DOI: https://doi.org/10.53555/nnpbs.v8i5.1305 Publication URL: https://nnpub.org/index.php/PBS/article/view/1305

A REVIEW ON ARSENIC TOXICITY AND ITS EFFECTS ON HUMAN HEALTH

Deep Sharma[1*], Varun Sharma[2],Hema Rani[3], Aashish Sharma[4]
[1,2,3]*Department of Pharmaceutical Sciences, DDM College of Pharmacy, Una-174303, INDIA*
[4]*Department of Pharmaceutical Sciences, IEC University, Baddi-174102, INDIA*

***Corresponding Author*:**
E-mail: deeppharma86@gmail.com

Abstract
Arsenic is a pollutant in the environment, and its poisoning of drinking water is considered a severe global health issue. It has been established that inorganic arsenic is extremely toxic, both acute and chronic. It enters in human body ingestion, inhalation, or skin absorption. After entering into the body it is distributed to large number of organs and increases the risk of a variety of diseases, including cardiovascular abnormalities, hepatotoxicity, neurotoxicity, and nephrotoxicity. Furthermore, only a few studies have shown that persistent exposure to arsenic causes carcinogenesis, particularly cancers of the skin, bladder, and lungs. It is very difficult to diagnose early symptoms of arsenicosis because such nonspecific symptoms may also be present in many other diseases. The current study looks at a variety of processes that play a role in arsenic- induced toxicity and end-organ damage.

Keywords: *Arsenic, arsenicosis, toxicity.*

1. Introduction

Arsenic is a naturally occurring metalloid, which means it has both metal and non-metal properties; it is commonly referred to as a heavy metal. Arsenic comes in a variety of forms known as allotropes. It is found in more than 245 minerals and is the twentieth most abundant element in the earth's crust. Human health is endangered by the inorganic forms, which mostly consist of arsenite (As III) and arsenate (As V) chemicals. Grey arsenic is the most common and widely used of the three arsenic allotropes, which include metallic grey, yellow and black arsenic. Arsenic is a common element that may be found in the earth's crust, saltwater and the human body. It makes up around five hundredths of one percent (0.00005 percent) of the earth's crust. It is divided into two species: arsenate and arsenite. Arsenite is far more flammable, soluble, and mobile than As (V).[1]Chronic arsenic toxicity is associated with various clinical manifestations called arsenicosis. Arsenicosis leads to cardiovascular dysfunction, neurotoxicity, nephrotoxicity, hepatotoxicity and carcinogenicity in human being.

1.1. Occurrence

Arsenic is found in the range of 1.5–3 mg/kg in the environment. Arsenic is found in the environment as a result of both natural and man-made sources. Arsenic is a naturally occurring element present in the earth's crust, soil, water, air, and plants and animals. Some agricultural and industrial sources might also discharge it into the environment. Arsenite concentrations in drinking water range from 0.01 to 3.7 mg/l (1.3–49 M). According to anthropogenic sources, arsenic can be obtained through man-made sources in a variety of products with China, the Soviet Union, France, Mexico, Germany, Peru, Namibia, Sweden, and the United States accounting for about 90% of global production. According to WHO recommendations, arsenic has a safety limit of 10 g/l and a maximum acceptable value of 50 g/l in drinking water. [2]

1.2. Uses of arsenic

Insecticides and pesticides containing arsenic were widely utilized over the world. Sodium arsenite and other inorganic arsenic compounds have traditionally been employed as non-selective soil sterilants to destroy weeds. Arsenic is also employed as desiccants and wood preservatives, in addition to insecticides and herbicides.[3,4] Arsenic compounds are also utilized to treat a variety of ailments. Arsenic has a long history of being used by peasants for skin cleanliness, suppleness, and other cosmetic advantages. It was also used to help those with breathing problems.[5,6] Fowler's solution (potassium arsenite), Donovan's solution (arsenic and mercuric iodides), Asiatic pills (arsenic trioxide and black pepper), de Valagin's solution (liquor arsenii chloridi), sodium cacodylate, arsphenamine (Salvarsan), neoarsphenamine, oxophenarsine hydrochloride (Mapharsen), arsthinol (Balarsen), acetarsone, tryparsamide and carbarsone are the most common medicinal preparations containing arsenic.[7]Despite the fact that it is only used for a few medical purposes, Arsenic is a well-known toxin that has a number of negative effects on physical and mental health.[8]

1.3. Exposure

Arsenic is a potent toxicant and its abundance in many natural forms makes it quite frequent to be exposed to it. As a result, the opportunity for arsenic toxicity research is immense. Arsenic is typically absorbed by eating and inhalation. Another secondary way of exposure is through the skin or dermal exposure. Humans can be exposed to arsenic through ingesting arsenic-laced food or drinking arsenic-laced water. Inhalation exposure can also occur through emissions from arsenic-containing fossil fuels, cotton gins, glass manufacturing operations, pesticide production facilities, smelters, and cigarette smoke. When working with preserved wood that has been treated with arsenic compounds, it is possible to get arsenic poisoning through the skin. [9]

1.4. Arsenic toxicity

Arsenic toxicity in the body depends on its chemical forms and oxidative stress as well as the physical state, absorption rate into the cells and its elimination rate, the nature of chemical substituents in toxic compounds etc. A number of studies have shown that when compared among the inorganic arsenic compounds and organic arsenic compounds, the inorganic ones are more toxic and the inorganic AsIII is more toxic than inorganic AsV.[10] The toxicity order of arsenic compounds may be depicted as Arsines > iAsIII > arsenoxides(org AsIII) > iAsV > arsonium compounds > As [11,12]

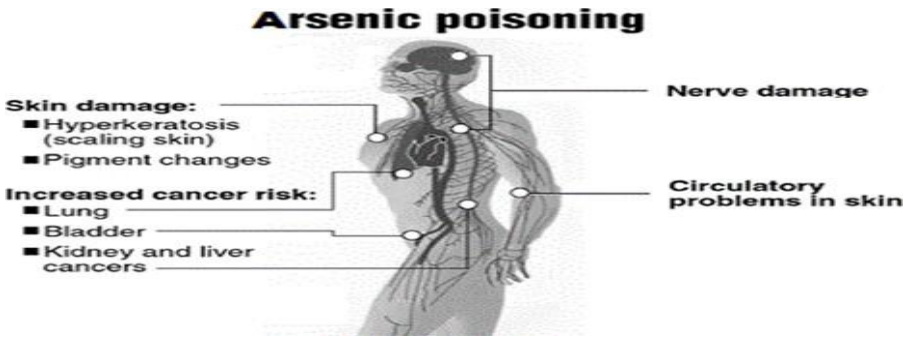

Fig. 1: Effect of arsenic on various body parts [12]

Overexposure to arsenic leads to a number of adverse physiological effects which include respiratory effects like laryngitis, tracheae bronchitis, rhinitis, pharyngitis, shortness of breath, chest sounds, nasal congestion and perforation of the nasal septum, [13] Cardiovascular effects like Raynaud's disease, myocardial infarction, myocardial depolarization, cardiac arrhythmias, thickening of blood vessels and their occlusion , Hematological effects like Anemia and leukopenia, gastrointestinal effects heartburn, nausea, abdominal pains and cramps, and moderate diarrhea, mild esophagitis, gastritis, or colitis with respective upper and lower abdominal discomfort[14], Renal effects like Proximal tubule degeneration, hematuria and proteinuria, [15] oliguria, shock and dehydration with a real risk of renal failure, [16] cortical necrosis and cancer.

1.5. Toxicokinetics

1.5.1 Absorption

90% absorption of ingested arsenic takes place through the gastrointestinal tract, wherein the major site of absorption is the small intestine. This absorption takes place through an electrogenic process involving a proton (H+) gradient.[17] The optimum pH required for the absorption of Arsenic is 5, although the pH in the small intestine is approximately 7.0 due to the presence of pancreatic bicarbonate secretions.[18]

1.5.2 Distribution

The bio availability of ingested inorganic arsenic varies depending on the matrix in which it is ingested (i.e. be it food, water, beverages or soil), the solubility of the arsenical compound itself and the presence of other food constituents and nutrients in the gastrointestinal tract. Tissue distributions of arsenic depend on blood perfusion, tissue volumes, diffusion coefficients, membrane characteristics, and tissue affinities.[19]

1.5.3 Metabolism & elimination

The absorbed arsenic undergoes methylation reaction in the liver. The methylation process is mediated by arsenic methyltransferase enzymes to form monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). DMA is the dominant metabolite according to many studies, while in human the urinary excretion consists under normal conditions, i.e. without excessive ingestion of inorganic arsenic of about 20% inorganic arsenic, 20% MMA and 60% DMA.

2. Organs toxicity

2.1 Arsenic induced cardiovascular dysfunction

Long-term exposure to inorganic arsenic may cause various cardiovascular disorders such as atherosclerosis, hypertension, ischemic heart diseases, and ventricular arrhythmias. Arsenite stimulates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase present in the plasma membrane of vascular endothelial cells and vascular smooth muscle cells (VSMC) to increase the generation of reactive oxygen species (ROS) such as superoxides and hydrogen peroxide. ROS generated during arsenite exposure couples with nitric oxide (NO) to form peroxynitrite, a strong oxidant implicated in the up regulation of inflammatory mediator such as cyclooxygenase-2.[21]ROS generated during arsenite exposure increases the expression of atherosclerosis related genes such as hemeoxygenase-1 (HO-1), monocyte chemo-attractant protein (MCP-1), and interleukin-6 (IL-6) and thus its exposure promotes the attachment, penetration, and migration of monocytes in VSMC. Arsenic alters focal adhesion proteins in VSMCs leading to their proliferation and migration. Further, arsenic increases the synthesis of inflammatory mediators such as leukotriene E_4 (LTE_4) and prostacyclin, tumor necrosis factor-alpha and nuclear factor kappa B in vascular endothelial cells to induce the pathogenic process of atherosclerosis.[22] Moreover, arsenic causes neurogenic inflammation of the blood vessel by increasing the release of substance P and endothelial neurokinin-1. Furthermore, arsenic activates protein kinase C alpha, which causes phosphorylation of beta-catenin and thus reverses the association between vascular endothelial cadherin and beta-catenin, along with the formation of actin stress fibers resulting in increased intercellular gap formation and permeability of the endothelium. Arsenite has been reported to decrease the activity of endothelial nitric oxide synthase (eNOS) and Akt/protein kinase B, which subsequently decreases the bioavailability of NO that may lead to vascular endothelial dysfunction and associated cardiovascular complications. Arsenite mediates vasoconstriction of the blood vessels by phosphorylating myosin light chain kinase (MLCK) and increases calcium sensitization leading to hypertension. Chronic exposure to arsenic induces oxidative stress and alters the release of vasoactive mediators in blood vessel leading to elevation of blood pressure. Arsenic trioxide develops ventricular

arrhythmia by inducing prolonged Q-T interval and action potential duration. Taken together, it may be suggested that arsenic induces cardiovascular dysfunction by inducing high oxidative stress, reducing the activation of eNOS and enhancing the phosphorylation of MLCK, which may be targeted for preventing arsenic exposure-associated cardiovascular complications [Fig.2]. Recently, a couple of studies from our laboratory demonstrated that treatment with either bis-(maltolato) oxovanadium, an inhibitor of protein tyrosine phosphatase, or rosiglitazone, an agonist of peroxisome proliferator activated receptor-gamma (PPAR-γ) markedly ameliorated sodium arsenite-induced vascular endothelial dysfunction in rats by enhancing the integrity of vascular endothelium, improving endothelium-dependent relaxation and reducing oxidative stress.[23]

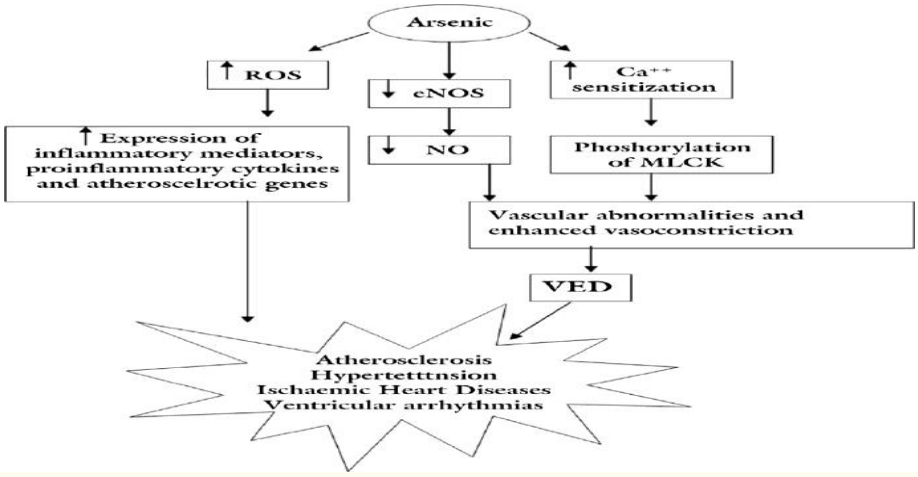

Fig.2: Pathological mechanisms involved in arsenic-induced cardiovascular dysfunction

2.2 ***ARSENITE-INDUCED NEUROTOXICITY***

Brain is a soft target for arsenic toxicity as it freely crosses blood-brain barrier. Arsenic exposure is associated with wide range of neurological complications in humans such as impaired memory, poor concentration, Parkinson's disease, Guillain-Barre like neuropathy, verbal comprehension, encephalopathy, and peripheral neuropathy.[24,25] The mechanism postulated for arsenic-induced neurotoxicity majorly involve oxidative stress with increased reactive oxygen species, lipid peroxides along with decrease in superoxide dismutase, and reduced glutathione levels. Arsenic exposure has been reported to alter metabolism of various neurotransmitters such as monoamines, acetylcholine, gamma amino butyric acid, and glutamate. In a recent study, a significant reduction in monoamines such as adrenaline, nor-adrenaline, dopamine, and serotonin has been observed in corpus striatum, frontal cortex, and hippocampus areas of brain on chronic arsenic exposure. Arsenite mediated neurotoxicity involves induction of apoptosis in the cerebral neurons by activating p38 mitogen-activated protein kinase (p38MAPK) and JNK3 pathways.[26] Moreover, arsenic exposure induces neurotoxicity by causing destabilization and disruption of cytoskeletal framework, eventually leading to axonal degeneration. The deficiency of thiamine (vitamin B1) is well known to induce neuronal complications. It is worthwhile to note that arsenic causes thiamine deficiency and inhibits pyruvate decarboxylase, which elevates blood pyruvate and hence causes encephalopathy. Arsenic-induced oxidative stress in the brain causes oxidative DNA damage and subsequent brain cell death and induces the degeneration of dopaminergic neurons resulting in Parkinson like symptoms. Acute arsenic toxicity decreases acetyl cholinesterase activity and hence causes cholinergic crisis like situation with altered mental status and weakness, which can be associated with peripheral neuropathy, neuropsychiatric abnormalities, and extrapyramidal disorders.[27] Moreover, arsenic affects the peripheral nervous system by disrupting the neuroskeletal integrity and thus markedly diminishes the nerve conduction velocity in the peripheral nerves to cause peripheral neuropathy. The exposure to arsenic and its metabolites monomethylarsonic acid and monomethylarsonous acid suppresses the NMDA receptors in hippocampus, which play a pivotal role in synaptic plasticity, learning, and memory, leading to neurobehavioral disorders and cognitive dysfunction. The chronic arsenic exposure is associated with morphological changes in axons and nerve fibres of the striatum which disturbs central structural organization. Hence, oxidative stress, induction of thiamine deficiency, and inhibitions of pyruvate decarboxylase, acetyl cholinesterase, reduction in biogenic monoamines seem to play a pivotal role in arsenic-induced neurotoxicity [Fig.3]. The animal models of arsenic toxicity are associated with inconsistent neurotoxicity because of varying doses, duration, and different salts of arsenic used in various studies. However, these have been able to provide deep insight into pathophysiological mechanisms involved in arsenic induced neurotoxicity.

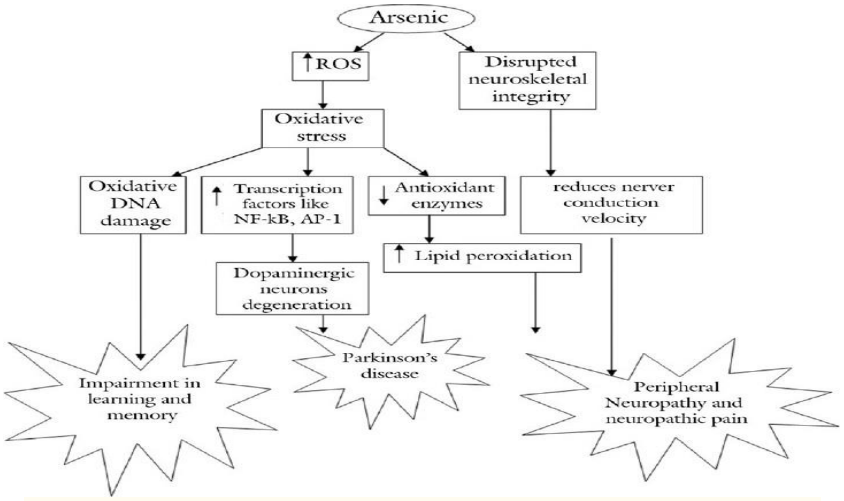

Fig.3: Pathological mechanisms involved in arsenic-induced neurotoxicity

2.3 ARSENIC-INDUCED NEPHROTOXICITY AND HEPATOTOXICITY

Arsenic concentrates in the kidney during its urinary elimination that affects the function of proximal convoluted tubules.[28] Arsenic-induced oxidative stress increases the expression of HO-1 and MAPK, which by regulating various transcription factors such as activator protein-1 (AP-1), activating transcription factor-2 (ATF-2), and Elk-1 lead to renal toxicity. Acute renal dysfunction due to arsenic exposure is characterized by acute tubular necrosis and cast formation with increase in blood urea nitrogen and creatinine levels. This arsenic-induced renal toxicity can be attenuated by *Curcuma aromatica* and *Corchorus olitorius*.[29] The kidney and liver are the primary targets for arsenic-induced toxicity, where the highest level of arsenic is detected in the liver than kidney. Arsenite increases the generation of ROS, which enhances lipid peroxidation and cellular damage in both hepatic and renal tissue. Chronic arsenic-mediated oxidative stress activates JNK and p38 MAPK and induces apoptosis in the hepatocytes. Further, arsenic-induced oxidative stress induces hepatic apoptosis by up regulation of pro-apoptotic proteins. A recent study has well documented that arsenite-induced apoptotic progression is aggravated by folate deficiency. Arsenic exposure leads to the incidence of hepatotoxicity as manifested by increase in the levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, and malionaldehyde. Hence, oxidative stress, apoptosis, and up regulation of transcription factors such as AP-1, ATF-2, and Elk-1 are the prospective target sites for arsenite-induced nephrotoxicity and hepatotoxicity [Fig.4].

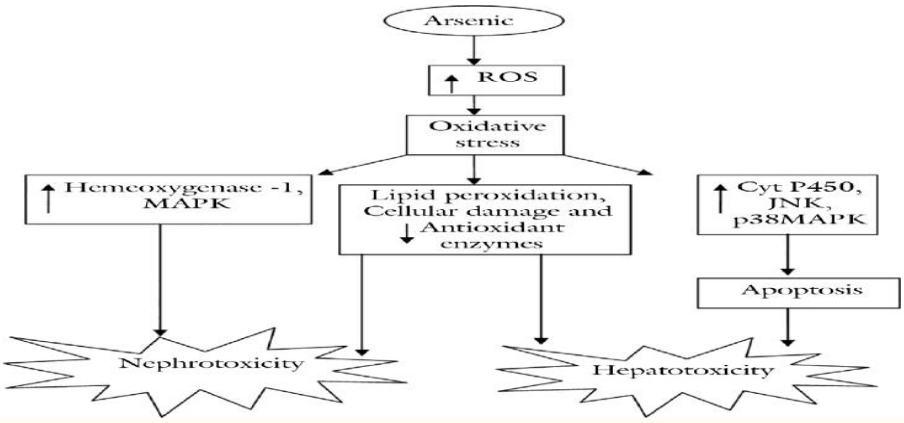

Fig.4: Pathological mechanisms involved in arsenic-induced hepatotoxicity and nephrotoxicity

2.4 Arsenic-induced carcinogenicity

The trivalent form of arsenic exhibits greater genotoxic effects than the pentavalent counterparts as it could be easily taken up by the cells. Although the exact molecular mechanism of arsenic carcinogenicity is not well understood, arsenic has been shown to possess tumor-promoting properties by inducing intracellular signal transduction, activating transcription factors, and changing the expression of genes that are involved in cell growth, proliferation, and malignant transformation. Further, it is has been postulated that arsenic induces MAPK signal transduction, which activates transcription factors such as AP-1 and NF-kB to alter various gene expression profile that may account for the induction of arsenic-associated carcinogenicity. Arsenic causes focal adhesion kinase activation, which mediates several downstream signaling pathways such as integrin, Src, Rho, Grb2, EGFR, ERK, and cadherins. These pathways are involved in cell adhesion, cell migration, cell survival, cell cycle control, carcinogenesis, and tumor cell necrosis.[30] DMA(V) and TMAO(V) generate oxidative stress and cause an elevation of 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage, which stimulates cell proliferation and induces carcinogenicity. Arsenic provokes proliferation of bladder epithelial cells and up regulates proto-oncogene expression such as c-fos, c-jun, and EGR-1, which may

collectively contribute to bladder cancer. Smoking has been shown to potentiate the effect of arsenic on the risk of bladder and lung cancer because both can act synergistically to cause DNA damage.[31] Arsenic induces skin cancer by acting synergistically with sunlight and blocking DNA repair, stimulating angiogenesis, altering DNA methylation patterns, dysregulating cell cycle control, and blocking physiological apoptosis. Oxidative stress seems to be the main culprit for arsenic-induced carcinogenicity, which can be prevented by antioxidants such as vitamin E, melatonin, and curcumin.[32] Taken together; various possible modes of carcinogenic action of arsenic proposed till date are increased oxidative stress, direct genotoxic effects, altered expression of growth factors, and altered DNA repairing mechanisms [Fig.5]

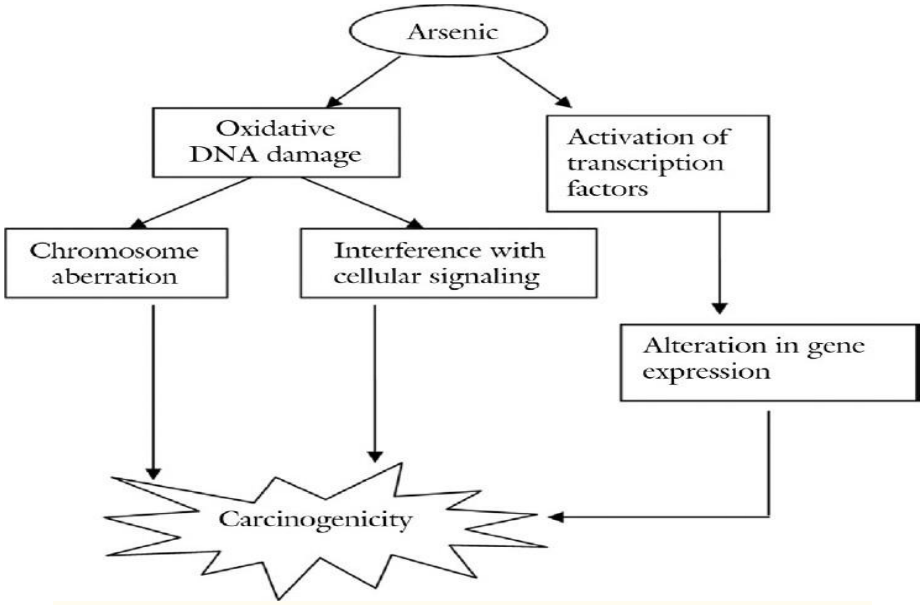

Fig.5: Pathological mechanisms involved in arsenic-induced carcinogenicity

Conclusion

The chronic exposure to arsenic through contaminated water may account for various poor health conditions. Arsenic increases oxidative stress, up regulates proinflammatory cytokines and inflammatory mediators, inactivates eNOS, and causes phosphorylation of MLCK to induce cardiovascular abnormalities. Further oxidative stress, inhibition of pyruvate decarboxylase, and acetyl cholinesterase seem to play a significant role in arsenic-induced neurotoxicity. Furthermore, arsenic induces nephrotoxicity and hepatotoxicity by increasing oxidative stress and apoptosis. In addition, arsenic exposure may cause carcinogenicity as it increases oxidative DNA damage and chromosomal aberration and interferes with cellular signaling pathways. Targeting and modulating the prior mentioned key pathological signaling mechanisms may provide novel pharmacological interventions to halt arsenic exposure-associated disorders.

REFERENCE

[1] Jomova K. Arsenic: toxicity, oxidative stress and human disease. *J Appl Toxicol*. 2011;31(2):95–107. doi:10.1002/jat.1649.
[2] On Chemical Safety IP. WHO: Environmental Health Criteria 224-Arsenic. International Programme on Chemical Safety, Geneva. 2001; Available from: https://apps.who.int/iris/handle/10665/42366.
[3] Mandal BK, Suzuki KT. Arsenic round the world: a review. *Talanta*. 2002;58(1):201–21.
[4] Arsenic-Eaters. *Boston Med Surg J*. 1854;51:189.
[5] Sollman T. A Manual of Pharmacology. *J Am Pharm Assoc*. 1957;37(3):131. doi:10.1002/jps.3030370320.
[6] Burger A. Medicinal Chemistry; 1970; 610–625.
[7] Sullivan RJ. Administration Publication No. APTD 69-26; 1969. Available from: https://www.govinfo.gov/content/pkg/FR-1990-06- 25/pdf/FR-1990-06-25.pdf.
[8] United Nations Synthesis Report on Arsenic in Drinking Water; 2001. Available from: https://www.ircwash.org/resources/united- nations-synthesis-report-arsenic-drinking-water.
[9] Maeda S. Arsenic in the Environment; 1994;155–187.
[10] Whitacre RW, Pearse CS. Arsenic and the Environment; 1972.
[11] Hindmarsh JT, McCurdy RF. Clinical and environmental aspects of arsenic toxicity. *Crit Rev Clin Lab Sci*. 1985;23(4):315–347. doi:10.3109/10408368609167122.
[12] Nagvi SM, Vaishnavi C, Singh H. Toxicity and metabolism of arsenic in vertebrates. vol. 2; 1994;55–91.
[13] Clarkson TW. Inorganic and organometal pesticides; 1991;545–552.
[14] Giberson A. Hemodialysis of acute arsenic intoxication with transient renal failure. *Arch Intern Med*. 1976;136
[15] Gerhardt RE. Chronic renal insufficiency from cortical necrosis induced by arsenic poisoning. *Arch Intern Med*. 1978;138.
[16] Rich CH, Biggs ML, Smith AH. Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. *IntJ Epidemiol*. 1998;561–569. doi:10.1093/ije/27.4.561.
[17] Gerhardt RE. Chronic renal insufficiency from cortical necrosis induced by arsenic poisoning. *Arch Intern Med*. 1978;1267– 1269.
[18] Piao F, Ma N, Hiraku Y, Murata M, Oikawa S, Cheng F, et al. Oxidative DNA damage in relation to neurotoxicity in the brain of mice exposed to arsenic at environmentally relevant levels. *J Occup Health.* 2005;445–449.
[19] Yip SF, Yeung YM, Tsui EY. Severe neurotoxicity following arsenic therapy for acute promyelocytic leukemia: potentiation by thiamine deficiency. *Blood.* 2002;3481–3482.
[20] Yip SF, Yeung YM, Tsui EY. Severe neurotoxicity following arsenic therapy for acute promyelocytic leukemia: potentiation by thiamine deficiency. *Blood.* 2002;3481–3482.
[21] Hansen ES. International Commission for Protection against Environmental Mutagens and Carcinogens. ICPEMC Working Paper 7/1/2. Shared risk factors for cancer and atherosclerosis-a review of the epidemiological evidence. *Mutat Res.* 1990;163–179.
[22] Bunderson M, Coffin JD, Beall HD. Arsenic induces peroxynitrite generation and cyclooxygenase-2 protein expression in aortic endothelial cells: possible role in atherosclerosis. *Toxicol Appl Pharmacol.* 2002;11–18.
[23] Pereira FE, Coffin JD, Beall HD. Activation of protein kinase C and disruption of endothelial monolayer integrity by sodium arsenite-Potential mechanism in the development of atherosclerosis. *Toxicol Appl Pharmacol.* 2007;164–177.
[24] Jindal S, Singh M, Balakumar P. Effect of bis (maltolato) oxovanadium (BMOV) in uric acid and sodium arsenite-induced vascular endothelial dysfunction in rats. *Int J Cardiol.* 2008;383–391.
[25] Piao F, Ma N, Hiraku Y, Murata M, Oikawa S, Cheng F, et al. Oxidative DNA damage in relation to neurotoxicity in the brain of mice exposed to arsenic at environmentally relevant levels. *J Occup Health.* 2005;445–449.
[26] Felix K, Manna SK, Wise K, Barr J, Ramesh GT. Low levels of arsenite activates nuclear factor-kappaB and activator protein-1 in immortalized mesencephalic cells. *J Biochem Mol Toxicol.* 2005;67–77.
[27] Namgung U, Xia Z. Arsenic induces apoptosis in rat cerebellar neurons via activation of JNK3 and p38 MAP kinases. *Toxicol Appl Pharmacol.* 2001;130–138.
[28] Patlolla AK, Tchounwou PB. Serum acetyl cholinesterase as a biomarker of arsenic induced neurotoxicity in sprague-dawley rats. *Int J Environ Res Public Health.* 2005;80–83.
[29] Burton CA, Hatlelid K, Divine K, Carter DE, Fernando Q, Brendel K, et al. Glutathione effects on toxicity and uptake of mercuric chloride and sodium arsenite in rabbit renal cortical slices. *Environ Health Perspect.* 1995;81–84.
[30]. Das AK, Bag S, Sahu R, Dua TK, Sinha MK, Gangopadhyay M, et al. Protective effect of *Corchorus olitorius* leaves on sodium arsenite-induced toxicity in experimental rats. *Food Chem Toxicol.* 2010;326–335.
[31] Liu J, Waalkes M. Focal adhesion kinase as a potential target in arsenic toxicity. *Toxicol Sci.* 2005;212–213.
[32] Bates MN, Smith AH, Cantor KP. Case-control study of bladder cancer and arsenic in drinking water. *Am J Epidemiol.* 1995;523–530.