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The Role of Arsenic on Skin Diseases, Hair Fall and Inflammation: An Immunological Review and Case Studies

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Abstract

In this recent era, occupational and accidental spills have been dramatically increased since last few decades due to globalization throughout the world. Concurrently, the concerns on health issues are being a burning question to the all corporate as well as health care professional personnel. Currently, arsenic and arsenic related problems have drawn a great attention as this compound acts not only as slow poison but also works as beneficial molecule in the treatment of some diseases. Laboratory animals showed several dysfunctions including keratinocytes dysfunctions, loss of hair and most importantly inflammation. Arsenic-mediated cell stress/oxidative stress also plays a major role in the development of multiple pathways like JNK, AP-1, PKC and caspase which further either lead to apoptosis or cancer. Countries like Bangladesh, India, Mexico, Chile and China are in great risk and the human from these areas are losing their lives due to chronic arsenic exposures. Therefore, this study will try to explain the proposed molecular mechanisms of arsenic-induced skin diseases, hair fall and inflammation. Finally, a possible treatment approach would be disclosed against arsenic-mediated disorders.

Keywords: Arsenic; Arsenic toxicity; Immunity; Inflammation

Introduction

In the present time, occupational, accidental and household incidents due to several organic and inorganic exposures have been drastically increased. At the same time, spill and exposure in the air, soil, water and food are considerably reported due to globalization [1]. Several toxins and poisons are accumulated in the environment which resulting chronic illnesses like pulmonary dysfunctions and chronic inflammation. Hazardous molecules in water have also been linked with several life threatening diseases like chronic obstructive pulmonary diseases (COPDs) and cancer [2]. In the meantime, the cost of the treatment as well as social and financial burden of a family is highly documented everywhere. Mortality and morbidity rate are noticeable high due to contaminated air and foods [3].

Arsenic affects almost all biological systems where it is distributed though it is well excreted through kidney but often accumulate in several tissues. The half-life of arsenic is very short and the normal value in blood concentration is <10 mcg/L. Arsenic-mediated dysfunctions have been well investigated for instances, in the heart, it produces dysfunctions (prolonged QT interval, ventricular tachycardia, hypovolaemia, myocardial depression and ventricular fibrillation) [4], hepatic damages (Jaundice, hepatomegaly and pancreatitis) [5], renal diseases (proteinuria, acute tubular necrosis with acute kidney injury) [6], blood disorders (bone marrow suppression, aplastic anaemia, acute haemolysis and basophilic stippling) [7], Brain disorders (Seizures, encephalopathy and coma) [8], lung diseases (bronchospasm, Pulmonary oedema, and acute respiratory failure) [9] and even turn to several types of cancer [10].

The metabolites of arsenic remain in blood, skin, hair, urine and some other area of body. As the metabolites of arsenic stay in blood for few hours so it is quite difficult to draw a conclusion for chronic arsenic exposures to individual [11]. Arsenic is generally excreted in urine but can also accumulate in many body tissues [12].Toxicity is due to arsenic's effect on many cell enzymes, which affect metabolism and DNA repair [13]. Skin disease as well as hair fall have been a great concern as these are mostly noticeable and visible scenarios. Arsenical dermatosis as a result of drinking tube well water has been evaluated in several villages in West Bengal where the arsenic level is 27.5 times higher than its normal limit [14]. A study has been also reported in Southwest Prefecture of Guizhou, China where approximately 200,000 people are at risk for such overexposures of burning high-arsenic-containing coal results in skin lesions are common problems, including keratosis of the hands and feet, pigmentation on the trunk, skin ulceration, and finally skin cancers [15].

Now-a-days, arsenic and arsenic related problems have been drawn every ones attention, especially, in public health community. With the growing concern of arsenic exposures, exact treatment approaches are not sufficient till now. Although, some antioxidant-based therapies are proving well against arsenic toxicity and related inflammatory diseases [16]. Hence, this study will try to correlate the possible molecular mechanisms for skin diseases as well as hair fall due to arsenic exposures. A few possible treatment strategies against arsenic-mediated problems would be disclosed in the current study.

History of Arsenic

Arsenic, generally known as a highly toxic compound to almost all multi cellular creatures though it was previously noticed that some bacteria utilize arsenic in their metabolic reactions [17,18]. By characteristics it is a heavy metal, can also be found as organic or inorganic form but mostly shows its harmful activities when remains in inorganic forms. This compound can be obtained in water, air and soil and can penetrate to a biological subject through gut, inhalation and skin [19,20]. Though it is known as a poison or toxin, it was also being used in the treatment of syphilis till 1950. It is now being used in some cases like acute promyelocytic leukaemia and other myeloproliferative disorders [21]. Once it was used as a pigment in color and due to its poisonous property it is still used as pesticides as well as insecticides in several agricultures fields [22]. In 1970, around 10,000 tons of arsenic was imported by USA for agriculture purposes, those were later sprayed to the crops and further no record was taken to follow up the wastage [23]. It was guessed that in 1940, there were some cases found in Hungary due to chronic arsenic exposure but it was not clear until 1982 when a group of people conducted a survey on arsenic exposure [24]. It is south Asian people have been suffering for several decades without knowing the reasons. Places like Bangladesh, West Bengal, China and some other countries of Asia are affecting the most due to groundwater. In 1995, it was first noticed skin diseases due to arsenic exposure at a conferences held in Dhaka Community Hospital [25]. After that around 1998, it was firstly questioned that how did arsenic get into the water? Since then several proposals have been made and it is still believed that due to pumping excess water from ground, the level of water seriously fall resulting to allow the oxidation of iron and following release of arsenic [26]. Several epidemiologic studies have been performed later to identify and counter attack arsenic and arsenic related problems. Currently, over 500 million people are living in the red zone of arsenic exposure only in South Asia [27]. Recently, contamination of arsenic with foods has been a great challenge for the current health care associates [28].

Effect of Arsenic on Skin

The skin is the largest organ in the body which basically protects the internal organs by serving as a barrier. Moreover, unnecessary invaders like microorganisms, radiation, heat, environmental irritants, and physical trauma are prevented by this layer. The skin exposes the most to either in household activities or occupational or outdoor work like "the skin comes in attach with water and to contribute to hand eczema or psoriasis". Drinking or exposure to direct water may increase the chance for developing skin infection or dermatitis [29]. Meanwhile, several theories have been proposed but it is still believed that exposure of skin by any harmful component may initiate pro-inflammatory cytokines. Once there is any wound is formed due to destructive stimuli, permanent epidermal keratinocyte invites and activates several mediators like Caspase-8 and RIPK3 those signal transcription factor like nuclear factor-kB which further release harmful cytokines like interleukin-1β and interleukin-1α [30]. Arsenic mediated destructive stimuli have been explain either through release of inflammatory cytokines or free radical-mediated oxidative stress [31].

Arsenic has been highly responsible for production of interleukin-1β in murine keratinocyte cell line (HEL30) which further linked with skin cancer [32]. Human Keratinocyte Apoptosis has been also noticed by arsenic exposure where arsenic interacts with FAS/FAS ligand Pathway, that further correlates with alterations in NF-kB and AP-1 Activity [33]. A recent population-based study investigated that polymorphism in TNF-α and IL-10 may develop several negative impacts like dermatological and non-dermatological dysfunctions which might lead to internal organ carcinoma [34]. Another population-based investigation found DNA methylation changes over time in people who develop arsenic-induced skin lesions on 900 Bangladeshi subjects [35]. Arsenic has also been observed as a hallmark of several diseases like hyperpigmentation, hyperkeratoses, and Bowen's disease. Chronic arsenic exposure to patients who were previously suffering from either hyperpigmentation or hyperkeratosis or Bowen's disease found to be more prone to have lung cancer [36]. Epigenetic modifications of the tumor suppressor genes with dermatological and non-dermatological subject's health, methylation status of p16 and DAPK genes were determined which linked with other life threatening conditions (Figure 1) [37].

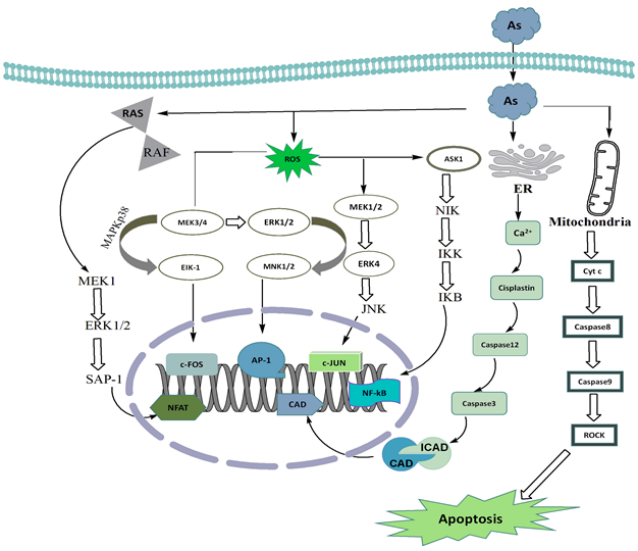

Figure 1: A numerous signalling pathways are responsible for the destruction of the skin cell by arsenic exposure. Arsenic causes ER stress, mitochondrial degradation and initiates the generation of reactive oxygen spices (ROS) inside skin cell. A series of signaling get activated by the stimulation of arsenic. ROS activates c-fos, AP-1, c-Jun, NF-kB transcription factor. These transcription factors are responsible for the production of various inflammatory cytokines. Activation of NFAT transcription factor via Ras/Raf mediated pathway is also facilitated by arsenic. NFAT transcription factor are linked with cancer in the process of cell motility at the basis of metastasis formation. Caspase-Activated DNase (CAD) transcription factor is often involved in the expression of caspase protein that is further responsible for cell death. Mitochondrial degradation by arsenic also causes cell death via caspase activation.

Subjects	Outcomes of the study	References
Model: Men and women from Bangladesh Age/Wt of model: N/A Duration: N/A	- Arsenic caused skin lesion by the conversion of monomethylarsonous acid to dimethylarsinic acid, and - MTHFR & GSTO1 polymorphisms resulted in skin lesions.	[38]
Model: Men and women from highly arsenic contaminated area. Age/Wt of model: N/A Duration:3 years	- Out of 11,746 participants 714 (130 female and 584 male) showed skin lesion as a result of arsenic exposure.	[39]
Model: 10,182 adults of male and female participants from Araihazar, BD Age/Wt of model: 18-75 years old Duration: 2000-2009	- 866 participants showed skin lesion out of 10,182 in which 613 were male and 253 were female.	[40]
Model: Male and female participants from Pabna, Bangladesh. Age/Wt of model: 18-76 years old Duration: 8.9 years	- Arsenic being metabolized, converted to monomethyl arsenic acid, dimethyl arsenic acid and % of inorganic arsenic which are responsible for skin lesion.	[41]
Model: 5,042 male from Araihazar, Bangladesh. Age/Wt of model: 18-75 Duration: October 2000- May 2002	- Of the total participants, 613 people developed skin lesion due to arsenic, and - Smoking and fertilizer use increased arsenic exposure to elevate the risk of skin lesion.	[42]
Model: 9,677 individuals from Araihazar, BD Age/Wt of model: 18-75 Duration: 2000-2009	Diet rich in gourds and root vegetables, increasing dietary diversity reduced arsenic induced skin lesion.	[43]
Model: 2,447 residents from southwestern Taiwan Age/Wt of model: N/A Duration: N/A	- Arsenic acted as co-carcinogen to cause lung cancer, and - Arsenic induced hyperkeratosis and cigarette smoking caused lung cancer	[36]
Model: 210 female participants from Laksam and Araihazar upazilla Age/Wt of model: 35-55 years old Duration: 2006-2007	- Women with arsenic induced skin lesion experienced shorter reproductive period in their life, and - Menopause occurred earlier to women affected with arsenic induced skin lesion.	[44]
Model: Male and female from Matlab, Bangladesh Age/Wt of model: N/A Duration: N/A	- People induced to arsenic at an early age are more susceptible to skin lesion, and - Arsenic induced skin lesions are more prevalent in men compared to women due to less efficient methylation of arsenic among men.	[45]
Model: 900 individuals from Pabna (2001-2003), 550 individuals from Pabna (2009-2011) Age/Wt of model: N/A Duration: 2001-2003, 2009-2011	- Reduction of arsenic exposure caused the individuals to recover from skin lesion.	[46]
Model: Age/Wt of model: Duration:	- Arsenic poisoning caused hair loss	[47]

Table 1: Various effects of arsenic on Human subjects.

Effect of Arsenic on Hair

It is still proposed that infection, malnutrition, physical stress, pregnancy, too much Vitamin A, lack of protein, heredity, hormonal imbalances, hypothyroidism, anemia, chemotherapies, aging, using anabolic steroids and using birth control pills are the main culprits for basic hair loss [48-50]. Presence of arsenic in blood and urine are easily detectable which help to identify any disease along with also contribute to solve a crime in case of slow poisoning. Detection of arsenic in hair has been also noticed in both acute and chronic cases [51]. The investigation for detection of arsenic is a difficult process as arsenic found in hair as a trace amount though it shows strong evidences in several investigations. Food, occupational and water containing arsenic are mostly prominent in hair scalp [52,53]. Several literatures evaluated that arsenic has the capabilities to stay in the hair scalp in both acute and chronic cases (Tables 1 and 2) [54]. Some literatures suggest that

arsenic can be detected within 2-5 months in acute cases and 12-18 months in chronic cases on human subjects [55,56].The exact molecular mechanism of hair fall or alopecia or baldness due to arsenic is yet to be clear but it is thought that oxidative stress and interaction of Wnt protein initiate further downstream pathways to reduce the tone of hair resulting hair loss (Figure 2) [47].

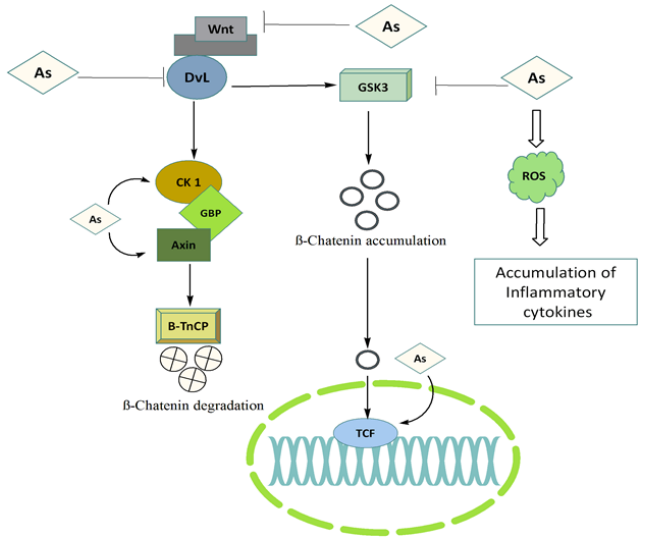

Figure 2: Arsenic-mediated Wnt signaling is mainly responsible for hair fall. Wnt signaling is activated when a Wnt protein binds to the N-terminal extra-cellular cysteine-rich domain of a Frizzled family receptor. Presence of excessive arsenic in the blood reduces the production of Wnt protein. Arsenic also interacts the signaling via degradation of β-catenin and by the introduction of Casein kinase 1 (CK1) in the signaling cascade. TCF transcription factor is another important protein for the expression of genes responsible for hair follicle. TCF are also involved in the Wnt signaling pathway, where they recruit the co-activator β-catenin to enhance their target gene elements. Arsenic often blocks the binding of TCF with the DNA. Along with that arsenic facilitate the production of free radicals, which initiate the expression of various inflammatory cytokines for hair fall.

Effect of Arsenic on Inflammation

Systemic or cellular inflammation is the ultimate host response against any foreign stimuli [57]. To protect host cells several biological responses like neutrophils, monocytes, macrophages and activation of lymphoid cells arrest harmful or unwanted or hazardous compounds [58,59]. Activation of macrophages, release several pro-inflammatory and inflammatory cytokines like tumor necrosis factors and interleukins which further aggravate the situation [60,61]. Harmful components often interact with toll like receptors (TLRs) which signal harmful transcription factors like nuclear factor-kB and activator proteins; interaction with human leukocytes antigen may induce cellular apoptosis [58,62]. Simultaneously, acute attack by foreign invaders might damage cell membrane [63], mitochondria [64] and nucleus [65]. On the other hand, chronic inflammation may lead to auto immune diseases as well as cancer [66]. Arsenic, often interferes with host immunity and may cause systemic inflammation by stimulating several immune cells like T-cells, antigen presenting cells and phagocytic cells [67]. The possible role of arsenic in the development of inflammation, infection and carcinoma have been proposed about 50 years ago since then several other studies have been trying to correlate with the molecular mechanisms [68]. Inflammatory and pro-inflammatory genes like interleukin-1beta, interleukin-6, chemokine (C-X-C motif) ligand 1, chemokine (C-X-C motif) ligand 2, CD14 antigen, activated leukocyte cell adhesion molecule and several other molecules have been observed due to arsenic exposed human subjects [69]. In addition, expression of nuclear factor-kB in newborn child have been also identified whose mothers were previously exposed in arsenic toxicity linked with systemic inflammation [70]. Cardiovascular inflammation has been previously reported due to chronic arsenic exposure on genetic mice model and exposure of arsenic on 3-week-old mice to 49 ppm as NaAsO2 in drinking water for 7 weeks developed atherosclerotic lesion formation in ApoE−/− mice [71]. Besides, chronic exposure of arsenic on animal model also confirmed cardiovascular diseases when 5-lipoxygenase (5-LO) products like leukotriene E4 (LTE4) and prostacyclin (PGI2) found significantly increased in the serum of arsenic-treated ApoE// LDLr/ mice [72]. In an another study,an increased level of TNF-α, iNOS, NF-kB, NADPH oxidase, caspase-3 and NO level were observed significantly high in the kidney tissue on the experimental rats, oral administration of sodium arsenite (NaAsO2), 5 mg/(kg day) for 4 weeks was given [73].

Effect of Arsenic on Other Organs

The ground poison, arsenic, not only affects skin and hair but also disturbs almost all the way has it travelled in human body. Arsenic-mediated cell stress often contributes in several organs damage e.g. vascular damages; kidney damages, reproductive organ dysfunction, brain damage, blood disorders and several other physiologies are suffered due to both acute and chronic arsenic exposures. Arsenic-induced myocardium abnormalities have been previously studied, when it applies on rats it reduced cardiomyocyte viability, increased reactive oxygen species (ROS) production and intracellular calcium overload, and induced apoptotic cell death by mitochondrial dependent caspase-3 activation and poly-ADP ribose polymerase (PARP) cleavage that further lead to increase IKK and NF-κB (p65) phosphorylation via oxidative mediated pathway and finally induce cardiac apoptosis [74]. Moreover, chronic inorganic arsenic exposure induces hepatic individual gene hypo methylation which leads to hepatic carcinoma [75]. While, arsenic exposure through drinking water induces oxidative stress and tissue damage in the kidney and brain by increasing lipid peroxidation, reduced glutathione content and the activities of superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase that eventually cause severe organ injuries [76]. Chronic arsenic exposure also decreased mitochondrial biogenesis and thus damage normal kidney functions [77]. Reproductive organ like testis has also been affected by acute arsenic toxicity, when it was applied on rats, iNOS and caspase-3 level were observed significantly high which ultimately suppressed testicular testosterone production [78]. Inorganic arsenic has been also linked with diabetes though the exact molecular mechanism is not well explained. Environmental toxins like arsenic induced oxidative stress in liver, pancreas and heart tissues that further lead in the development of diabetes [79,80].

Possible Treatments strategies on Arsenic Toxicity

Arsenic not only produces skin diseases and hair fall but also induce the situations like cell stress which lead to other organ damages. On the other hand, it conducts with immunity and by which finally linked with life threatening cancer [81]. Several approaches have been proposed so far on several animal models and human subjects. Both natural and synthetic components have been found effective against arsenic and arsenic-mediated problems. It is mostly hypothesized that arsenic-mediated damages are the outcome of oxidative stress, thus antioxidant therapies are mostly prescribed [82,83]. Very limited literatures on treatment of skin diseases and hair fall induced by arsenic are found on internet searching or only few studies have been investigated. However, many authors linked that arsenic-induced dysfunctions are mediated through oxidative stress [83,84]. A randomized trial on Bangladeshi subjects (121 men and women) whom vitamin E, selenium, vitamin E and selenium (combination), or placebo and were treated for 6 months and after that period skin lesion found improved although the treatment was not statically significant [85]. The biological targets of arsenic are largely unknown till now. The explorations for several other targets are still investigation for new proteins and receptors. Arsenic induces oxidative DNA damage in mammalian cells so inhibition of oxidative stress/damage may prevent from arsenic-mediated dysfunctions [86].

Subjects	Outcomes of the study	References
Model: Swiss albino mice. Age/Wt of model: 6 weeks old Molecule: Hyacinth root powder Duration: 8 weeks	- Hyacinth root powder prevented mice growth retardation and tail wounding, and - Prevented the distortion of the shape of blood cells and serum enzymes, e.g. lactate dehydrogenase, alkaline phosphatase, and serum glutamic pyruvic transaminase.	[87]
Model: HaCaT cell line Age/Wt of model: N/A Molecule: Monoisoamyldimercaptosuccinic acid Duration: 25 hours	- Reduced oxidative stress by inducing antioxidant enzymes such as, superoxide dismutase, glutathione peroxide, and - Restored apoptotic enzymes like caspase-3 and caspase-9.	[88]
Model: Healthy male albino rats of Wistar strain Age/Wt of model: 170-180 g Molecule: Daily trisulfide Dose: 80mg/kg/body wt Duration:4 weeks	- Reduced the levels of thiobarbituric acid, malondialdehyde, MCV and HCV, and - Reduced ROS level and increased WBC, RBC and platelets.	[89]
Model: Male Wistar rats Age/Wt of model: Molecule: Nanocurcumin Dose: 15 mg/kg Duration:4 weeks	- Prevented the inhibition of δ-aminolevulinic acid dehydratase, and - Nanocurcumin removed arsenic from blood because of enhanced bioavailability and chelating potential.	[90]
Model: N/A Age/Wt of model: N/A Molecule: Feric chloride Duration: 30 min	- FeCl3 removed arsenic (III, IV, V) by coagulation which is influenced by pH.	[91]
Model: Adult male Sprague-Dawley rats Age/Wt of model: 4 weeks old Molecule: Biochanin A Dose: 20 mg/kg/body wt/ day Duration:6 weeks	- Attenuated hepatic markers like AST, ALT, and - Ameliorated hematological toxicity by increasing the HCT, MCV, and MCH, but decreasing the MCHC, withnormal RBC, HG, RDW, CHCM, and HDW	[92]
Model: Healthy adult male albino rats Age/Wt of model: 170-190 kg Molecule: Silibinin Dose: 75 mg/kg BW/day Duration: 4 weeks	- It prevented the reduction of DNA damage in hepatocytes, and - Decreased total bilirubin, elevated the activities of membrane bound ATPases, glucose-6-phospate dehydrogenase, total sulfydryl groups, vit-C and E.	[93]
Model: Male Wistar rats Age/Wt of model: 90 g Molecule: DMSA and Captopril	- DMSA elevated the level of blood δ-aminolevulinic acid dehydratase, and - Captopril in combination with DMSA decreased TBARs levels and arsenic concentration from blood and soft tissues.	[94]

Dose: 50 mg/kg once daily Duration: 5 days		
Model: Female Wistar rats Age/Wt of model: 141-219g Molecule: Buffalo epiphyseal proteins Dose: 100 microgram/kg/ body wt Duration: 28 days	- Prevented lipid peroxidation in brain, cardiac and hepatic tissues, and - Increased the levels of catalase, SOD and reduced glutathione levels.	[95]
Model: Male Swiss albino mice Age/Wt of model: 60-70 days Molecule: N-Acetyl Cysteine Dose: 75 mg/kg body wt Duration: 35 days	- Increased the activity levels of testicular 3 beta- and 17beta- hydroxysteroid dehydrogenases and circulatory levels of testosterone resulting in the improvement of steroidogenesis, and - Elevated the weights of reproductive organs by increasing epididymal sperm count, motile sperms and viable sperms	[96]

Table 2: Effects of protective molecules against arsenic-mediated toxicity.

Case 1

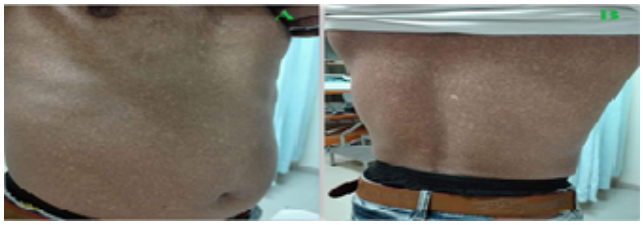

Figure 3: A 39 years old male visited hospital to discuss his skin related problems. After knowing the history and background it was confirmed that he was suffering from raindrop patterned dyspigmentation due to arsenic poisoning. He had no history of skin diseases and other family history of skin diseases. The person was exposed in arsenic poisoning his whole life until he visited.

Case 2

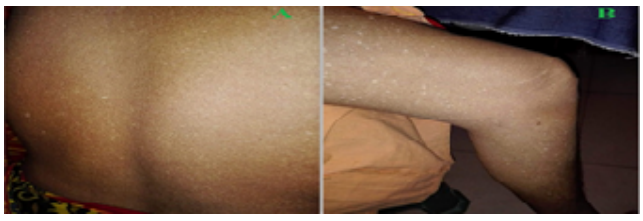

Figure 4: A 37 years old woman admitted in the clinic and found hypo and hyperpigmentation over thong due to chronic arsenic exposure from tube well water. The woman had no such past history of other skin diseases. The physician explained it was symmetrically distributed.

Case 3

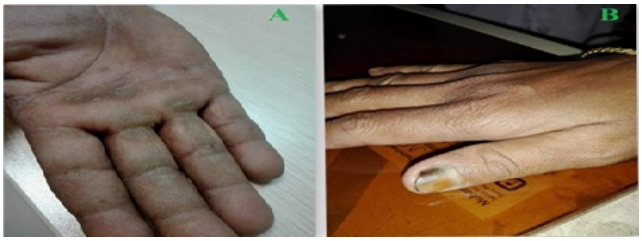

Figure 5: A 45 years old woman visited at hospital and found diffuse hyperkeratinization and hyperpigmentation of palm and sole while examined by the physician. The skin was scaly, fissuring and cracky. The nails were found discoloration.

Recommendations

In all the 3 cases (Figures 3,4 and 5) the subjects were asked to perform the tests like Blood CBC, Urine P/M/E, Stool P/M/E, Chest X-ray, RBC, ECG, Serum creatinine, Serum urea and skin biopsy.

Treatment

Food/Life style: Stop taking arsenic containing water and Diet rich in Protein.

Topical: keratolytic ointment, (3%/6% salicylic acid) and Lactic acid cream.

Systemic: Antioxidants

Conclusion and Future Directions

Recent literatures have proved several destructive properties on both animal and human subjects due to arsenic exposures. Arsenic and arsenic-mediated organ dysfunctions have been a global issue which evolved as a serious concern in the health sectors. Countries like Bangladesh and India are suffering most due to negative impacts on health. As skin and hair are the most visible parts of a biological system, it should be more focused in sense of treatment approaches.

Arsenic induced skin diseases as well as hair fall are increasing theatrically, as a result, effective strategies to treat these conditions are being emerged. Likewise, the treatment on topical application, concern on the prevention for other organs and circulation must be considered first. Removal of arsenic toxin from drinking water and foods by suitable technologies are the most important control and management strategies. Antioxidant treatments are currently being prescribed against arsenic-mediated oxidative stress but this approach has been limited to cure properly. Current researches must conduct some alternative ways against arsenic-mediated dysfunctions.

Conflict of Interest

None to declare.

References

1. Lelieveld J, Evans JS, Fnais M, Giannadaki D, Pozzer A (2015) The contribution of outdoor air pollution sources to premature mortality on a global scale. Nature 525: 367-371.
2. Lin HJ, Sung TI, Chen CY, Guo HR (2013) Arsenic levels in drinking water and mortality of liver cancer in Taiwan. J Hazard Mater 262: 1132-1138.
3. Abdul KS, Jayasinghe SS, Chandana EP, Jayasumana C, De Silva PM (2015) Arsenic and human health effects: A review. Environ Toxicol Pharmacol 40: 828-846.
4. Zhao XY, Li GY, Liu Y, Chai LM, Chen JX, et al. (2008) Resveratrol protects against arsenic trioxide-induced cardiotoxicity in vitro and in vivo. Br J Pharmacol 154: 105-113.
5. Santra A, Maiti A, Das S, Lahiri S, Charkaborty SK, et al. (2000) Hepatic damage caused by chronic arsenic toxicity in experimental animals. J Toxicol Clin Toxicol 38: 395-405.
6. Meliker JR, Wahl RL, Cameron LL, Nriagu JO (2007) Arsenic in drinking water and cerebrovascular disease, diabetes mellitus, and kidney disease in Michigan: a standardized mortality ratio analysis. Environ Health 6: 4.
7. Flora SJ, Bhadauria S, Pant SC, Dhaked RK (2005) Arsenic induced blood and brain oxidative stress and its response to some thiol chelators in rats. Life Sci 77: 2324-2337.
8. Vahidnia A, van der Voet GB, de Wolff FA (2007) Arsenic neurotoxicity--a review. Hum Exp Toxicol 26: 823-832.
9. Mazumder DNG, Haque R, Ghosh N, De Binay K, Santra A, et al. (2000) Arsenic in drinking water and the prevalence of respiratory effects in West Bengal, India. Int J Epidemiol 29: 1047-1052.
10. Chen CJ, Chen CW, Wu MM, Kuo TL (1992) Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. Br J Cancer 66: 888-892.
11. Tam G, Charbonneau S, Bryce F, Pomroy C, Sandi E (1979) Metabolism of inorganic arsenic (74As) in humans following oral ingestion. Toxicol Appl Pharmacol 50: 319-322.
12. Emadi A1, Gore SD (2010) Arsenic trioxide - An old drug rediscovered. Blood Rev 24: 191-199.
13. Lynn S, Gurr JR, Lai HT, Jan KY (2000) NADH oxidase activation is involved in arsenite-induced oxidative DNA damage in human vascular smooth muscle cells. Circ Res 86: 514-519.
14. Chakraborty AK, Saha KC (1987) Arsenical dermatosis from tubewell water in West Bengal. Indian J Med Res 85: 326-334.
15. Liu J, Zheng B, Aposhian HV, Zhou Y, Chen ML, et al. (2002) Chronic arsenic poisoning from burning high-arsenic-containing coal in Guizhou, China. Environ Health Perspect 110: 119.
16. Zhang Y, Duan X, Li J, Zhao S, Li W, et al. (2016) Inorganic Arsenic Induces NRF2-Regulated Antioxidant Defenses in Both Cerebral Cortex and Hippocampus in Vivo. Neurochem Res 41: 2119-2128.
17. Organization WH: Arsenic: Geneva, Switzerland; 1981.
18. Ma LQ, Komar KM, Tu C, Zhang W, Cai Y, et al. (2001) A fern that hyperaccumulates arsenic. Nature 409: 579.
19. Hughes MF (2002) Arsenic toxicity and potential mechanisms of action. Toxicol Lett 133: 1-16.
20. Van Geen A, Zheng Y, Goodbred Jr S, Horneman A, Aziz Z, et al. (2008) Flushing history as a hydrogeological control on the regional distribution of arsenic in shallow groundwater of the Bengal Basin. Environ Sci Tech 42: 2283-2288.
21. Ratnaike RN (2003) Acute and chronic arsenic toxicity. Postgrad Med J 79: 391-396.
22. Gorchev HG, Ozolins G (1984) WHO guidelines for drinking-water quality. WHO Chron 38: 104-108.
23. Burros M (2006) chicken with arsenic? is that OK. The New York Times.
24. Csalagovits I (1993) Arsenic-bearing artesian waters of Hungary. Annual report of the Geological Institute of Hungary 11: 85-92.
25. Das D, Chatterjee A, Mandal BK, Samanta G, Chakraborti D, et al. (1995) Arsenic in ground water in six districts of West Bengal, India: the biggest arsenic calamity in the world. Part 2. Arsenic concentration in drinking water, hair, nails, urine, skin-scale and liver tissue (biopsy) of the affected people. Analyst 120: 917-924.
26. Harvey CF, Swartz CH, Badruzzaman ABM, Keon-Blute N, Yu W, et al. (2005) Groundwater arsenic contamination on the Ganges Delta: biogeochemistry, hydrology, human perturbations, and human suffering on a large scale. Comptes Rendus Geoscience 337: 285-296.
27. Chakraborti D, Rahman MM, Chatterjee A, Das D, Das B, et al. (2016) Fate of over 480 million inhabitants living in arsenic and fluoride endemic Indian districts: Magnitude, health, socio-economic effects and mitigation approaches. J Trace Elem Med Biol 38: 33-45.
28. Sambu S, Wilson R (2008) Arsenic in food and water--a brief history. Toxicol Ind Health 24: 217-226.
29. Meding B, Lindahl G, Alderling M, Wrangsjö K, Anveden Berglind I (2013) Is skin exposure to water mainly occupational or nonoccupational? A population-based study. Br J Dermatol 168: 1281-1286.
30. Vince JE (2015) When Beauty Is Skin Deep: Regulation of the Wound Response by Caspase-8, RIPK3, and the Inflammasome. J Invest Dermatol 135: 1936-1939.
31. Liao WT, Lu JH, Lee CH, Lan CCE, Chang JG, et al. (2017) An Interaction between Arsenic-Induced Epigenetic Modification and Inflammatory Promotion in a Skin Equivalent during Arsenic Carcinogenesis. Journal of Investigative Dermatology 137: 187-196.
32. Corsini E, Asti L, Viviani B, Marinovich M, Galli CL (1999) Sodium arsenate induces overproduction of interleukin-1a in murine keratinocytes: role of mitochondria. J Invest Dermatol 113: 760-765.
33. Liao WT, Chang KL, Yu CL, Chen GS, Chang LW, et al. (2004) Arsenic induces human keratinocyte apoptosis by the FAS/FAS ligand pathway, which correlates with alterations in nuclear factor-?B and activator protein-1 activity. J Invest Dermatol 122:125-129.
34. Banerjee N, Nandy S, Kearns JK, Bandyopadhyay AK, Das JK, et al. (2011) Polymorphisms in the TNF-a and IL10-gene promoters and risk of arsenic-induced skin lesions and other non-dermatological health effects. Toxico Sci : kfr046.
35. Seow WJ, Kile ML, Baccarelli AA, Pan WC, Byun HM, et al. (2014) Epigenome-wide DNA methylation changes with development of arsenic-induced skin lesions in Bangladesh: A case–control follow-up study. Environmental and molecular mutagenesis 55: 449-456.
36. Hsu LI, Chen GS, Lee CH, Yang TY, Chen YH, et al. (2013) Use of arsenic-induced palmoplantar hyperkeratosis and skin cancers to predict risk of subsequent internal malignancy. Ame J Epidemol : kws369.
37. Banerjee N, Paul S, Sau TJ, Das JK, Bandyopadhyay A, et al. (2013) Epigenetic modifications of DAPK and p16 genes contribute to arsenic-induced skin lesions and nondermatological health effects. Toxico Sci 135: 300-308.
38. Ahsan H, Chen Y, Kibriya MG, Slavkovich V, Parvez F, et al. (2007) Arsenic metabolism, genetic susceptibility, and risk of premalignant skin lesions in Bangladesh. Cancer Epidemiol Biomarkers Prev 16: 1270-1278.

39. Ahsan H, Chen Y, Parvez F, Zablotska L, Argos M, Hussain I, et al. (2006) Arsenic exposure from drinking water and risk of premalignant skin lesions in Bangladesh: baseline results from the Health Effects of Arsenic Longitudinal Study. Am J Epidemiol 163: 1138-1148.
40. Argos M, Kalra T, Pierce BL, Chen Y, Parvez F, et al. (2011) A prospective study of arsenic exposure from drinking water and incidence of skin lesions in Bangladesh. Am J Epidemiol 174: 185-194.
41. Kile ML, Hoffman E, Rodrigues EG, Breton CV, Quamruzzaman Q, et al. (2011) A pathway-based analysis of urinary arsenic metabolites and skin lesions. Am J Epidemiol 173: 778-786.
42. Melkonian S, Argos M, Pierce BL, Chen Y, Islam T, et al. (2011) A prospective study of the synergistic effects of arsenic exposure and smoking, sun exposure, fertilizer use, and pesticide use on risk of premalignant skin lesions in Bangladeshi men. Am J Epidemiol 173: 183-191.
43. Pierce BL, Argos M, Chen Y, Melkonian S, Parvez F, et al. (2011) Arsenic exposure, dietary patterns, and skin lesion risk in bangladesh: a prospective study. Am J Epidemiol 173: 345-354.
44. Yunus FM, Rahman MJ, Alam MZ, Hore SK, Rahman M (2014) Relationship between arsenic skin lesions and the age of natural menopause. BMC Public Health 14: 419.
45. Lindberg AL, Rahman M, Persson LA, Vahter M (2008) The risk of arsenic induced skin lesions in Bangladeshi men and women is affected by arsenic metabolism and the age at first exposure. Toxicol Appl Pharmacol 230: 9-16.
46. Seow WJ, Pan WC, Kile ML, Baccarelli AA, Quamruzzaman Q, et al. (2012) Arsenic reduction in drinking water and improvement in skin lesions: a follow-up study in Bangladesh. Environ Health Perspect 120: 1733.
47. Olsen EA, Canfield D (2016) SALT II: A new take on the Severity of Alopecia Tool (SALT) for determining percentage scalp hair loss. J Am Acad Dermatol 75: 1268-1270.
48. Yip L, Zaloumis S, Irwin D, Severi G, Hopper J, et al. (2016) Thyroid profile and serum ferritin and vitamin D3 levels are also important as their deficiencies can also lead to similar hair loss. Hair Transplantation 27: 63.
49. Kolivras A, Thompson C (2016) Distinguishing diffuse alopecia areata (AA) from pattern hair loss (PHL) using CD3(+) T cells. J Am Acad Dermatol 74: 937-944.
50. Hindmarsh JT (2002) Caveats in hair analysis in chronic arsenic poisoning. Clin Biochem 35: 1-11.
51. Smith S, Hendry EB (1934) ARSENIC IN ITS RELATION TO THE KERATIN TISSUES. Br Med J 2: 675-677.
52. Young EG, Rice F (1944) On the occurrence of arsenic in human hair and its medicolegal significance. J Laboratory Clin Med 29: 439-446.
53. Samanta G1, Sharma R, Roychowdhury T, Chakraborti D (2004) Arsenic and other elements in hair, nails, and skin-scales of arsenic victims in West Bengal, India. Sci Total Environ 326: 33-47.
54. Rasheed H, Kay P, Slack R, Gong YY, Carter A (2017) Human exposure assessment of different arsenic species in household water sources in a high risk arsenic area. Sci Total Envir.
55. Serrano IN, Ballesteros MTL, Pacheco SSF, Álvarez SI, Colón JLL (2016) Total and speciated urinary arsenic levels in the Spanish population. Sci Total Environ 571: 164-171.
56. Sarker MMR (2011) Assessment of arsenic exposure to human, concentrations in tube well water and urine, and body mass index. Int J Environm Sci Develop 2: 38.
57. Mohib MM, Hasan I, Chowdhury WK, Chowdhury NU, Mohiuddin S, et al. (2016) Role of Angiotensin II in Hepatic Inflammation through MAPK Pathway: A Review. J Hepa 2: 13.
58. Chowdhury N, Farooq T, Abdullah S, Mahadi A, Hasan M (2016) Molecular Enzymology and Drug Targets Matrix Metalloproteinases (MMP), a Major Responsible Downstream Signaling Molecule for Cellular Damage-A Review. Mol Enz Drug Tar 2.
59. Reza HM, Sagor MAT, Alam MA (2015) Iron deposition causes oxidative stress, inflammation and fibrosis in carbon tetrachloride-induced liver dysfunction in rats. Bangladesh J Pharmacol 10: 152-159.
60. Alam MA, Chowdhury MRH, Jain P, Sagor MAT, Reza HM (2010) DPP-4 inhibitor sitagliptin prevents inflammation and oxidative stress of heart and kidney in two kidney and one clip (2K1C) rats. Diabetology & metabolic syndrome 7 :1-10.
61. Sagor MAT, Tabassum N, Potol MA, Alam MA (2015) Xanthine Oxidase Inhibitor, Allopurinol, Prevented Oxidative Stress, Fibrosis, and Myocardial Damage in Isoproterenol Induced Aged Rats. Oxidative Med Cell Longevity 2015: 9.
62. Chowdhury MRH, Sagor MAT, Tabassum N, Potol MA, Hossain H, et al. (2015) Supplementation of Citrus maxima Peel Powder Prevented Oxidative Stress, Fibrosis, and Hepatic Damage in Carbon Tetrachloride (CCl4) Treated Rats. Evid Based Complement Alternat Med : 10.
63. Sagor AT, Chowdhury MR, Tabassum N, Hossain H, Rahman M, et al. (2015) Supplementation of fresh ucche (Momordica charantia L. var. muricata Willd) prevented oxidative stress, fibrosis and hepatic damage in CCl treated rats. BMC Complement Altern Med 15: 115.
64. Abu Taher S, Hasan Mahmud R, Nabila T, Biswajit S, Anayt U, et al. (2016) Supplementation of rosemary leaves (Rosmarinus officinalis) powder attenuates oxidative stress, inflammation and fibrosis in carbon tetrachloride (CCl4) treated rats. Current Nutrition & Food Science 12: 1-8.
65. Reza HM, Tabassum N, Sagor MAT, Chowdhury MRH, Rahman M, et al. (2016) Angiotensin-converting enzyme inhibitor prevents oxidative stress, inflammation, and fibrosis in carbon tetrachloride-treated rat liver. Toxicol Mech Methods : 46-53.
66. Mohib MM, Rabby SMF, Paran TZ, Hasan MM, Ahmed I, et al. (2016) Protective role of green tea on diabetic nephropathy -A review. Cogent Biol : 1248166.
67. Ahmed S, Khoda SM-E, Rekha RS, Gardner RM, Ameer SS, et al. (2011) Arsenic-associated oxidative stress, inflammation, and immune disruption in human placenta and cord blood. Environ Health Perspect 119: 258-264.
68. Stone OJ (1969) The effect of arsenic on inflammation, infection, and carcinogenesis. Tex Med 65: 40-43.
69. Wu MM, Chiou HY, Ho IC, Chen CJ, Lee TC (2003) Gene expression of inflammatory molecules in circulating lymphocytes from arsenic-exposed human subjects. Environ Health Perspect. 111: 1429.
70. Fry RC, Navasumrit P, Valiathan C, Svensson JP, Hogan BJ, et al. (2007) Activation of inflammation/NF-kappaB signaling in infants born to arsenic-exposed mothers. PLoS Genet 3: e207.
71. Srivastava S, Vladykovskaya EN, Haberzettl P, Sithu SD, D'souza SE, et al. (2009) Arsenic exacerbates atherosclerotic lesion formation and inflammation in ApoE-/-mice. Toxicol Appl Pharmacol 241: 90-100.
72. Bunderson M, Brooks DM, Walker DL, Rosenfeld ME, Coffin JD, et al. (2004) Arsenic exposure exacerbates atherosclerotic plaque formation and increases nitrotyrosine and leukotriene biosynthesis. Toxicol Appl Pharmacol 201: 32-39.
73. Prabu SM, Muthumani M (2012) Silibinin ameliorates arsenic induced nephrotoxicity by abrogation of oxidative stress, inflammation and apoptosis in rats. Mol Biol Rep 39: 11201-11216.
74. Ghosh J, Das J, Manna P, Sil PC (2009) Taurine prevents arsenic-induced cardiac oxidative stress and apoptotic damage: Role of NF-?B, p38 and JNK MAPK pathway. Toxicol Appl Pharmacol 240: 73-87.
75. Chen H, Li S, Liu J, Diwan BA, Barrett JC, et al. (2004) Chronic inorganic arsenic exposure induces hepatic global and individual gene hypomethylation: implications for arsenic hepatocarcinogenesis. Carcinogenesis 25: 1779-1786.
76. Sankar P, Telang AG, Kalaivanan R, Karunakaran V, Suresh S, et al. (2016) Oral nanoparticulate curcumin combating arsenic-induced oxidative damage in kidney and brain of rats. Toxicol Ind Health 32: 410-421.
77. Gong X, Ivanov VN, Davidson MM, Hei TK (2015) Tetramethylpyrazine (TMP) protects against sodium arsenite-induced nephrotoxicity by suppressing ROS production, mitochondrial dysfunction, pro-

inflammatory signaling pathways and programed cell death. Arch Toxicol 89: 1057-1070.

78. Fouad AA, Albuali WH, Jresat I (2014) Protective effect of thymoquinone against arsenic-induced testicular toxicity in rats. Z Naturforsch C 8: 175-181.
79. Patel HV, Kalia K (2013) Role of hepatic and pancreatic oxidative stress in arsenic induced diabetic condition in Wistar rats. J Environ Biol 34: 231.
80. Kuo CC, Howard BV, Umans JG, Gribble MO, Best LG, et al. (2015) Arsenic exposure, arsenic metabolism, and incident diabetes in the strong heart study. Diabetes Care 38: 620-627.
81. Hsu KH, Tsui KH, Hsu LI, Chiou HY, Chen CJ (2016) Dose-Response Relationship between Inorganic Arsenic Exposure and Lung Cancer among Arseniasis Residents with Low Methylation Capacity. Cancer Epidemiol Prevent Biomarkers.
82. Srivastava M, Ma LQ, Singh N, Singh S (2005) Antioxidant responses of hyper-accumulator and sensitive fern species to arsenic. J Exp Bot 56: 1335-1342.
83. Shri M, Kumar S, Chakrabarty D, Trivedi PK, Mallick S, et al. (2009) Effect of arsenic on growth, oxidative stress, and antioxidant system in rice seedlings. Ecotoxicol Environ Saf 72: 1102-1110.
84. Jomova K, Jenisova Z, Feszterova M, Baros S, Liska J, et al. (2011) Arsenic: toxicity, oxidative stress and human disease. J Appl Toxicol 31: 95-107.
85. Verret WJ, Chen Y, Ahmed A, Islam T, Parvez F, et al. (2005) A randomized, double-blind placebo-controlled trial evaluating the effects of vitamin E and selenium on arsenic-induced skin lesions in Bangladesh. J Occup Environ Med 47: 1026-1035.
86. Kessel M, Liu SX, Xu A, Santella R, Hei TK (2002) Arsenic induces oxidative DNA damage in mammalian cells. Mol Cell Biochem 234-235: 301-8.
87. Sarker J, Sabrina R, Ahsan N, Hossain K, Kumar Ghosh P, et al. (2012) Reduction of sodium arsenite-mediated adverse effects in mice using dietary supplementation of water hyacinth (Eichornia crassipes) root powder. Avicenna J Med Biotechnol 4: 148-154.
88. Pachauri V, Srivastava P, Yadav A, Kushwaha P, Flora SJ (2013) MiADMSA protects arsenic-induced oxidative stress in human keratinocyte 'HaCaT'cells. Biol Trace Elem Res 153: 396-402.
89. Sumedha N, Miltonprabu S (2013) Arsenic induced oxidative hematotoxicity in rats and its protection by diallyl trisulfide. Int J Biol Pharmaceut Res 4: 507-515.
90. Yadav A, Flora S (2016) Nanocurcumin Prevents Oxidative Stress Induced following Arsenic and Fluoride Co-exposure in Rats. Defence Life Sci J: 1.
91. Qiao J, Jiang Z, Sun B, Sun Y, Wang Q, et al. (2012) Arsenate and arsenite removal by FeCl 3: effects of pH, As/Fe ratio, initial As concentration and co-existing solutes. Sep Purif Technol 92: 106-114.
92. Jalaludeen AM, Ha WT, Lee R, Kim JH, Do JT, et al. (2016) Biochanin A Ameliorates Arsenic-Induced Hepato- and Hematotoxicity in Rats. Molecules 21: 69.
93. Muthumani M, Prabu SM (2012) Silibinin potentially protects arsenic-induced oxidative hepatic dysfunction in rats. Toxicol Mech Methods 22: 277-288.
94. Kalia K, Narula GD, Kannan G, Flora S (2007) Effects of combined administration of captopril and DMSA on arsenite induced oxidative stress and blood and tissue arsenic concentration in rats. Comp Biochem Physiol C Toxicol Pharmacol 144: 372-379.
95. Bharti VK, Srivastava R, Sharma B, Malik J (2012) Buffalo (Bubalus bubalis) epiphyseal proteins counteract arsenic-induced oxidative stress in brain, heart, and liver of female rats. Biol Trace Elem Res 146: 224-229.
96. Reddy PS, Rani GP, Sainath S, Meena R, Supriya C (2011) Protective effects of N-acetylcysteine against arsenic-induced oxidative stress and reprotoxicity in male mice. Journal of Trace Elements in Medicine and Biology 25: 247-253.