Review Paper:

Effects of arsenic-induced toxicosis (Arsenicosis) on human health and its prevention

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Abstract

Owing to widespread groundwater pollution, arsenic is one of the most extreme worldwide ecological toxicants and induces cytotoxic activity and other chronic diseases for millions of people and also animals. Because of geologic and anthropogenic activities, arsenic pollution is widely spread. Long-term toxicity caused by arsenic can lead to the development of arsenicosis related to skin lesions, hepatomegaly, splenomegaly, cognitive dysfunction, cardiovascular and peripheral vascular disease, hypertension, diabetes mellitus, hepatic fibrosis and hematological, gastrointestinal, immunological, endocrine and multi-cancer neurological disorders.

Till date no effective treatment or medicine is available in global market to prevent arsenic induced toxicosis. Only use of safe water and well nourished foods can help to prevent further exposure. Recently, chelation therapy is recognized as a good remedial action to reduce and to eliminate the acute arsenic toxicity

Keywords: Arsenic, chronic arsenic exposure, skin lesions, carcinogenesis, arsenic health effects, chelation therapy.

Introduction

Contamination of natural environments by heavy metals has currently become a global concern for the environment[61] and such an issue has emerged in developing nations of the long-term overuse of contaminated irrigated drainage, resulting in increased accumulation of heavy metals in the soil[4,41]. Heavy metals like copper, zinc, iron, manganese etc. are necessary for plant metabolism as micronutrient elements and play a key role in monitoring various metabolic and signaling pathways, but heavy metals have a detrimental impact on plant morphology, physiology, biochemistry[24,25,38,45,86] at elevated concentrations and also decrease biomass accumulation[6,22,26,87] as a consequence of unfavorable effects upon key metabolic processes such as photosynthesis[63], mineral nutrition[77] and interaction with water[51]. These heavy metals can also cause cell toxicity because of the generation of oxidative stress[2,52,64,72,75].

Arsenic is not heavy metal but one of the most extreme environmental toxicants in the world and generated ROS such as superoxide radical ($O_2^{\cdot -}$), hydroxyl radical (OH) and hydrogen peroxide (H_2O_2) in different cell frameworks[59] and causes oxidative stress[68] bringing about cell damage by enacting oxidative flagging pathways. It is a naturally occurring metalloid ubiquitously found in both organic and inorganic forms. Arsenic contamination is widespread due to geologic and anthropogenic activities[17,18]. Drinking water where the concentration may vary from 0.01mg / l to 4.0 mg / l is one of the most common sources of arsenic poisoning. Recently, the concentration of arsenic in drinking and other sources of water has also risen as a result of industrial or agrochemical discharge and is also present in many food varieties.

In corn, carrots, onions and potatoes, large levels of arsenic are also reported. Rice from India and Bangladesh has a high percentage of inorganic arsenic (80%) as compared to the USA (42%), which is possibly dependent on cultivation and growing conditions. Accute arsenic toxicity has been documented in many countries due to drinking arsenic-contaminated water[30,67,70] and associated with skin lesions such as spotted melanosis, hyperkeratosis, leucomelanosis, de-pigmentation of the raindrop, gangrenous arms, hepatomegaly, splenomegaly, cognitive dysfunction, stomach pain, shaking, salivation, vomiting, diarrhoea, depression, anorexia, dehydration, stupor, cold limbs, subnormal temperature[60], cardiovascular, cerebrovascular and peripheral vascular (Black), hepatic fibrosis, circulatory and nervous system symptoms, restrictive lung disease , hypertension, changes in pigmentation[9], diabetes mellitus, reproductive disease, ischaemic heart disease[44] and various cancers such as cancers of the skin, bladder, lung , liver and kidney[78] in humans[Fig. 1] as well as chlorosis, necrosis, root damage and changes in plant biochemicals including antioxidant enzymes in plants.

The toxicity of arsenic compounds focuses very much on the state of oxidation and the chemical composition of the arsenic compounds. Pentavalent arsenic is less hazardous than trivalent and is converted to trivalent with bio-transformation.

In this study, the impacts of arsenic toxicity on human health, biotransformation of arsenic and prevention are illustrated. Till date, no effective therapy for the prevention of arsenic-induced toxicosis is available on the global market. To avoid more exposure, only the use of clean water and very well-nourished food can support it.

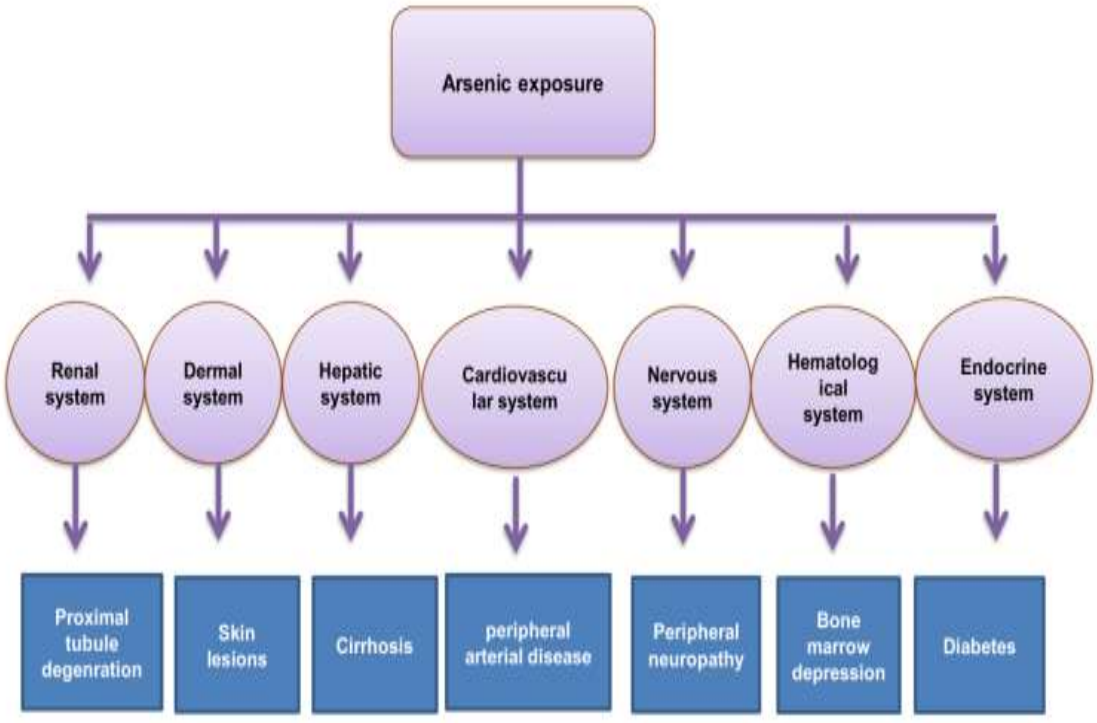

Fig. 1: Effect of arsenic on human health

Chelation therapy has recently been considered as a key treatment for reducing and removing the symptoms of acute arsenic exposure. In the present communication, we deal with the effects of arsenic toxicity on human health, biotransformation of arsenic and its prevention.

Sources of arsenic

Arsenic drinking water contamination is a serious problem in the world. Inorganic arsenic is a natural component of the earth's crust, widely dispersed in soil and water[50,54] and generally accumulated in mineral deposits containing sulfur. Arsenic contaminated water that is used for agriculture can prove harmful to plants through its absorption to the toxic level[19,39] and gets widely spread throughout the plant and animal kingdom through the food chain and causes ecological and health threats[1]. Six million people in India are suspected of being exposed to arsenic polluted water (about 50µg / lit)[55,82,83] while in Nepal, about 5 million people are exposed to arsenic-contaminated groundwater.

Amongst the worst cases of environmental contamination is the arsenic crisis in Bangladesh and approximately 25 million people are exposed to arsenic-contaminated groundwater[10]. In Peru, Argentina, Thailand, Bolivia, China, Cambodia, Chile, Vietnam, Mongolia and Japan, arsenic contamination in drinking water has been identified[36,57].

Metabolism of arsenic

Inorganic arsenic is absorbed from the skin and GIT, while the lungs absorb arsenic gas. Nandi et al[53] have stated that the greatest proportion of arsenic accumulates in chronic arsenic ingestion in the lungs, gastrointestinal tract, liver, kidneys, heart, muscles and nervous system respectively. Inorganic arsenic in humans is found in monomethylarsonic acid (MMA) and dimethyl arsenic acid (DMA), both of which are less reactive and less cytotoxic to tissue components and are more readily excreted in urine as a biomarker of chronic exposure to arsenic[23]. Arsenic biotransformation occurs primarily by MMA(V) and DMA(V) enzymatically in the liver along with other organs[76].

$$iAs(V) \rightarrow iAs(III) \rightarrow MMA(V) \rightarrow MMA(III) \rightarrow DMA(V)$$

Glutathione initially reduces the oxidation state of arsenic from +5 to +3, after that iAs(III) is methylated to form MMA(V) by S-adenosyl methionine, which is subjected to the second methylation through the intermediate metabolite MMA(III) to form DMA(V)[73]. The activity of the two methylations depends on the iAs / MMA and MMA / DMA ratio. If the proportion of iAs / MMA is higher, the first step results in poor methylation. Good methylation, on the other hand, takes place if the ratio of MMA / DMA is poor. The order of toxicity of arsenicals in arsenic biotransformation is MMA(III)>As(III)>As(V)> MMA(V)=DMA(V).

Thus, MMA(III) intermediate metabolite is extremely toxic than other arsenicals which may be responsible for the carcinogenesis and other effects caused by arsenic[71]. It was also noted that arsenic is coordinated with SH-groups of several enzymes and hinders biochemical reactions, coagulates proteins and blocks the production of ATP[23] [Fig. 2].

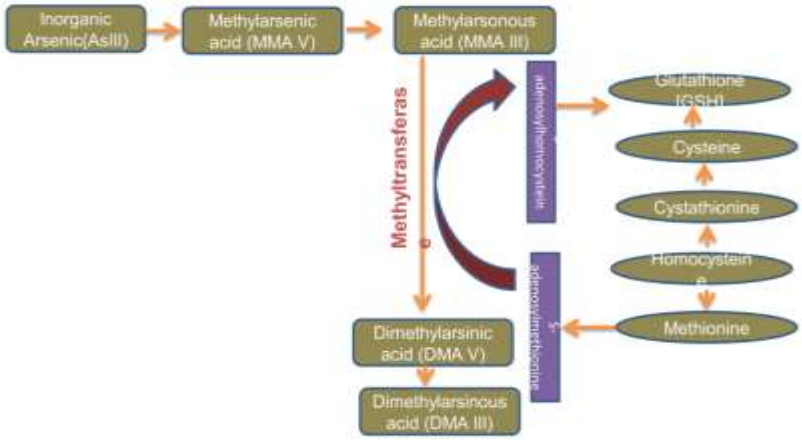

Fig. 2: Metabolism of arsenic in human beings

Effect of chronic arsenic exposure human and animals

Arsenic is one of the most serious global environmental toxicants due to the extensive contamination of groundwater and causes carcinogenicity[11,48] and other chronic diseases[85] to millions of people as well as animals[88]. Chronic ingestion of inorganic arsenic (iAs) through drinking water and airborne particles affects nearly every major organ and organ system in the body and causes multisystem adverse health effects like toxic hepatitis, chronic dermatitis with excessive pigmentation and hyperkeratosis skin lesions like spotted melanosis, hyperkeratosis, leucomelanosis, raindrop de-pigmentation, gangrenous extremities, hepatomegaly, splenomegaly, cognitive impairments, abdominal pain, trembling, salivation, vomiting, diarrhoea, depression, anorexia, dehydration, stupor, cold extremities, subnormal temperature[60], cardiovascular, cerebrovascular and peripheral vascular disease, hypertension[9], hepatic fibrosis, effects on the circulatory and nervous system, restrictive lung disease, diabetes mellitus, reproductive disease, ischaemic heart disease[44], neurological effects, chronic lung disease and multiple cancer like skin, bladder, lung, liver and kidney cancer[78,79] in humans and neuritis that ultimately results in atrophy of the optic nerve and blindness[46], gastro-enteritis dehydration, diarrhoea, laryngitis characterized by abdominal pain, dysentery, toxaemia, nervous signs in animals, a sweet garlicky odour in breath and stool[28,58]. Death may occur within a few days and some times in less than one hour[83].

Guha et al[28] also reported that chronic arsenic poisoning leads to skin irritation and color changes, hair loss, nausea, GIT disturbance and bone marrow depression, which cause massive hemoglobinuria and acute renal failure. Skin pigmentation of chronic arsenic toxicity is due to melanin and commonly characterized as finely raindrop and multiple forms which also stated arsenical keratosis, which occurs on the palms, soles and trunk[29]. Arsenic contaminated drinking water is also responsible for spontaneous abortion, infant mortality and growth retardation in children[62].

The chronic arsenic toxicity in cattle causes fibrosis which is characterized by stiffness and asymmetrical enlargement of hocks or other joints of the limbs[71]. Acute and sub-acute arsenic toxicity in goat was characterized by increased heart rate, respiration rate, diarrhea, stiff gait, lameness, tremor, drooling of saliva, convulsion, congested mucous membrane, paresis of limb and death[7].

Dermatological effects: Skin lesions are one of the most common symptoms of chronic exposure to arsenic at an arsenic concentration of > 100µg / L that may appear within a month or several years of exposure[20] resulting in keratosis, melanosis, skin cancer, especially basal cell carcinoma and squamous cell carcinoma, invasive squamous cell carcinoma[43]. Melanosis which involves diffusion melanosis (hyperpigmentation), spotted melanosis (spotted pigmentation), non-melanoma (depigmentation), leucomelanosis and hypopigmentation, is assumed to be an early and much more frequent manifestation and exhibits a distinctive pattern of the raindrop and occurs on the trunk of the body, while keratosis is believed to be a sensitive marker of a more advanced stage of arsenicosis[20] which especially appears on palm and sole in a different manner as a late feature of arsenical-dermatosis and later on transformed to squamous cell carcinoma.

Hypopigmentation (leucomelanos) also occurs but less often than melanosis or keratosis. It was found that after decreasing exposure for up to several years, the risk of skin lesions did not decrease. Significantly increased risks for basal cell carcinoma and squamous cell carcinoma have been noted in the United States, where arsenic exposure is typically lower[43].

Effect on the respiratory system and lungs: Chronic exposure to inorganic arsenic as in form of particulate matter

and by other pathways mainly affects the lungs and induces inflammation of nasal mucosa, larynx, bronchi[34], pulmonary insufficiency, rhino-pharyngo-laryngitis, tracheobronchitis[82], high chronic cough, lung cancer and bronchopulmonary disease[8,36]. Inorganic arsenic causes an indirect genotoxic carcinogen of the lungs, skin and other human internal organs due to DNA repair enzyme (DNA ligase enzyme) inhibition, DNA methylation, tubulin dynamics and mitosis intervention, induction of oxidative stress, cell clone immortalization promotion.

For those who had arsenic-induced skin lesions and used drinking water of high arsenic concentration (approximately 7500µg / l), the prevalence odds ratio (POR) was increased in comparison with those who had normal skin and used drinking water of low arsenic concentration (approximately 50µg / l)[46,49]. A noticeable dose-dependent linear trend in mortality rate ratios (MMRs) for linear cancer has been identified with increasing arsenic concentrations in drinking water ranging from 170-800µg / L[14].

Effects on the nervous system: Severe neurological disorders have been reported in children aged 6 to 10 years and in adults with damaged cognitive and motor functions caused by exposure to arsenic[27,32,56,81]. Reversible peripheral neurological dysfunction, behavioral changes, confusion, disorientation, cognitive impairment, increased prevalence of the cerebrovascular disease, in particular cerebral infarction[15] and long-term exposure causing peripheral neuropathy are the negative impacts of chronic exposure to arsenic-contaminated drinking water on the nervous system. Based on a case study of a group of persons in China, it was found that exposed persons with arsenic suffered from different types of neurological disorders including irregular distal sensation, decreased temperature and pressure sensation, adiaphoresis (absence or lack of perspiration) compared to normal persons[86].

Cancerous activity of arsenic: Arsenic and its salts including sodium arsenite, potassium arsenite, calcium arsenite, copper arsenite, lead arsenite, copper aceto arsenite, calcium arsenite and lead arsenate are the main ecological toxicants causing carcinogenicity and other chronic diseases[85] through the generation of ROS to millions of people as well as animals, fostering oxidative stress[74] and may harm DNA. By changing the pattern of methylation, cell-cycle dysregulation, angiogenesis stimulation, blocking physiological apoptosis, cause various types of cancer such as bladder, skin and lung[5,33,40] [Fig. 3] and triggers MAPK signal transduction pathways which altered the profile of different gene expression through AAP-1 and NF-KB[84].

In females, arsenic can impact malignancy development by upsetting the role of estrogen receptors and suppressing the signaling pathway of estrogen[12,21]. Arsenic is surely a potential metallo-estrogen[3] and contributes to cell proliferation in the breast cancer cell line that reacts to estrogen[65]. Epidemiological examinations have demonstrated that long-term exposure to arsenic can result in multiple cancers such as skin, bladder, prostate, lung, liver and kidney[13,78].

Regardless of the high poisonous character of arsenic and its salts, it has been utilized in medication for thousands of years for the treatment of a variety of neoplastic sicknesses particularly intense promyelocytic leukemia[80], skin and breast cancer[31]. Stunning viability for the therapy of hematological cancer, particularly acute promyelocytic leukemia (APL) is one of the most malignant types of acute leukemia and has appeared in countless clinical preliminaries of As_2O_3. A few studies have indicated that As_2O_3 assists with improving illness prevention[66] which can be utilized as the absolutely most significant compound for APL treatment.

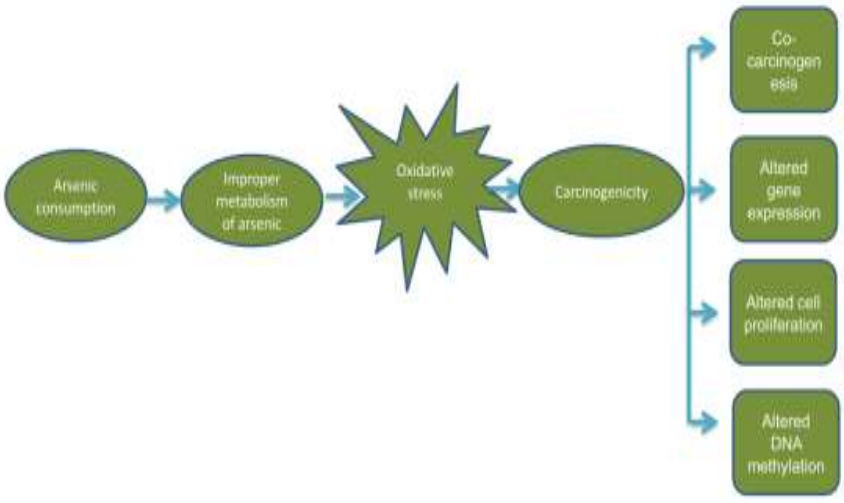

Fig. 3: Effect of arsenic induced oxidative stress on different metabolic system

It has likewise been reported that As_2O_3 has been utilized to hinder cell development and induce apoptosis in numerous human cancer cells including human promyelocytic leukemia cells and breast cells[37] and it is the most well-known threat in females and is a significant reason for death in the world. Prescribed dosages of 1 % aqueous solution of As_2O_3 have additionally been accounted to contribute to a remarkable remission of some forms of leukemia[88]. Arsenic compounds alone or in association with other known therapeutic agents such as cyclophosphamide, methotrexate, doxorubicin, 5-fluorouracil, cisplatin, vinblastine, taxol, taxotere, mitomycin C, have recently been reported to be used in the treatment of primary and metastatic breast, lung, ovary, colon, renal, non-small cell lung, prostate, head, neck, central nervous system and bladder cancer.

It has additionally been viewed that few organic arsenic compounds which are known to be significantly less harmful or non-poisonous than inorganic arsenic are utilized as an intense anticancer agent against strong tumors[47].

It has been indicated that As_2O_3 is utilized at a specific concentration to hinder cell development and prompt apoptosis in a few human malignancy cells by interacting gradually with the sulfhydryl (SH) group of several enzymes such as glutathione and cysteine and inhibiting the biochemical response. Enzymes and proteins having a sulfhydryl (SH) group play an important role to detoxify reactive oxygen species, generated by the toxicity of arsenic.

Prevention

Recognizing the severity of arsenicosis and other harmful effects of arsenic among a significant percentage of people worldwide, there is still no appropriate treatment or medication available on the world market to date. The most important and vital remedial action for chronic arsenic toxicity (arsenicosis) is to use clean drinking water and well-nourished food to avoid further exposure and to raise awareness among sufferers of the adverse health effects of arsenicosis and its prevention with dietary supplements. Diets with low-protein, fat, vitamin and mineral diets affect the biotransformation of arsenic that does not excrete arsenic from the body and may increase the risk of skin lesions and other malignant diseases caused by arsenic. The micronutrients like calcium, iron and zinc also help to reduce arsenic toxicity by interaction at the primary site of action. Vitamin and antioxidant deficiencies increase the body's reactive oxygen species (ROS) which can trigger tissue damage and other adverse effects. It has been noted that people who use highly contaminated water (about 400g/l) with well-nourished food do not have skin lesions[17].

Chelation therapy has recently been recognized as a successful remedial action for reducing and removing the acute toxicity of arsenic. This therapy is based on the principle that ligand binds strongly with arsenic to form a non-toxic and more soluble complex which excretes out through urine. This therapy could remove large stores of arsenic from the body within hours. The most commonly used chelating ligand for acute arsenic and other heavy metal poisoning is 2,3- dimercapto propanol, which is commercially known as British anti-lewisite (BAL), but due to its toxicity, it is less commonly used. Presently, thiol chelating agents such as DMSA (meso 2,3 – dimercapto succinic acid), DMPS (sodium 2,3-dimercaptopropane-1-sulfonate), MiADMSA (monoisoamyl meso-2,3-dimercaptosuccinic acid) are more frequently used for the treatment of acute and chronic arsenic toxicity. These chelating agents form complexes with MMA(III), which is the most toxic intermediate arsenical in biomethylation and also reduces oxidative stress generated by chronic arsenic toxicity.

Conclusion

No treatment is available to prevent arsenic induced toxicosis. Presence of arsenic cause many diseases including cancer. But some type of cancer can be cured by arsenic.

References

1. Abedi T. and Mojiri A., Arsenic uptake and accumulation mechanisms in rice species, *Plants*, **9**, 129 **(2020)**

2. Anjum S.A., Tanveer M., Hussain S., Shahzad B., Ashraf U., Fahad S., Hassan W., Jan S., Khan I. and Saleem M.F., Osmoregulation and antioxidant production in maize under combined cadmium and arsenic stress, *Environ Sci Pollut Res*, **23(12)**, 11864-75 **(2016)**

3. Aquino N.B. et al, Role of cadmium and nickel in estrogen receptor signaling and breast cancer: metalloestrogens or not?, *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev*, **30**, 189–224 **(2012)**

4. Arora M., Kiran B., Rani S., Rani A., Kaur B. and Mittal N., Heavy metal accumulation in vegetables irrigated with water from different sources, *Food Chem*., **111**, 811-815 **(2008)**

5. Bates M.N., Smith A.H. and Cantor K.P., Case-control study of bladder cancer and arsenic in drinking water, *Am J Epidemiol*., **141**, 523–30 **(1995)**

6. Beyer W.N., Green C.E., Beyer M. and Chaney R.L., Phytotoxicity of zinc and manganese to seedlings grown in soil contaminated by zinc smelting, *Environ Pollut.*, **179**, 167176 **(2013)**

7. Biswas U. et al, Chronic toxicity of arsenic in goats, clinicobiochemical changes, pathomorphology and tissue residues, *Small Rumin Res*., **38**, 229-235 **(2000)**

8. Borgono J.M., Vicent P., Venturino H. and Infante A., Arsenic in the drinking water of the city of Antofagasta: Epidemiological and clinical study before and after the installation of the treatment plant. Environ Health, *Perspect.*, **19**, 103-105 **(1997)**

9. Cebrian M.E., Albores A., Connelly J.S. and Bridges J.W., Assessment of arsenic effects on cytosolic heme status using tryptophanpyrrolase as an index, *J. Biochem. Toxicol*., **3**, 77-86 **(1998)**

10. Chakraborti D. et al, Arsenic groundwater contamination in Middle Ganga Plain, Bihar, India, a future danger?, *Environ Health Persp*., **111**, 1194-1201 **(2003)**

11. Chandrakar V., Naithani S.C. and Keshavkant S., Arsenic-induced metabolic disturbances and their mitigation mechanisms in crop plants: A review, *Biologia*, **71**, 367–377 **(2016)**

12. Chatterjee A. and Chatterji U., Arsenic abrogates the estrogen-signaling pathway in the rat uterus, *Reprod Biol Endocrinol*, **8**, 80 **(2010)**

13. Chen C.J., Chen C.W., Wu M. and Kuo T.Z., Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water, *Br J Cancer*., **66**, 888-92 **(1992)**

14. Chen C.L. et al, Arsenic in drinking water and risk of urinary tract cancer: a follow-up study from northeastern, *Taiwan Cancer Epidemiol Biomarkers Prev*., **19(1)**, 101-110 **(2010b)**

15. Chiou H.Y., Huang W.I. and Su C.L., Dose-response relationship between the prevalence of cerebrovascular disease and ingest inorganic arsenic, *Stroke*, **28**, 1717-23 **(1997)**

16. Chowdhury M.T.A., Deacon C.M., Steel E., Imamul Huq S.M., Paton G.I., Price A.H., Williams P.N., Meharg A.A. and Norton G.J., Physiographical variability in arsenic dynamics in Bangladeshi soils, *Sci. Total Environ*., **612**, 1365–1372 **(2018)**

17. Chowdhury U.K., Biswas B.K., Chowdhury T.R., Samanta G., Mandal B.K., Basu G.C., Chanda C.R., Lodh D., Saha K.C., Mukherjee S.K., Roy S., Kabir S., Qumruzzaman Q. and Chakraborti D., Ground water arsenic contamination in Bangladesh and West Bengal, India, *Environ. Hith. Perspect*., **108**, 393-397 **(2000)**

18. Cui J., Zhao Y., Li J., Beiyuan J., Tsang D.C., Poon C., Chan T., Wang W. and Li X., Speciation, mobilization and bioaccessibility of arsenic in geogenic soil profile from Hong Kong, *Environ. Pollut*., **232**, 375–384 **(2018)**

19. Das D. et al, Arsenic in groundwater in six districts of West Bengal, India, *Environ Geochem Health*, **18**, 5-15 **(1996)**

20. Das N.K. and Sengupta S.R., Arsenicosis diagnosis and treatment, *Indian J Dermatol Venereol Leprol*., **74(6)**, 571-581 **(2008)**

21. Davey J.C. et al, Arsenic as an endocrine disruptor: effects of arsenic on estrogen receptor-mediated gene expression in vivo and cell culture, *Toxicol Sci.*, **98**, 75–86 **(2007)**

22. Ebbs S.D., Bradfield S.J., Kumar P., White J.C., Musante C. and Ma X., Accumulation of zinc, copper, or cerium in carrot (Daucus carota), *Environ Sci Nano*., **3**, 114-126 **(2015)**

23. El-Demerdash F.M., Yousuf M.I. and Radwan F.M.E., Ameliorating effect of curcumin on sodium arsenite-induced oxidative damage and lipid peroxidation in different rat organs, *Food Chem Toxicol*., **47**, 249-54 **(2009)**

24. Gangwar S., Singh V.P., Prasad S.M. and Maurya J.N., Modulation of manganese toxicity in Pisum sativum L. seedlings by kinetin, *Sci Hortic*., **126**, 467-474 **(2010)**

25. Gautam S., Anjani K. and Srivastava N., In-vitro evaluation of excess copper affecting seedings and their biochemical characteristics in Carthamus tinctorius L. (variety PBNS-12), *Physiol Mol Biol Plants*, **22**, 121-129 **(2016)**

26. Ghavri S.V. and Singh R.P., Growth, biomass production and remediation of copper contamination by Jatropha curcas plant in industrial wasteland soil, *J. Environ Biol*., **33**, 207-212 **(2012)**

27. Gong G. et al, Low-level groundwater arsenic exposure impacts cognition: a project FRONTIER study, *J. Environ Health*, **74(2)**, 16-22 **(2011)**

28. Guha Mazumder D.N., Chronic arsenic toxicity, clinical features, epidemiology and treatment, experience in West Bengal, *J Environ Sci Health*, Part A, **38**, 141-63 **(2003)**

29. Guha Mazumder D.N., Chronic arsenic toxicity and human health, *Indian J Med Res*., **128**, 436-47 **(2008)**

30. Guha Mazumder D.N., Ghoshal U.C., Saha J., Santra A., De B.K., Chatterjee A., Dutta S., Angle C.R. and Centeno J.A., Randomized placebo-controlled trial of 2,3-dimercapto succinic acid in therapy of chronic arsenicosis due to drinking arsenic-contaminated subsoil water, *Clin. Toxicol*., **36**, 683-690 **(1998)**

31. Haller J.S., Therapeutic mule: the use of arsenic in the nineteenth century materia medica. *Pharmacy in History*, **17**, 87-100 **(1975)**

32. Hamadani J.D. et al, Critical windows of exposure for arsenic associated impairment of cognitive function in pre-school girls and boys: a population-based cohort study, *Int. J Epidemiol*., **40(6)**, 1593-1604 **(2011)**

33. Hays A.M., Srinivasan D., Witten M.L., Carter D.E. and Lantz R.C., Arsenic and cigarette smoke synergistically increase DNA oxidation in the lung, *Toxicol Pathol*., **34**, 396– 404 **(2006)**

34. Hina C.H., Pinto S.S. and Nelson K.W., Medical problems associated with arsenic exposure, *J. Occup. Med*., **19**, 391-396 **(1997)**

35. IARC (WHO), Some drinking water disinfectants and contaminants, including arsenic, monographs on the evaluation of carcinogenic risk to humans, France Lyon, 84 **(2004)**

36. IARC (WHO), A review of human carcinogens: Arsenic, metals, fibers and dust, Lyon **(2012)**

37. Iriyama N. et al, Aquaporin 9, a promising predictor for the cytocidal effects of arsenic trioxide in acute promyelocytic leukemia cell lines and primary blasts, *Oncol Rep*., **29(6)**, 2362-8 **(2013)**

38. Izquierdo-Vega J.A. et al, Diabetogenic effects and pancreatic oxidative damage in rats subchronically exposed to arsenic, *Toxicol Lett.*, **160**, 135-142 **(2006)**

39. Jin Y. et al, Study on the toxic effects induced by different arsenicals in primary cultured rat astroglia, *Toxicol Appl Pharmacol*., **196**, 396-403 **(2004)**

40. Klein C.B., Leszczynska J., Hickey C. and Rossman T.G., Further evidence against a direct genotoxic mode of action for arsenic-induced cancer, *Toxicol Appl Pharmacol*., **222**, 289–97 **(2007)**

41. Lu Y., Yao H., Shan D., Jiang Y., Zhang S. and Yang J., Heavy metal residues in soil and accumulation in maize at long term wastewater irrigation area in T Ongliao, China, *J Chem*., **2015**, 628280 **(2015)**

42. Majumdar K.K. et al, Systemic manifestations in chronic arsenic toxicity in absence of skin lesions in West Bengal, *Indian J Med Res*., **129**, 75-82 **(2009)**

43. Maloney M., Arsenic in dermatology, *Dermatol. Surg.*, **22**, 301-304 **(1996)**

44. Mandal B.K. and Suzuki K.T., Arsenic round the world: A review, *Talanta*, **58**, 201-235 **(2002)**

45. Mathur S., Kalaji H.M. and Jajoo A., Investigation of deleterious effects of chromium phytotoxicity and photosynthesis in the wheat plant, *Photosynthetica*, **54**, 1-9 **(2016)**

46. Mazumdar D.N., Haque R., Ghosh N., De B.K., Santra A., Chakraborti D. and Smith A.H., Arsenic in drinking water and the prevalence of respiratory effects in West Bengal, India, *Int. J. Epidemiol*., **29**, 1047-1052 **(2000)**

47. Meharg A.A. and Rahman M.M., Arsenic of Bangladesh paddy field soils: implications for rice contribution to arsenic consumption, *Environ Sci Technol.*, **37**, 229-334 **(2003)**

48. Mehmood T., Bibi I., Shahid M., Niazi N.K., Murtaza B., Wang H., Ok Y.S., Sarkar B., Javed M.T. and Murtaza G., Effect of compost addition on arsenic uptake, morphological and physiological attributes of maize plants grown in contrasting soils, *J. Geochem. Explore*, **178**, 83–91 **(2017)**

49. Milton A.H. et al, Chronic arsenic exposure and adverse pregnancy outcomes in Bangladesh, *Epidemiology*, **16(1)**, 82-86 **(2005)**

50. Morton W.E. and Dunnette D.A., Health effects of environmental arsenic, In, Arsenic in the Environment, Part II, Human Health and Ecosystem Effects, Nriagu J.O., ed., New York, John Wiley and Sons, 17-34 **(1994)**

51. Mukhopadhyay M. and Mondal T.K., Effect of aine and boron on growth and water relations of Camellia Sinensis L.O. Kuntze cv. T-78, *Natl Acad Sci Lett*., **38**, 283-286 **(2015)**

52. Nanda R. and Agarwal V., Elucidation of zinc and copper-induced oxidative stress, DNA damage and activation of defense system during seed germination in Cassia Angustifolia Vah. L, *Environ Exp Bot*., **125**, 31-41 **(2016)**

53. Nandi D., Patra R.C. and Swarup D., Oxidative stress indices and plasma biochemical parameters during oral exposure to arsenic in rats, *Food Chem Toxicol*., **44**, 1579-1584 **(2006)**

54. NCR (National Research Council), Arsenic in drinking water. Washington DC, National Academy of Sciences Press **(1999)**

55. Pal A. et al, Additional danger of arsenic exposure through inhalation from burning of cow dunk cakes laced with arsenic as a fuel in arsenic affected villages in Ganga-Meghna- Brahmaputra plain, *J Environ Monit.*,**10**, 1067-1070 **(2007)**

56. Parvez F. et al, Arsenic exposure and motor function among children in Bangladesh, *Environ Health Prospect*, **119**, 1665-1670 **(2011)**

57. Queirolo F. et al, Total arsenic, lead and cadmium levels in vegetables cultivated at the Andean village of northern China, *Sci Total Environ*., **255**, 75-84 **(2000)**

58. Radostits O.M. et al, Contribution of arsenic from the agricultural food chain to cow milk is a highly arsenic prone zone in Nadia District of West Bengal in India, Nature proceeding, HDL **(2008)**

59. Rafiq M., Shahid M., Abbas G., Shamshad S., Khalid S., Niazi N.K. and Dumat C., Comparative effect of calcium and EDTA on arsenic uptake and physiological attributes of *Pisum sativum*., *Int.J. Phytoremed.*, **19**, 662–669 **(2017)**

60. Rana T. et al, Evidence of antiapoptotic of Pleurotus Florida lectin against chronic arsenic toxicity in renal cells of rats, *J Environ Pathol Toxicol Oncol*., **31**, 39-48 **(2012)**

61. Recatala L., Peris M. and Sa J., Assessing heavy metal sources in agricultural soils of a European Mediterranean area by multivariate analysis, *Chemosphere*, **65**, 863-872 **(2006)**

62. Rich C.H., Browning S.R., Picciotto I.H., Ferrcco C., Peralta C. and Gibb H., Chronic arsenic exposure and risk of Indian Mortality in two areas of Chile, *Environ Hlth Perspect*, **108**, 667-673 **(2000)**

63. Rodriguez E., Santos C., Azevedo R., Moutinho-Pereira J., Correia C. and Dias M.C., Chromium(VI) induces toxicity at the different photosynthetic level in pea, *Plant Physiol Biochem.*, **53**, 94-100 **(2012)**

64. Rui H., Chen C., Zhang X., Shen Z. and Zhang F., Cd-induced oxidative stress and lignifications in the root of two Vicia sativa L. Varieties with different Cd tolerances, *J. Hazard Mater*., **301**, 304-313 **(2016)**

65. Ruiz-Ramos R. et al, Sodium arsenite alters cell cycle and MTHFR, MT1/2 and c-Myc protein levels in MCF-7 cells, *Toxicol Appl Pharmacol*., **241**, 269–74 **(2009)**

66. Rzygoda G., Feldmann Jr. and Cullen W.R., Microbial Methylation of Metalloids: Arsenic, Antimony and Bismuth, *Appl Organomet Chem.*, **15**, 457-462 **(2001)**

67. Santra A. et al, Hepatic manifestations in chronic arsenic toxicity, *Ind. J. Gastroenterol*, **18**, 152-155 **(1999)**

68. Shi H., Shi X. and Liu K.J., Oxidative mechanism of arsenic toxicity and carcinogenesis, *Mol Cell Biochem*, **255**, 67-78 **(2004)**

69. Smith A.H., Lingas E.O. and Rahman M., Contamination of drinking water of arsenic in Bangladesh, A public health emergency, *Bull World Health Org*., **78**, 1093-103 **(2000)**

70. Smith A.H. et al, Arsenic induced skin lesions among atacameno people in North China despite good nutrition and centuries of exposure, *Environ. Hlth. Perspect*, **108**, 617-620 **(2000)**

71. Styblo M., Del Razo L.M., Vega L., Germolec dr., Le-Cluyse E.L., Hamilton G.A., Reed W., Wang C., Cullen W.R. and Thomas, Comparative toxicity of trivalent and pentavalent inorganic and methylated arsenicals in rat and human cells, *Arch. Toxicol*., **74**, 289-299 **(2000)**

72. Thounaojam T.C., Panda P., Mazumdar P., Kumar D., Sharma G.D., Sahoo L. and Panda S.K., Excess copper-induced oxidative stress and response of antioxidants in rice, *Plant Physiol Biochem*., **53**, 33-39 **(2012)**

73. Thomas D.J., Styblo M. and Lin S., The cellular metabolism and systematic toxicity of arsenic, *Toxicol Appl. Pharmacol*., **176**, 127-144 **(2001)**

74. Valco M., Rhodes C.J., Moncol J., Izakovic M. and Mazur M., Free radicals, metals and antioxidants in oxidative stress-induced cancer, *Chem Biol Interact*., **160**, 1-40 **(2006)**

75. Vanhoudt N., Vandenhove H., Horemans N., Wannijn J., Bujanic A., Vangronsveld J. and Cuypers A., Study of oxidative stress-related responses induced in Arabidopsis thaliana following mixed exposure to uranium and cadmium, *Plant Physiol Biochem*., **48**, 879-886 **(2010)**

76. Vahter M., Mechanisms of arsenic biotransformation, *Toxicology*, **181-182**, 211-217 **(2002)**

77. Verney P., Gauthier-Moussard C. and Hitmi A., Interaction of bioaccumulation of heavy metal chromium with water relation, mineral nutrition and photosynthesis in developed leaves of Lolium perenne L., *Chemosphere*, **68**, 1563-1575 **(2007)**

78. Waalkes M.P., Liu J., Ward J.M. and Diwan B.A., Mechanisms underlying arsenic carcinogenesis: hypersensitivity of mice exposed to inorganic arsenic during gestation, *Toxicology*, **198**, 31-38 **(2004)**

79. Wang S.E. et al, Prevalence of non-Insulin-Dependent Diabetes Mellitus and related vascular disease in Southwestern arseniasis-endemic and non- endemic areas in Taiwan, *Environ Hlth. Perspect*, **111**, 155-159 **(2003)**

80. Wang Z.Y. and Chen Z., Acute promyelocytic leukemia: from highly fatal to highly curable, *Blood*, **111**, 2505-15 **(2008)**

81. Wasserman G.A. et al, Water arsenic exposure and intellectual function in 5-year old children in Araihazar, Bangladesh, *Environ Health Prospect*, **115**, 285-289 **(2007)**

82. WHO, Arsenic Environment Health Criteria 18, Geneva, World Health Organization, 142-3 **(1981a)**

83. WHO, Environmental health criteria-224, arsenic and arsenic compounds, second ed., World Health Organization, Geneva **(2003)**

84. Yang C. and Frenkel K., Arsenic-mediated cellular signal transduction, transcription factor activation and aberrant gene expression: implications in carcinogenesis, *J Environ Pathol Toxicol Oncol*., **21**, 331–42 **(2002)**

85. Yoshida T., Yamauchi H. and Fan S.G., Chronic health effects in people exposed to arsenic via the drinking water, dose-response relationships in a review, *Toxicol Appl Pharmacol*., **198**, 243-52 **(2004)**

86. Zang Y., Xianyun R., Zhenrong Z., Qin D., Geyon Z., Xiufen L. and Meiyun Z., Effects of high arsenic drinking water on the resident's nervous system, 4th International conference on arsenic exposure and health effects, San Diego, CA, June 18- 22, 173 **(2000)**

87. Zhao H., Wu L., Chai T., Zhang Y., Tan J. and Ma S., The effects of copper, manganese and zinc on plant growth and elemental accumulation in the manganese-hyperaccumulator *Phytolacca Americana*, *J Plant Physiol*., **169**, 1243–1252 **(2012)**

88. Zhu J., Chen Z., Lallemand-Breifenbach V. and de The H., How acute promyelocytic leukaemia revived arsenic, *Nat Rev. Cancer*, **2**, 1-9 **(2002)**

89. Zhu N., Qiao J. and Yan T., Arsenic immobilization through regulated ferrolysis in paddy field amendment with bismuth impregnated biochar, *Sci. Total Environ.*, **648**, 993–1001 **(2019)**.

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