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Toxicological Aspects Related to Environmental Arsenic Exposure

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Abstract

Heavy metals can be described as those naturally occurring metals or metalloids which have considerably high atomic weight. Generally, Arsenic (As), Lead (Pb), Mercury (Hg), Cadmium (Cd) and Chromium (Cr) are regarded as heavy metals in matters concerning public health due to their significant ill effects on the environment. Heavy metals including arsenic result in biomagnification involving a significant increase in their concentration as we move from lower to higher trophic levels across the food chain up to humans. The toxic effects depend upon many factors like the chemical nature, route, duration and dose of exposure along with the age, gender, genetic makeup and nutritional status of the exposed animals. Arsenic exists both in organic and inorganic forms and is considered to be one of the systemic toxicants known to cause damage to multiple organs even at minuscule levels of exposure. Arsenic is a necessary ultra-trace element for various organisms and has several valuable industrial applications in the manufacturing of pesticides, pyrotechnics, semiconductor devices, solar cells, light-emitting diodes, integrated circuit chips, etc. On the other hand, arsenic is a major environmental pollutant and has also been listed as Category I carcinogen for humans by the International Agency for Research on Cancer. Apart from its carcinogenic potential, arsenic also has mutagenic, teratogenic and epigenetic effects on various animals. This review briefly outlines the different modes of arsenic exposure, description of toxic effects of arsenic, its clinical manifestations and underlying molecular mechanisms as determined by various studies carried out on different animal models. Preventive measures for arsenicosis and various modes of treatment have also been discussed. Conclusively, environmental exposure to arsenic should be minimized by using appropriate protective gear and equipment, to reduce the associated health hazards.

Keywords: Heavy metals; Arsenic; Cytotoxicity; Histopathological; Carcinogenicity; Environmental exposure

Introduction

We have witnessed an increased environmental deterioration in the past century due to anthropogenic activities like industrialization and urbanization which in turn have proved to be increasingly damaging for human health. Heavy metals naturally occur as trace elements (having very low concentrations in ppb or <10ppm). Their increased content in the environment can be traced to both natural phenomena (volcanic eruptions, weathering of rocks and leaching) and human activities (increased utilization in agriculture, industries like mining, foundries and smelters). The ill effects of heavy metals have attracted the attention of the global scientific community and various researches are being carried out around the world to monitor the effect of these toxicants on human health as well as on other animals. ^{75}As, a stable and heavier isotope of arsenic is regarded as a great risk to public health. Among other heavy metals, it has been observed that arsenic concentrates in the crust of earth, bedrocks and leaches gradually into the water table, becoming a part of the food chain through drinking water and absorption by plants (Vahter, 2008; Riaz et al., 2023; Kaur et al., 2023; Hassan and Mohammed, 2023).

Humans are exposed to inorganic forms of arsenic through occupational exposure and by consuming contaminated food, water, air. Organic arsenic mainly reaches humans through consumption of contaminated seafood like fish, oysters, prawns and mussels. Long-term exposure to arsenic, even in small concentrations leads to a plethora of health complications in humans, collectively referred to as 'Arsenicosis' (McCarty et al., 2011; Langat et al., 2024). More than 0.1 billion people across the world are exposed to arsenic concentrations of >50µg/L (Moon et al., 2012) through drinking water and contaminants generated through industrial processes (Lindberg et al., 2008). Arsenic enters the human body through three main routes – absorption through skin, inhalation and oral route. It exists in oxidized/pentavalent [As (V)] and reduced/trivalent [As (III)] forms, both of which are readily absorbed in the Gastro-Intestinal tract and get accrued up in the tissues and body fluids (Ueki et al., 2004). Arsenic has been found in human skin, lungs, liver and kidney (Hong et al., 2014). Around 70% of Arsenic is excreted by the kidneys through urine but, compared to organic forms of arsenic, inorganic arsenic takes greater time to get excreted (Goyer and Clarkson, 1996). Exposure to larger doses of arsenic, even for a short duration results in 'acute arsenic toxicity' which progresses quickly causing damage to multiple organs and may be fatal. On the other hand, exposure to small doses of arsenic for prolonged periods results in 'chronic arsenic toxicity' which is carcinogenic and causes malignant tumor development (Vahter et al., 2006; Wasserman et al., 2004) and deformation of body extremities. Lower to medium doses of arsenic (10–300µg/L) entering the body by means of drinking water also causes various medical conditions like – lesions on skin, disorders of cardio-vascular system, neurological complications, respiratory disorders, diabetes, hampering hepatic and renal functions (Chen et al., 2009). Furthermore, ingestion of inorganic forms of arsenic (primarily through drinking water) may cause tumors in various organs like bladder, kidneys, lungs, liver and skin over and above other circulatory and neurological complications (Mandal et al., 2001). A direct correlation has been found between exposure to arsenic and increased susceptibility to diabetes mellitus (type II) (Walton et al., 2004). Arsenic has also been found to induce chronic hypertension (Abir et al., 2012). It has been found to profoundly suppress spermatogenesis and the release of gonadotropins and testosterone in rats (Sarkar et al., 2003). Apart from these, ingestion of inorganic arsenic leads to various skin related disorders like hyperkeratosis, hyperpigmentation and periorbital swelling. If consumed in high doses, it may lead to spontaneous abortion. Health effects of exposure to arsenic and its clinical manifestations can be broadly categorised as per table 1.

Table 1. Four stages of exposure to arsenic and their clinical manifestations (Mahmud et al., 2016)

Stage 1	Pre-clinical	Hair, nails and urine show a high concentration of arsenic metabolites upon biomonitoring with no clinical symptoms
Stage 2	Clinical	Melanosis, spotted keratosis, leukokeratosis, non-pitting edema, conjunctival congestion
Stage 3	Internal complications	Effect on brain, cardiovascular system, lungs, liver, kidney, gonads, endocrine glands, spleen and muscles leading to multiple organ dysfunction
Stage 4	Malignancy	Bowen's disease, squamous and basal cell carcinoma, carcinogenic effect on urinary bladder, skin, lungs, uterus and many other organs

Common methods of biomonitoring

Biomonitoring of heavy metal toxicity is carried out using various tissues, blood, urine, hair and nails as samples (Amaral et al., 2008; Bencko, 1995; Bormann de Souza et al., 2009; D'Ilio et al., 2000; Pereira et al., 2004; Rodrigues et al., 2008; Sanna et al.,2008; Violante et al., 2000). Exposure to any kind of foreign chemicals affects the homeostasis of our body and this distortion of internal metabolic equilibrium is expressed in our metabolites like proteins and body fluids like blood and urine, tissues like hairs and nails. A mineral analysis test of hair tissue is considered as a standard test for the biomonitoring of trace elements and heavy metals in humans and animal species all across the world (Muller, 1996; Bhattacharya et al., 2004; Chatterjee et al., 2004; Gobel, 1998; Laker, 1981; Manson and Zlotkin, 1985; Underwood, 1997). Human scalp hairs are generally taken for biomonitoring because of some advantages such as hair fall is a common problem, so samples

can be collected in sufficient amounts. They are easy to handle, store and transport. Hair have been found to process higher concentrations of Mercury than in blood and other fluids (WHO, 1990). People having long term occupational exposure and children have been found to be more prone to heavy metal poisoning (Duarte et al., 1989; Hambidge et al., 1982; Vahter, 2008).

Toxic effects of arsenic on various organ systems

Skin

Men are more likely to develop arsenic-induced skin disorders as compared to women (Lindberg et al., 2008) like skin lesions, melanosis, keratosis and pigmentation of trunk and extremities (Rahman et al., 2009; Hopenhayn, 2006) [Figure 1]. In some cases, dermal lesions may appear after 5-10 years of exposure (Mazumder et al., 1998). Pigmentation of skin along with hyperkeratosis/thickening of palm and sole were reported in 103 out of 156 patients exposed to arsenic through contaminated sources of drinking water (concentration = 0.05 to 3.2mg/L) in the state of West Bengal, India (Mazumder et al., 1998).

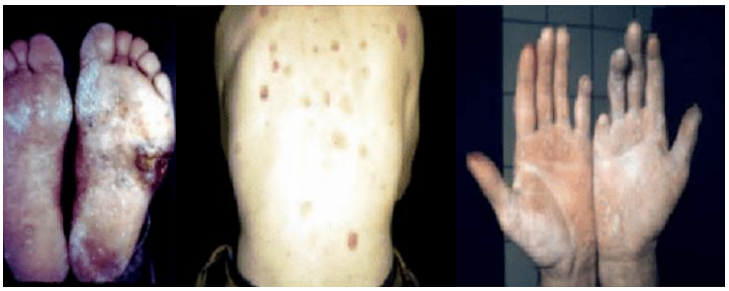

Fig. 1. Patients showing skin keratosis, amputated digits and skin cancer (Hopenhayn, 2006)

Nervous system

Arsenic can cross the blood-brain barrier easily (Mundey et al., 2013). High accumulation of arsenic has been observed in hypophysis (Sanchez-Pena et al., 2010). Sensory nerves are more vulnerable to harm caused by arsenic than motor nerves. Oxidative stress induced by arsenic has been found to be a major factor responsible for neurotoxicity (Mundey et al., 2013). Arsenic induces neuronal apoptosis via activation of p38 and c-Jun N-terminal kinase-3 (JNK3) and mitogen-activated protein kinases (Namgung and Xia, 2001). Chronic exposure to arsenic leads to change in the levels of neurotransmitters like dopamine, norepinephrine, acetylcholine etc. (Kannan et al., 2001; Rodríguez et al., 2003). Arsenic is also reported to cause central and peripheral neuropathies (Rodriguez et al., 2003), however peripheral neuropathy is more common and significant (Mukherjee et al., 2003). Clinical symptoms include headache, hallucinations, seizures and coma (Bartolome et al., 1999). There may be development of Paraesthesia, a feeling of pain and numbness in the soles of the feet chiefly due to damage caused to the peripheral nerves (Vahidnia et al., 2007).

Respiratory system

Evidence of direct correlation between arsenic exposure and increased mortality due to respiratory diseases has been investigated (Parvez et al., 2011). Occupational exposure to arsenic is mainly through inhalation (dust or fume) while mining or milling of ores. It leads to respiratory complications like chronic cough, laryngitis, bronchitis and rhinitis (Saha et al., 1999). Abnormal wheezing chest sounds, shortness of breath and blood in sputum may be seen in arsenic exposed patients (Parvez et al., 2010) along with tuberculosis (Parvez et al., 2012; Parvez et al., 2013) and development of non-malignant lung diseases (Dauphiné et al., 2011).

Reproductive system and development

Arsenic reduces fertility in both males and females. As a highly potent teratogen, it causes foetal growth retardation and death (Golub et al., 1998; Tabocova et al., 1996). Arsenic may induce dysfunction of testes by way of declined testosterone synthesis, increased cellular apoptosis and gonadal tissue necrosis (Davila-Esqueda et al., 2012; Shen et al., 2013). Arsenic exposure through drinking water may cause pregnancy complications like abortions and premature delivery

(Chakraborti et al., 2003). Prenatal arsenic exposures may lead to health-related complications in later stages of life as a consequence of epigenetic modifications (Farzan et al., 2013; Smith et al., 2012).

Hepatic system

Liver carries out the detoxification of various arsenic species (Watanabe and Hirano, 2013) which may lead to arsenic induced hepatotoxicity in some cases (Ratnaike, 2003). Early clinical symptoms may include bleeding from oesophageal varices, ascites, jaundice and enlargement of liver (Kapaj et al., 2006). Blood serum analysis at that time shows increased levels of liver enzymes (Jomova et al., 2011; Kapaj et al., 2006). Another study also revealed increased levels of bilirubin and enzymes including alanine transaminase, aspartate transaminase, alkaline phosphatase in blood serum (Das et al., 2012). Later stages of chronic arsenic exposure may cause formation of hepatic lesions, along with hepatic fibrosis, non-cirrhotic portal fibrosis, ultimately leading to complete liver failure (Kapaj et al., 2006). The molecular mechanisms involve increased oxidative stress, elevated Reactive Oxygen Species (ROS) activity leading to the activation of significant kinase signalling molecules like C-Jun N-Terminal Kinases (JNK), p38 Mitogen Activated Protein Kinase (p38 MAPK) (Suzuki and Tsukamoto, 2006) and Cytochrome-P450 (Bashir et al., 2006) which are responsible for inducing apoptosis of hepatocytes and tissue necrosis. Enlargement of liver along with higher levels of globulin, alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase enzymes was observed in population affected by arsenic exposure (0.05-3.2 mg/L) in West Bengal state of India (Mazumder et al., 1998).

Renal system

Elimination of arsenic through urine may sometimes lead to concentration of arsenic in kidneys (Madden and Fowler, 2000). Clinical manifestations of arsenic mediated renal cytotoxicity include hypourea, increased levels of serum creatinine, elevated concentration of blood urea nitrogen and proteinuria followed by acute renal tubule necrosis (Sasaki et al., 2007). Nephrotoxicity induced by arsenic causes malfunctioning of proximal convoluted tubules (Madden and Fowler, 2000) and may cause significant damage to capillaries and glomeruli of nephrons (Rahman et al., 2009). Increased mortality rate due to kidney disease upon exposure to high levels of arsenic was observed in multiple countries including United States (Lewis et al., 1999; Meliker et al., 2007), Taiwan (Tsai et al., 1999), Chile (Smith et al., 2012a) and Bangladesh (Lokuge et al., 2004). Molecular mechanism behind arsenic induced renal toxicity involves elevated ROS activity and increase in oxidative stress leading to increased expression of Hemeoxygenase-1, Mitogen Activated Protein Kinase (MAPK) and other signalling pathways that regulate transcription factors such as activating transcription factor-2, activator protein-1 and ETS domain containing protein ELK-1, followed by suppression of peroxisome functioning (Parrish et al., 1999; Sasaki et al., 2007).

Endocrine system

Disruption of endocrine system by arsenic is an established fact (Davey et al., 2007; Davey et al., 2008). Majority of endocrine glands including thyroid (Ciarrocca et al., 2012), pancreas (Lu et al., 2011), gonads (Davila-Esqueda et al., 2012; Shen et al., 2013), hypothalamus and pituitary (Goggin et al., 2012), thymus (Ahmed et al., 2012) are affected by arsenic toxicity. Exposure to arsenic through ground water (2–22 µg/L) has been reported to cause hypothyroidism among inhabitants of West Texas counties (Gong et al., 2015). Arsenic accumulates in pancreas, reducing the viability of the β-cells resulting in hyposecretion of insulin, ultimately leading to diabetes (Lu et al., 2011). Arsenic induced insulin resistance and β-cell dysfunction is initiated by formation of reactive oxygen species (ROS), release of nuclear factor–κB (NF–κB), cytokines [tumor necrosis factor α (TNFα) and interleukin-6 (IL-6)] followed by inhibition of peroxisome proliferator activated receptor γ (PPARγ) (Tseng, 2004). Arsenic also disrupts gastrointestinal secretions which is clinically manifested by symptoms such as nausea, vomiting and diarrhoea, enhanced thirst, burning sensation on lips, problem while swallowing, abdominal cramps, pain and dehydration (Ratnaike, 2003; Uede and Furukawa, 2003; Vantroyen et al., 2004). Dyspepsia was

reported in 60 people out of a group of 156 arsenic (0.05-3.2mg/L) exposed individuals in West Bengal, India (Mazumder et al., 1998).

Cardiovascular system

High arsenic exposure leads to cardiovascular diseases (CVD) like atherosclerosis, hypertension and arrhythmia (Chang et al., 2004; Wang et al., 2007; Chen et al., 2011). Inhalation of inorganic arsenic for longer periods may have detrimental effects on heart and blood vessels (Navas-Acien et al., 2005; Lewtas, 2007; States et al., 2009). Arsenic contaminated drinking water also has negative impacts on the cardiovascular system (Rahman et al., 2009). Hypertension due to arsenic exposure has been disclosed in multiple countries including Bangladesh (Huda et al., 2014), Iran (Dastgiri et al., 2010), Taiwan (Wang et al., 2011), India (West Bengal) (Mazumder et al., 2012) and China (Li et al., 2013; Zhang et al., 2013). In south-west Taiwan chronic arsenic exposure led to community outbreak of endemic black foot disease (BFD) [Figure 2] which is a specific type of peripheral vascular disease (PVD) (Tseng et al., 2005) having clinical symptoms such as high degree of arteriosclerosis, progressive arterial occlusions and consequent gangrene of lower extremities. Arsenic mediated oxidative stress may result in decreased antioxidant production and hyper contraction of blood vessels (Lee et al., 2005).

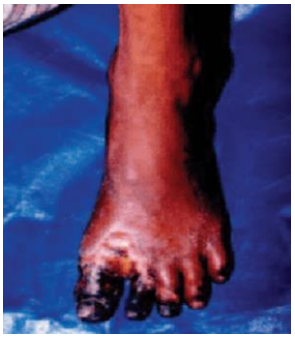

Fig. 2. Patient showing black foot disease (BFD) which is a specific type of peripheral vascular disease (PVD) (Hopenhayn, 2006)

Haematopoietic system

Arsenic affects the hematopoietic organs like bone marrow and spleen. Highest accumulation of arsenic (2 to 3 times higher as compared to other organs like heart, liver and kidney) was observed in spleen (Zheng et al., 2014). Various arsenic species bind to haemoglobin and accumulate in the red blood cells inducing haemolysis (Lu et al., 2004). Reduced longevity of erythrocytes leads to anemia which is one of the most commonly observed symptoms in populations exposed to arsenic. Intravascular haemolysis, leukopenia, and thrombocytopenia are some of the signs of chronic arsenic exposure (Hall, 2002; Pakulska and Czerczak, 2006). Depression of bone marrow activity and megaloblastic erythropoiesis occurs occasionally due to arsenic induced toxicity (Feussner et al., 1979; Szymanska-Chabowska et al., 2002).

Immune system

Disruption of innate immunity has been spotted in both experimental animals and humans due to exposure to inorganic arsenic (Srivastava et al., 2013). There has been direct quantitative correlation between immune system suppression and arsenic exposure (Selgrade, 2007). The major targets of inorganic arsenic accumulation are tissue macrophages leading to immunotoxicity. Macrophages exposed to arsenic exhibit suppressed expression of surface antigen markers, rapidly losing their adhesion capabilities thereby affecting endocytosis and phagocytosis (Lemarie et al., 2006). Arsenic inhibits maturation of monocytes into macrophages and hence increases susceptibility towards infections (Sakurai et al., 2006). Malfunction in unfolded protein response (UPR) signalling pathway is the underlying mechanism responsible for impaired macrophage functioning (Srivastava et al., 2013). Arsenic induces a plethora of auto-immune disorders like diabetes, atherosclerosis and skin cancers of non-melanoma type (Banerjee et al., 2009). Inorganic arsenic hampers the development, activation, proliferation and function of lymphocytes (Banerjee et al., 2009; Martin-Chouly et al., 2011; Ostrosky-Wegman et

al., 1991) through increase in free radical production, raised oxidative stress, apoptosis, damage to DNA strands, modification of DNA bases, crosslinking of proteins and lipid peroxidation (Singh et al., 2013). Pregnant women exposed to arsenic showed significant reduction in placental CD+3 T cells along with decreased size and repressed function of thymus (Ahmed et al., 2014).

Arsenic induced malignancy in various organs

Carcinogenic potential of arsenic is well established (Kligerman and Tennant, 2007). It has been graded as a group-1 carcinogen by the International Agency for Research on Cancer, being capable of inducing high degree of carcinogenicity in humans (Chen et al., 2003). Arsenic exposure may lead to tumor formation in human skin (Surdu, 2014), lungs (Celik et al., 2008), urinary bladder (Radosavljević and Jakovljević, 2008), liver (Wang et al., 2014a), and prostate gland (Benbrahim-Tallaa and Waalkes, 2008). However, the precise molecular mechanisms behind arsenic mediated cancer development in various organs of the human body are still under investigation.

Epigenetic changes

Epigenetics can be defined as the study of changes brought about in the living organisms by the alteration of gene expression rather than modification of the DNA itself (Wu Ct et al, 2001). Majority of heavy metal toxicants, including arsenic, negatively affect the regulation of various epigenetic mechanisms in humans related to methylation of DNA, expression of microRNA and post-translational modifications in the histone proteins (Bailey and Fry, 2014; Marsit, 2015). There is strong evidence suggesting that epigenetic interference through gene methylation might be the potential cause of arsenic mediated cytotoxicity and carcinogenic activity (Reichard and Puga, 2010; Ren et al., 2011). A study conducted in Bangladesh has indicated positive relation between exposure to arsenic and gene specific DNA methylation of blood leukocytes (Argos et al., 2015). Long term exposure to arsenic has been linked with elongation of telomere length (Zhang et al., 2013). Various arsenic species can cross the placental barrier and hence may substantially hinder normal mechanisms of epigenetic imprinting of the foetus (Vahter, 2009). Significant downregulation of gene expression has been observed in all the three germinal layers (ectoderm, mesoderm and endoderm) of animal model embryos exposed to arsenic in-vitro, inducing severe birth defects and increased mortality rate (Flora and Mehta, 2009). Detrimental epigenetic modifications by arsenic resulted in down regulation of the expression of tumor suppressive Death-associated protein kinase 1 (DAPK1) along with tumor suppressor p16 genes, resulting in enhanced susceptibility towards arsenic mediated skin malignancy (Banerjee et al., 2013). Skin lesions due to arsenic exposure have been associated with hypermethylation of rhomboid family member 1 (RHBDF1) gene (Smeester et al., 2011).

Histopathological manifestation of arsenic cytotoxicity in animal models

Multiple researches are being carried out using animal models (primarily fish and mice) to find the molecular mechanism of arsenic-induced cytotoxicity. Arsenic exposure leads to increased oxidative stress in tissues and this seems to be the main factor for arsenic-mediated cytotoxicity in mice. Oxidative stresses are indicated in degenerative histopathological changes in various organs, especially in tissues of the kidney, liver, blood vessels, brain, etc. In an experiment, Swiss albino mice were treated with Sodium arsenite ($NaAsO_2$) dissolved in distilled water (150 mg/L/day) and served as drinking water. Control mice were given distilled water and normal mice feed. These two different groups of mice were maintained for 8 weeks (Noman et al., 2015).

The degeneration in kidney tissue of arsenic-treated mice involves significant damage to the proximal convoluted tubules, hyperplasia in the epithelium tissue of urinary bladder, significant increase in levels of BUN (Blood urea nitrogen), NAG (N-acetyl-beta-glucosaminidase) and PUA (plasma uric acid). These tests are important parameters used to monitor kidney function in people suffering from acute or chronic kidney dysfunction. Arsenic-induced peroxidation of lipids in the kidney causes severe oxidative damage to the tissue thereby leading to significant deterioration of renal function. Almost all the researches have marked the liver as a major target organ of damage caused by arsenic. The degeneration in liver tissue of arsenic treated mice involves significant necrosis of hepatic parenchyma, elevated levels of blood serum concentration

of hepatic enzymes like alkaline phosphatase (ALP), aspartate transaminase (AST) and alanine transaminase (ALT). Generation of free radical species due to oxidative stress seems to disturb the pro-oxidation and antioxidant homeostasis in the liver resulting in hepatic degeneration

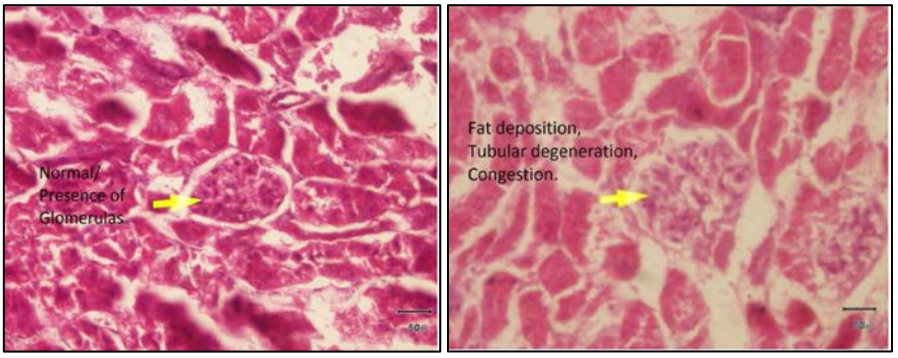

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Fig. 3. A) Photomicrograph of kidney showing normal tissue structure in control group mice; **B)** Photomicrograph of kidney indicating deposition of fat, congestion, tubular and intratubular degeneration in arsenic-treated mice (Noman et al., 2015)

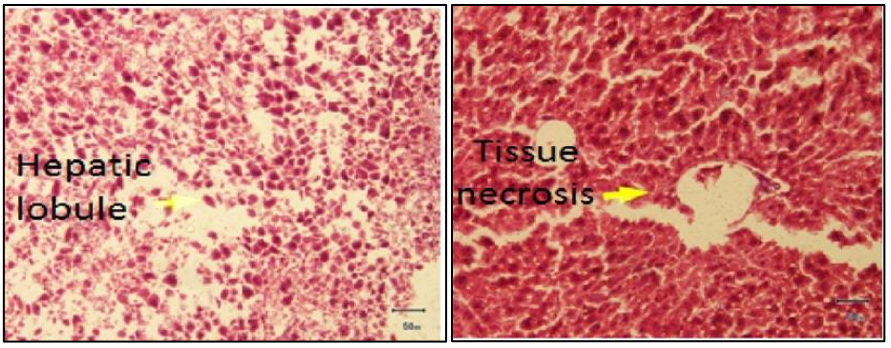

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Fig. 4. A) Photomicrograph of liver showing normal tissue structure in control group mice; **B)** Photomicrograph of liver showing significant hepatic tissue necrosis in mice treated with arsenic (Noman et al., 2015)

In another experiment, Female Wistar albino rats were administered 50 ppm Sodium arsenite ($NaAsO_2$) dissolved in drinking water. Control rats were served normal distilled water. These two groups were maintained for 90 days and then euthanized (Al-Forkan et al. 2016). Though there was no mortality, cellular edema, localised tissue necrosis and monocyte inflammatory cell infiltration was observed in kidney, liver, spleen and heart tissues of more than half of the arsenic exposed rats.

Prevention

As it's nearly impossible to totally eliminate arsenic contamination from our environment, water and food resources, so prevention seems the most likely cure. In areas affected by high levels of arsenic contamination in groundwater sources, it is recommended to harvest rainwater and use it for drinking purposes after appropriate filtration. Several studies have found direct corelation between state of malnourishment and severity of arsenic mediated cytotoxicity. In such cases, consumption of good quality balanced diet especially rich in proteins, vitamins and anti-oxidants along with clean, potable drinking water is advised. The most significant remedial measure for the people already suffering from arsenicosis is to immediately block the route of further arsenic exposure, whether through skin, inhalation or oral consumption. Creating awareness among the masses about the clinical symptoms and seeking immediate medical assistance can go a long way to check the spread of arsenic toxicity at community level.

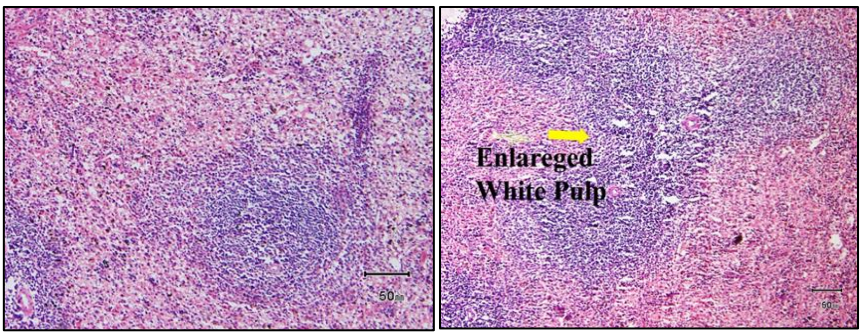

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Fig. 5. A) Photomicrograph of spleen showing normal tissue structure in control group mice; **B)** Photomicrograph of spleen showing enlarged white pulp area in mice treated with arsenic (Al-Forkan et al., 2016)

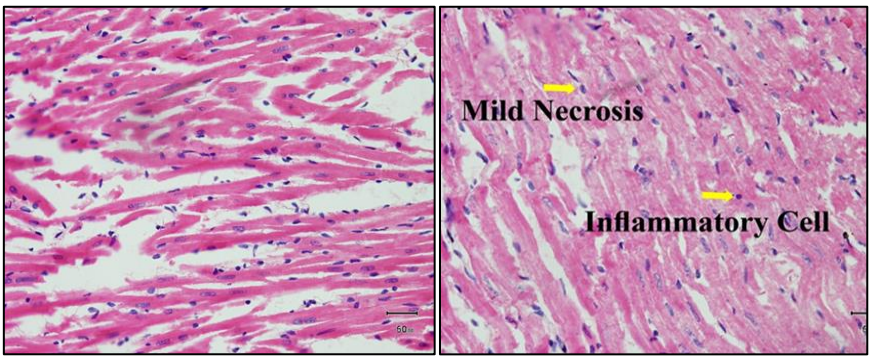

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Fig. 6. A) Photomicrograph of heart showing normal cardiac tissue structure in control group mice; **B)** Photomicrograph of heart showing mild to moderate necrosis of cardiac tissue and presence of inflammatory leucocyte cells in arsenic-treated mice (Al-Forkan et al., 2016)

Treatment

Increased oxidative stress in the tissues by generation of free radicle reactive species is the main mechanism behind arsenic mediated cytotoxicity. Therefore, both natural and synthetic compounds, which have anti-oxidant properties, can help to reduce the oxidative stress and can be used for the treatment.

Some of the medicinal plants having very high potential for treatment of arsenic toxicity are *Allium sativum* (Mehrandish et al., 2019), *Curcuma longa* (Adegboyega et al., 2012), *Silybum marianum, Ocimum sanctum* leaf extract (Sharmila Banu et al., 2009), *Mentha piperita* leaf extract (Sharma et al., 2007), *Moringa oleifera* leaf extract (Sheikh et al., 2014) and *Camellia sinensis* (green tea) (Acharyya et al., 2014). Algae *Spirulina* fortified with Vitamin A has been found to be very effective in successfully eliminating arsenic from the body of goats (Ghosh et al., 2014).

Selenium (Se) has been found to have tremendous potential for mitigation of arsenic toxicity because of its high antioxidant properties (Krohn et al., 2016). Consumption of selenium rich foods in the diet resulted in increased rate of excretion of arsenic through urine, thereby offering significant relief in chronic cases of arsenic led poisoning (Smits et al., 2019). Zinc (Zn) is also being widely used in chelation therapy to counter the arsenic mediated cytotoxicity (Chasapis et al., 2020). Zinc inhibits the teratogenic activity of arsenic by suppressing the formation of reactive free radicals, thereby reducing the oxidative stress in the tissues and reinstating the equilibrium of antioxidants (Nasiry et al., 2017).

Gaps and Future Perspectives

Despite the fact that near about 100 million people across the world are affected by it, the genesis of arsenic pollution has not been fully understood yet. The problem becomes worse by the fact

that there is no set protocol or specific mode of action for dealing with the spread of chronic arsenic toxicity. The future course of action to mitigate the harmful effects of arsenic poisoning relies on sensitization of general public as well as that of administrative authorities. There is a pressing need to identify geographical areas having excessive arsenic concentration, followed by effective legislations and regular monitoring to check the spread of arsenic pollution beyond those areas. Various national and international agencies need to come forward, provide collaboration and funding to encourage research for developing effective strategies to check arsenic pollution.

Conclusion

Increasing arsenic contamination of the environment, drinking water and food is an alarming issue. The practical difficulties involved in removal of arsenic from water and food resources along with its widespread side-effects on human health has made this to be a problem of massive concern. Almost all human organ systems, functions and cellular processes are affected by arsenic toxicity. This review finds the generation of oxidative stress in multiple body organs as the major cause of arsenic induced cytotoxicity, as reported by various studies. The integumentary system shows the primary clinical signs in the form of lesions and hyperpigmentation. As determined by various histopathological studies, liver, kidney and nervous tissue exhibit high degree of damage in the form of elevated tissue necrosis and apoptosis. Arsenic has a detrimental effect on reproductive organs and hampers foetal growth. Disruptions of endocrinal secretions and suppression of immune system activity by arsenic mediated cytotoxicity has also been clearly indicated in various studies. The precise mechanisms behind carcinogenic activity and epigenetic effects induced by various arsenic species need further research and detailed investigation. Prevention against exposure to arsenic in any form, along with adequate supply of balanced diet and clean drinking water is the best way forward to check the spread of arsenicosis. Chelation therapy using zinc, selenium and use of medicinal plants having antioxidant properties are the main treatment approaches for affected individuals. Further advanced investigations and researches are required to identify the precise molecular mechanisms behind arsenic induced toxicity including malignancy in multiple human organs.

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