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Editorial

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Challenges in the field of toxicity of metals in India including the development of new treatment

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Emerging occupational and environmental health problems are currently major priorities that need to be tackled along with existing traditional public health problems like communicable diseases, malnutrition, poor environmental sanitation, and inadequate medical facilities. Although toxicologists have expressed deep concern and have prioritized these issues, public awareness, toxicological databases, suitable early diagnosis, specific preventive and therapeutic measures are some of the major issues which requires major attention. Among various strategies which may address these issues include use of modern technologies, amenities, and resources for detecting toxic substances or their derivatives at nanogram (ng) levels.These steps will be important to specifically quantify various toxicants and facilitate future research in order to (i) safe and specific therapeutic or preventive measures and (ii) early diagnosis/ biomarkers to examine effects at the molecular level. It has recently been realized that most of the diseases related to toxicants are incurable; therefore, the best course of action in dealing with them is prevention (Flora, 2008).

Heavy metal induced toxicity and its associated complications have become a major issue in the medical world. Heavy metals accumulation in the environment and their associated health hazards still need to be extensively studied as there are many unanswered questions like early diagnosis and specific treatment particularly in case of chronic exposure. Exposure to heavy metals (like lead, cadmium and mercury) or metalloids like arsenic come from a variety of sources, including gasoline, fertilizers, paints, sewage sludge, ground water, wastewater irrigation, pesticides, coal burning residues, domestic and industrial effluents, and petrochemicals. Heavy metals are characteristic representatives of toxic substances which are not biodegradable, enter the food chain, and accumulate in living systems. Increased concentrations and accumulation of Heavy metals can cause severely damaging effects and associated complications in living organisms and can even lead to the death of the organism. Heavy metals toxicity generally lessens energy levels and can severely damage and decrease the function of the brain, kidney, lungs, and liver. Frequent and continuous exposure to heavy metals or metalloids leads to physical, muscular, and neurological degeneration, emulating disorders such as Parkinson's disease, Alzheimer's disease, Wilson's disease, muscular dystrophy, and multiple sclerosis etc. Exposure to lead toxicity causes ionic and oxidative stress conditions in living organisms, occurring due to an imbalance in free radical production and antioxidant levels which normally neutralize or detoxify the reactive intermediates. Antioxidants can protect against free radical mediated damage, providing its reducing equivalents from sulphur groups of cysteine to reactive oxygen species (ROS) and making them stable (Flora *et al.*, 2013). Elevated levels of ROS damages the cells and cellular components, which results in a harassed condition at the cellular level. The ionic mechanism of lead or arsenic toxicity also causes substantial deviations in apoptosis, ionic transportation, cell adhesion, inter- and intra-cellular signalling, protein folding and maturation, the release of neurotransmitters, and enzyme regulation (Pachauri *et al.,* 2013).

Arsenic contamination in ground water in the Ganga-Brahmaputra fluvial plains in India and Padma-Meghna fluvial plains in Bangladesh has been found to have a huge impact on human health and its consequences have been reported as the world's biggest natural ground water calamities (Flora, 2011). In India, West Bengal, Jharkhand, Bihar, Uttar Pradesh in the flood plains of the Ganga, Assam and Manipur in the flood plains of the Brahmaputra and Imphal rivers Rajnandgaon village in Chattisgarh state have been reported to be affected by arsenic contamination in ground water (National Rural Drinking Water Program, 2013); The maximum permissible limit of arsenic recommend by WHO in potable safe drinking water is 0.01 mg l^{-1}; however, in India the acceptable level is 0.05 mg l^{-1} due to the absence of potable drinking water. Subsequent to its high level in drinking water arsenic gains it's entry in our body, leading to chronic multi system disorder known as arsenicosis.

The scope of arsenic contamination of drinking water, and the threat it poses to global health, is much more widespread than previously believed. As many as 140 million people worldwide may have been exposed to drinking water with arsenic contamination levels higher than the World Health Organization's (WHO) provisional guideline of 10 μg l^{-1}. Arsenic poisoning is worst in Bangladesh, where an estimated 35-77 million people are at risk from drinking groundwater contaminated by naturally-occurring arsenic. Another 6 million are at risk in West Bengal, India. However, numerous cases have now been reported from China, Chile, Cambodia, Laos, Burma, Pakistan, Nepal, Vietnam, Taiwan, Iran, Argentina, Finland, the United States and several other Indian States. Groundwater in Australia are also known to be contaminated with arsenic, and the landscape contains 'hot spots' from its former widespread use as an insecticide to protect livestock and crops nearly a century ago. Researchers are currently working to understand the pathology and various approaches for the management of arsenic poisoning worldwide. However, there are very few studies currently being done or in progress as far management of arsenic poisoning are concerned. With all the available literature it has been proved that arsenic is a potent toxic substance for which safe and specific counter measures are required to overcome its poisoning. Chelation therapy has been suggested treatment of arsenic poisoning (Flora and Pachauri, 2010). Several chelating drugs have been studied to understand the chelation of arsenic but they have been compromised with shortcomings/ limitation. These drugs include British anti-lewisite (BAL): It is a lipophilic drug which can be distributed both intra and extracelluarly. It has been used since World War II. It contains two sulfhydryl groups to form a stable non-toxic five membered ring with arsenic. Due to its instability and ability to oxidize soon it is difficult to store. One of its major drawbacks is the significant elevation of brain lead and arsenic level due its rapid mobilization. Other shortcomings include allergic conditions, extremely painful intramuscular injection. D-Penicillamine - It is a penicillin degrading product which has been used as a chelator (particularly against lead and copper) since long. It has the ability to chelate arsenic too. Studies have found that it is effective against acute arsenic toxicity. It also possesses many adverse effects such as nausea, vomiting, hematuria, rashes etc. which has led to the development of thiol chelators such as DMSA and DMPS. Meso-2, 3-Dimercaptosuccinic Acid (Succimer, DMSA): It is an orally active and less toxic analogue of dimercaprol. Its major drawback has been its extracellular distribution which makes it incapable to remove arsenic from its intracellular sites. Other side effect includes skin reaction, elevated liver enzymes, gastrointestinal discomfort etc., 2, 3-Dimercaptopropane-1-Sulfonic Acid (DMPS): It is a sodium salt of 2, 3 dimercaptopropane-1-sulfonic acid, and a derivative of BAL. DMPS is water soluble. DMPS has a highly specific effect on MMA metabolism or urinary excretion in humans, although the mechanism by which DMPS reduces arsenic burden is not fully established. Minor symptoms like headache, fatigue, nausea, taste impairment, pruritus, and rash have been observed due to it.

The side effects or shortcomings associated with conventional chelating drugs have led researchers to develop less toxic analogue. Hydrophilic chelators like meso-2, 3-dimercapto succinic acid effectively promote renal metal excretion, but as indicated above their ability to access intracellular metals is weak. Monoisoamyl 2,3-Dimercaptosuccinic acid (MiADMSA) was developed by our group as a potential drug candidate that is still in its developmental phase. Studies till date highlight the efficacy and safety of new molecule in chronic arsenic toxicity in experimental animals. The brain targeted polymeric based nanoparticles loaded with MiADMSA could also be more effective than bulk MiADMSA alone and reduce the required dose of chelating agent (Naqvi *et al.*, 2020). Another future approach to tackle the issue of developing a safe and effective antidotes could be surface modification of MiADMSA loaded polymeric nanoparticles which may provide an excellent strategy to overcome the blood brain barrier and hence, can be used further to enhance the therapeutic efficacy of MiADMSA in reducing the arsenic burden from the brain and prevent the impairment of cognitive function.

MiADMSA is being a newer chelating agent for the chronic arsenic poisoning treatment and currently in clinical phase I study (Flora *et al*., 2022). The novelty of the proposed work is to reduce the dose of MiADMSA utilizing nanotechnological approach and hence, reducing the undesirable side effects of MiADMSA. Elimination half-life of MiADMSA was found to be approximately 4 hr post oral administration in rats (Flora *et al.*, 2012). The drug candidates having the elimination half-life of 2-8 hr are ideal candidate for the design of sustained release drug products. The release of MiADMSA can be extended by its encapsulation in the polymeric nanoparticles. The prolonged release of MiADMSA from nanoparticles could be beneficial in the treatment of chronic arsenic poisoning as it requires long term treatment. Thus, it will be interesting to develop and multifunctional polymeric nanoparticles loaded with MiADMSA to improve its therapeutic efficacy for improved treatment of chronic arsenic poisoning and therapeutic monitoring (Yadav and Flora, 2016).

Ayurvedic therapies is also an area which need to be explored against toxicity of metals. It may provide relief with reduced adverse effects, even after prolonged administration. In Ayurvedic medicine, ingredients of natural origin, including whole plants or certain portions of the plant, animal sources, and minerals, are used for therapeutic purposes as medicines, both alone and in combination. Nowadays, alternative medicines are being used extensively to reduce heavy metal-induced toxicity (Flora, 2011, Flora *et al.*, 2022). The aim of suggesting phytomedicine as alternative systems of medicine can help to neutralize and overcome metal/ metalloid induced toxicity. Studies using animal models (mice, rats, and hamsters), cell culture studies using various cell lines, *in vitro* studies, including docking studies and bioinformatics tools, and human clinical trials will help to understand the mechanisms and associated complications.

In brief, I suggest few potential research areas which include but are not limited to; studying mechanisms of action of phytoconstituents to neutralize metal-induced toxicity, understanding the pathogenesis and alternative therapy of heavy metal toxicity, heavy metal/ metalloid toxicity and diagnosis using molecular, genetic, and biochemical biomarkers of oxidative stress-related diseases, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and muscular dystrophy, environmental and occupational exposure to heavy metals, risk assessment, and dietary modifications to reduce toxicity, phytochemicals in heavy metal toxicity and therapy, animal models, cell cultures, and bioinformatic tools to study and understand the toxicity and healing mechanisms, neurotoxicity, nephrotoxicity, hepatotoxicity and lung toxicity of heavy metals and possible remedies.

Finally, few words about *Journal of Environment Biology*. it has been an honour to be associated with this journal for last 30 years as Member Editorial Board, Reviewer and as an author. I have seen its journey from a regional journal to an international journal of repute. This would not have possible but for the passionate and single handed efforts of Professor R.C. Dalela, the Editor-in-Chief of the journal. The popularity of the journal has grown manifold and it's so heartening to see number of interesting articles being published from researchers abroad. The impact factor of the journal has shown a steady upward growth but it is still need to travel miles before it achieve the rank among the top 10 in the area of Environmental Biology. I feel we need to have more special issues and minimum 2-3 review article every issue by experts of varied fields. We also need to consider a separate section on Toxicology, phytomedicine/ phyto-toxicology, in addition to emphasis on environment pollution.

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