily eliminated from drinking water as it is less mobile than arsenate form As (V). The co-precipitation of Arsenate can be done with metallic cations. The arsenite is dependent on pH and it is predominately non-charged below pH value 9.2. For the oxidation of arsenite to arsenate, many oxidizing agents are commonly used such as oxygen (O_2), hypochlorite (HClO), permanganate (HMnO_4) and hydrogen

peroxide (H_2O_2). But the naturally occurring oxygen present in the air is the most preferable method for the oxidation. O_2 is readily available, but this process takes weeks for oxidation [67]. The oxidation of arsenite can be catalyzed through bacteria and other catalysts such as powdered activated carbon, copper and highly acidic and basic solution. High temperature is also affecting the oxidation process. It increases the oxidation process [68].

2) Coagulation and Filtration

Precipitation is the basic chemical process which is used to form a low solubility solid mineral of dissolved arsenic such as calcium arsenate, this solid can easily be removed through filtration and sedimentation. On the addition of coagulants the dissolved compounds like arsenic become insoluble and form solids, this is known as co-precipitation. The effective treatment used for arsenic removal includes coagulation and filtration either using metal salts or lime softeners. Many suspended and dissolved constituents from water other than arsenic like iron, fluoride, phosphate manganese etc can easily be removed through this method. The aluminium and ferric salts are most commonly used for arsenic removal from water but ferrous sulphate salt has been reported less effective [69-72]. Under optimum conditions 99% arsenic removal is possible with either ferric or aluminium salts and for very less arsenic concentration alum should not be used.

3) Ion exchange

Ion exchange is a physical chemical process widely used for the softening of water in which ions are swapped between a solution phase and solid resin phase. The solid resin phase is based on three dimensional cross linked networks to which charged functional groups are attached. These functional groups can be categorising as acidic and basic according to their strength weak or strong [73]. Ion exchange process is independent to the pH of drinking water. Pre-oxidation of arsenite is necessary as arsenite is being uncharged and cannot be removed by ion exchange process. It also affects the solid resin and resin needs to be regenerated by washing with NaCl solution.

5. Arsenic Poisoning in Humans

Arsenic exposure to humans can be from either natural source or industrial source. As reported worldwide, arsenic is being exposed via drinking water, air, food and beverages. Drinking water exposure is increasing due to over withdrawal of groundwater for irrigation and increasing contamination from industrial operations of arsenic containing insecticides and herbicides. The common pathway for absorption of arsenic is by ingestion or inhalation. Trivalent arsenic oxides may be absorbed through skin as it is more soluble than the pentavalent arsenic oxide [74]. If ingested, the reaction will mimic the acute gastrointestinal irritation. Because of rapid biotransformation of arsenic in liver, the ingested arsenic has a shorter half-life than inhaled arsenic [75]. If contact is by inhalation, then respiratory irritation will dominate as early symptoms. Various potential symptoms will reflect in the organs in contact with vascular circulation once arsenic is absorbed in the body.

Arsenic gets in contact with the human body by ingestion, inhalation and skin absorption. Most of the arsenic is absorbed in the blood stream by lungs and gastrointestinal tract in case it is inhaled or ingested. Gastrointestinal tract absorbs maximum of 95 % of ingested arsenite and further it gets distributed to various organs including skin, liver, lungs and kidney [76].

Toxic effects of arsenic in humans depend on the amount of arsenic intake, which is further divided into acute, sub-acute and chronic toxicity respectively.

Acute poisoning: Acute toxicity is a condition where arsenic is ingested deliberately or accidentally through contaminated food or drink. The range of fatal dose of arsenic trioxide is usually around 200-300 mg during a period not exceeding 24 hours. But the exposure of small amount of arsenic trioxide to unhealthy body can also lead to life threatening problems or even death. Although the human body can tolerate small doses of arsenic trioxide (up to 10 mg) without any physiological effects.

Clinic-pathological observations in acute arsenic poisoning:

| Affected Organ System | Signs and symptoms |
|-----------------------|---|
| 1. Gastrointestinal | Garlic odor on the breath, severe abdominal pain, nausea and vomiting, thirst, mucosal erosion, heart burn, dehydration, anorexia, heartburn, bloody or rice water diarrhea, and dysphagia[77]. |
| 2. Neurological | headache, weakness, lethargy, delirium, encephalopathy, hyperpyrexia, tremor, disorientation, seizure, stupor, paralysis, leg/muscular cramps, paresthesia, hyperesthesia, neuralgia[78] |
| 3. Dermatologic | Delayed appearance of Mee's lines in nail beds, dermatitis, melanosis, and Vesiculation. |
| 4. Renal | Hematuria, oliguria, glycosuria, uremia, acute tubular necrosis with partial and complete renal failure, and renal cortical necrosis. |
| 5. Hematologic | Anemia, thrombocytopenia, granulocytopenia, hematuria and leucopenia. |
| 6. Cardiovascular | Altered myocardial depolarization, Q-T Prolongation, ventricular fibrillation, ventricular tachycardia, hypertension and shock.[79] |
| 7. Respiratory | Irritation of nasal mucosa, pharynx, larynx, and bronchi, pulmonary edema, bronchitis, pneumonia, and nasal septum perforation. |
| 8. Hepatic | Yellow atrophy, elevated liver enzymes, fatty infiltration, congestion, central necrosis, cholangitis, and cholecystitis. |

Sub-acute poisoning: Sub- acute toxicity in human body is developed due to repeated intake of small doses of arsenic compounds. Initially it stimulates irritation in respiratory tract and later it dominates the gastrointestinal tract.

Clinic-pathological observations in sub acute arsenic poisoning:

| Affected Organ System | Signs and symptoms |
|-----------------------|---|
| 1. Gastrointestinal | Difficulty in swallowing, abdominal pain, vomiting, diarrhea, and dehydration. |
| 2. Neurological | Numbness, tingling, and "pins and needles" sensations in the hands and feet, distal weakness, quadriplegia, and, in rare instances, respiratory muscle insufficiency, fever and facial edema. |
| 3. Cardiovascular | Cardiomyopathy, ventricular dysrhythmias (atypical ventricular tachycardia and ventricular fibrillation), and congestive heart failure, hypovolemia and hypotension. |

Chronic poisoning: Chronic arsenic poisoning is due to excessive accumulation of arsenic in the body due to continuous exposure to arsenic compounds through occupational exposure or natural contaminant of drinking water. The effects of chronic poisoning can still be seen years after exposure to arsenic compounds has stopped as it replaces phosphorus in the bones and get permanently binded.

Clinico-pathological observations in chronic arsenic poisoning:

| Affected Organ System | Signs and symptoms |
|-----------------------|---|
| 1. Gastrointestinal | Esophagitis, gastritis, colitis, abdominal discomfort, anorexia, malabsorption, and/or weight loss. |
| 2. Neurological | Polyneuritis and motor paralysis, Hearing loss, mental retardation, encephalopathy, symmetrical peripheral Polyneuropathy, electromyographic abnormalities. |
| 3. Dermatologic | Hyper pigmentation, Skin lesions, palm plantar hyperkeratosis, Desquamation, Melanosis, Bowen's disease, facial edema, |
| 4. Endocrine | Diabetes mellitus. |
| 5. Hematologic | Bone marrow hypoplasia, Aplastic anemia, Leucopenia, Thrombocytopenia, Impaired folate metabolism, Karyorrhexis. |
| 6. Cardiovascular | Arrhythmias, Pericarditis, Blackfoot disease (gangrene with spontaneous amputation), Raynauds syndrome, Acrocyanosis (intermittent), Ischemic heart disease, Cerebral infarction, Carotid atherosclerosis, Hypertension, Microcirculation abnormalities |
| 7. Respiratory | Rhinopharyngolaryngitis, Tracheobronchitis, Pulmonary insufficiency (emphysematous lesions), Chronic restrictive/obstructive diseases. |
| 8. Hepatic | Cirrhosis, Portal hypertension without cirrhosis, Fatty degeneration, hepatic neopalsis, hepatic blood vessel damage and fibrosis |

Fulminant poisoning: Fulminant poisoning is caused by ingestion of massive dose of arsenic compounds which simultaneously causes death without any clinic – pathological symptoms

Treatments to Remove Arsenic Poisoning:

To minimize the harmful effects of arsenic and remove arsenic from the body, it is necessary to treat the person at

the earlier stage of exposure as it immediately gets absorbed in the blood and start destroying the blood cells. Further it affects the kidney and urinary tract.

The most effective methods of treatment include:

- 1) Escape the person from the exposed area in case of arsine gas. In case of ingestion inhibit the food intake.
- 2) Transfusion of blood within short period of exposure.
- 3) Perform hemodialysis before arsenic binds to the tissues.
- 4) To remove unabsorbed arsenic, bowel irrigation must be used.

Chelating agents were proved to be successful in reacting with arsenic and eliminate it from the body. Chelating agents must be used under medical supervision as they are toxic. Some of the chelating agents and their use are listed below:

| Sr. no | Chelating Agent | Therapeutic use |
|--------|---|--|
| 1 | DMSA & DMPS | Chronic arsenic toxicity can be treated effectively[80] |
| 2 | Penicillamine (monothiol agent) | It can be orally administered to remove arsenic poisoning |
| 3 | BAL (British Antilewisite) | Used as a chelator when arsenic extraction from tissue is required, treatment for severe arsenic poisoning [81]. |
| 4 | 2,3-dimercapto succinic acid (Dithiol agent) | Recently reintroduced drug that appears to be promising agent for treating arsenic poisoning. |
| 5 | Dithiol & monothiol agents (BAL) Penicillamine SMSA | A Specific line of treatment for relief of clinical manifestations and chelating reduction of arsenic stores in the body, reducing subsequent-cancer risk. |

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