## 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].
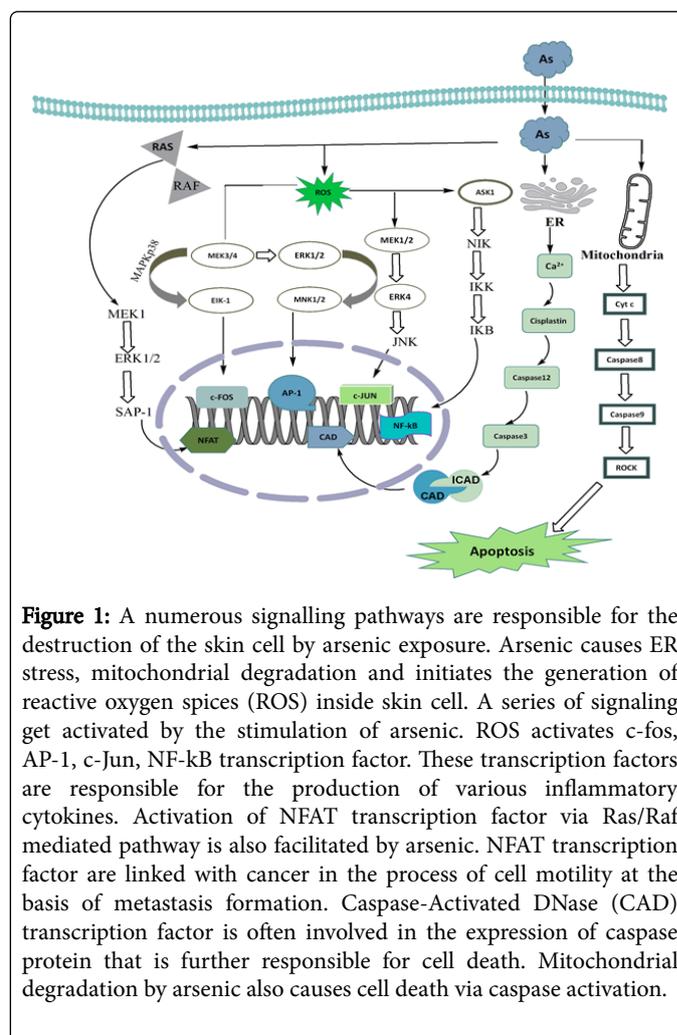
Figure 1: A numerous signalling pathways are responsible for the destruction of the skin cell by arsenic exposure. Arsenic causes ER stress, mitochondrial degradation and initiates the generation of reactive oxygen spices (ROS) inside skin cell. A series of signaling get activated by the stimulation 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].
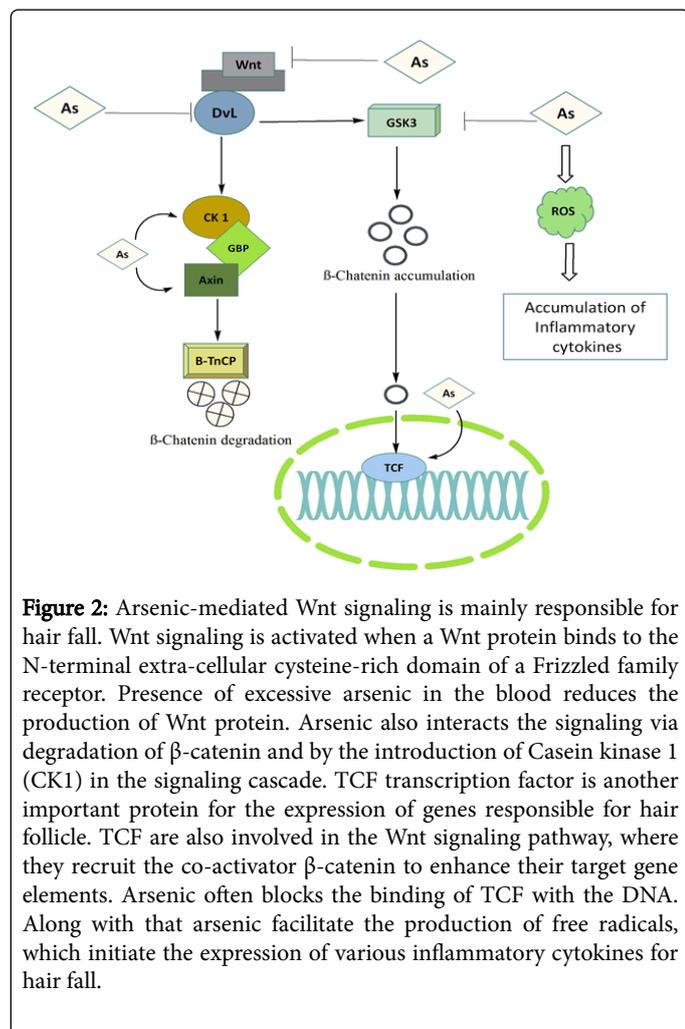
Figure 2: Arsenic-mediated Wnt signaling is mainly responsible for hair fall. Wnt signaling is activated when a Wnt protein binds to the N-terminal extra-cellular cysteine-rich domain of a Frizzled family receptor. Presence of excessive arsenic in the blood reduces the production of Wnt protein. Arsenic 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.

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