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Review Article

The blood toll of arsenic: addressing hematological disorders and future directions

Rubia Mondal[1]*, Raghwendra Mishra[2], Jeet Maity[3], Prakriti Chanda[3], Samhita Das[3], Maitree Dey[4], Subhadeep Ghoshal[1], Tandra Ghosh[1], Prabir Kumar Mukhopadhyay[3]

[1]Department of Physiology, All India Institute of Medical Sciences, Kalyani, West Bengal, India
[2]Department of Physiology, Ananda Mohan College, Affiliated to University of Calcutta, Kolkata, West Bengal, India
[3]Department of Life Sciences, Presidency University, Kolkata, West Bengal, India
[4]Department of Physiology, University of Kalyani, Kalyani, West Bengal, India

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***Correspondence:**
Dr. Rubia Mondal,
E-mail: rubia.mondal@gmail.com

ABSTRACT

Arsenic contamination is a critical global health threat, with the hematological system being a primary target of its toxicity. This review synthesized current scientific literature from PubMed and Web of Science to document arsenic-induced hematotoxicity and evaluate the efficacy of various amelioration strategies. Inorganic arsenic uses a variety of cell membrane transporter proteins, including different proton and phosphate transporters and the anion exchanger Band 3 protein for entry into the cell. Glucose transporters, aquaporins, and ATP-binding cassette transporters are used for the extrusion of arsenic. The markers of hematotoxicity are shown to be severely altered in arsenic-treated fish and mammalian models. Moreover, significant alterations, including DNA methylation, altered T cell populations, increased PBMCs associated with marked neutropenia, apoptosis of blood monocytes, etc., were observed in leucocytes. Transformation of discoidal erythrocytes to echinocytes, followed by spheroechinocytes and eryptosis, is considered an impending cause for arsenic-induced anaemia. Chelating agents, various plant extracts, and/or nutraceutical agents such as ascorbic acid, α-tocopherol, and lipoic acid are found to be protective against arsenic-induced hematotoxicity. This comprehensive documentation offers a clear overview of the research conducted in this vital area, indicating that the management of arsenic-induced hematotoxicity is achievable with the aforementioned compounds or extracts. A comparative analysis using secondary data is essential to ascertain the potency and efficacy of various ameliorative agents. This would provide a complete understanding of hematological arsenicosis and guide future directions for remedial measures.

Keywords: Arsenic, Hematology, Anaemia, Echinocyte, Leucocyte, Nutraceutical

INTRODUCTION

Arsenic, a naturally occurring and widely distributed metalloid which exists in four oxidation states, i.e., +5, +3, 0 and -3, is a potent environmental pollutant responsible for multiple organs damage and oncogenesis. A major source of human exposure to arsenic is arsenic-contaminated groundwater used for drinking and agricultural purposes, and levels in several countries, including India, are well above the permissible limit of 0.05 mg/l set by the WHO.[1] Arsenic toxicity, also known as arsenicosis, is a serious health concern around the world, and it has been estimated that more than 150 million people are affected by it worldwide. Arsenic toxicity has different reversible and irreversible, clinical and subclinical manifestations, of acute, sub-chronic and chronic nature. Acute poisoning results in nausea, vomiting, abdominal pain, diarrhoea, renal and

respiratory disorders, along with hematological anomalies, whereas chronic exposure can cause a wide range of disorders, including specific skin lesions like pigmentation, along with keratosis, non-malignant lung disease, dyspepsia, black foot disease, urinary bladder and lung cancers.[2]

The major routes by which arsenate [H_2AsO_4- and $HASO4_2$-] and arsenite [H_3AsO_3- and H_2AsO_3-], the primary inorganic arsenic species responsible for toxic effects, enter the human body are oral, dermal exposure and inhalation, being other minor routes. Ingested arsenic is absorbed in the small intestine through an electrogenic process involving a proton gradient and finally travels via the portal vein to liver. In the liver, it undergoes biomethylation to give rise to organic arsenic derivatives monomethylarsenous (MMAIII) and dimethylarsenous (DMAIII) ions, which are then released into circulation. The presence of several sulfhydryl (-SH) group-containing proteins, along with low-molecular-weight compounds such as glutathione and cysteine, further aids in the retention of arsenic in circulation, making hematological cells an easy target for arsenic poisoning and its toxic manifestations.

Although studies related to arsenic-mediated anaemia, its signalling and the subsequent mitigation reports are available in the literature, there is a dearth of collective information available for researchers engaged in this field. Hence, the main purpose of the present article is to thoroughly review the arsenic-induced hematological alterations and erythrocyte morphological response and to critically discuss the possible remedial measures with dietary supplements to overcome hematotoxicity caused by arsenic poisoning.

METHODS

A comprehensive literature search was executed utilizing the PubMed and Web of Science databases. The scope of inclusion was strictly limited to full-text scientific journal articles, without imposing any temporal constraints. Although a substantial body of research exists concerning arsenic toxicity, its preventive strategies, and mechanisms of action, publications directly pertinent to the specific objectives of this review were found to be limited. Consequently, no date restrictions were applied during the literature survey. The search strategy employed the following keywords: "Arsenic," "Arsenic toxicity," "Blood," 'Hematology," and "Remedy." Trends in publication volume across decades and the geographical distribution of publishing countries, specifically pertaining to arsenic-mediated hematological alterations and their ameliorative measures, are visually represented using a bar diagram and a lollipop plot, respectively (Figure 1). All graphical presentations were generated using RStudio. Figures were created using Biorender and Chembiodraw ultra 12.0.

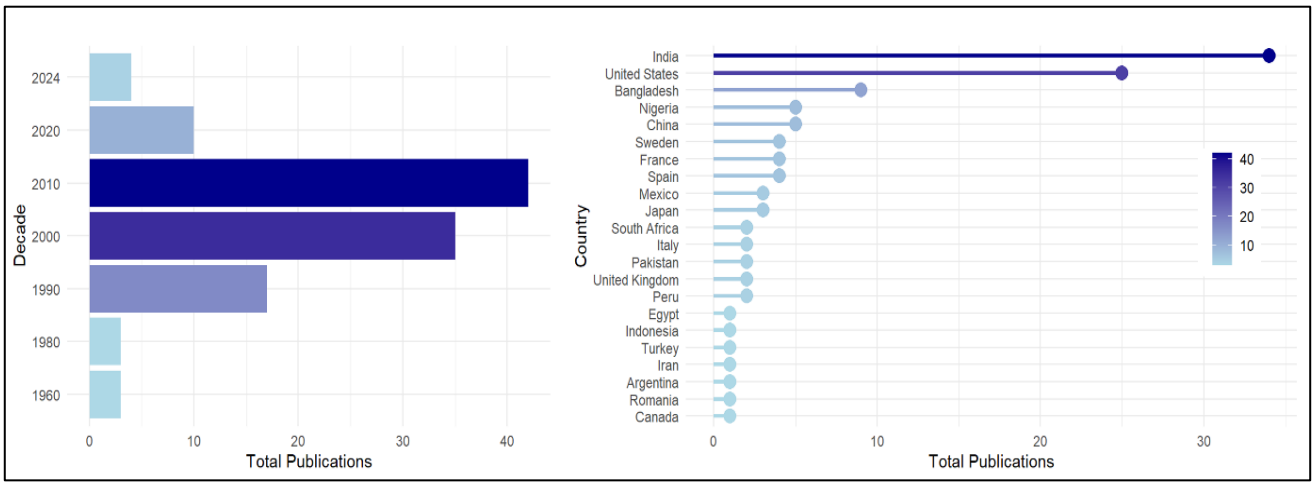

Figure 1: Temporal trends in publication output and their geographical distribution across various provinces, spanning the period from 1960 to 2025, are graphically presented.

TEMPORAL AND GEOGRAPHICAL PUBLICATION TRENDS

Between 2010 and 2020, publications concerning the hematological effects of arsenic reached their zenith (Figure. 2). Pinpointing the exact reasons for any perceived decline in research output on arsenic toxicity and blood-related alterations is challenging without comprehensive publication trend data, though this article offers a glimpse into the subject's research trajectory. It's plausible that as arsenic remediation efforts in drinking water become more widespread, the urgency for research into novel interventions and protracted health consequences might diminish, thereby contributing to a perceived dip in publications. Nevertheless, country-specific publication trends indicate a sustained and significant research focus on this topic, with India at the forefront. Furthermore, contemporary research consistently unearths previously unrecognized

dimensions of arsenic contamination in the Bengal Basin. Therefore, a comprehensive review of this topic still highlights the need for further research.

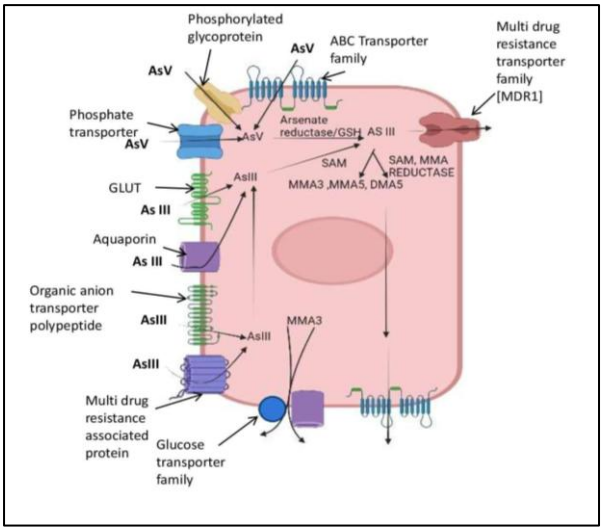

Figure 2: Uptake and intracellular transporters of arsenic species.

UPTAKE AND INTRACELLULAR TRANSPORT OF ARSENIC

The main route of exposure of inorganic arsenic is oral, and the intestinal epithelium is the first physiological barrier that it must cross in order to get absorbed. It has been observed that the Caco-2 cells (a colorectal cell line), prefer arsenate (AsV) among different arsenic species.[3] The study further suggested the possible involvement of phosphate transporters (due to structural analogy between arsenate and phosphate, the phosphate inhibited arsenic uptake by cells) and H+-dependent transporter (as the acidic environment in the stomach and proximal intestine favoured arsenic absorption) in the uptake of arsenic. The sodium-coupled phosphate transporters were also reported to be involved in arsenic uptake. Among its different subtypes, type IIb (Na-Pi-IIb) has the highest affinity for arsenate compared to type IIa (Na-Pi-IIa) and type IIc (Na-Pi-IIc). Involvement of certain other transporters in arsenic uptake by different cells has also been reported which include glucose transporters (GLUT2 and 5), sodium-glucose co-transporter (SGLT), organic anion transporting polypeptides (OATP), aquaporin's (AQP 7, 9 and 10), P-glycoprotein (P-gp), MDR1 (Multi drug resistance protein 1)/ABCB1, multidrug resistance-associated protein1, 2 and 3 (MRP-1, 2& 3).[4] Though very little information is available regarding the arsenic influx in erythrocyte, except the role of erythroid anion exchanger 1 (AE1), also known as Band3 protein, which is involved in the preferential uptake of arsenate but not for arsenite. Several interesting studies explored some other unique transporters, namely arsenite-specific resistance protein (Acr3p), yeast cadmium resistance factor (Ycf1p, a member of the ABC transporter family) involved in efflux of arsenic from cytosol either by pumping out or by vacuolization. Recent review literature stated that arsenic compounds are extruded from the cells by specialized arsenic efflux pumps such as ArsB, Acr3, ArsK or ArsP, or are transformed with the help of enzymes like ArsC, ArsM, or GAPDH prior to efflux.[5] The mode of transport and intracellular uptake of arsenic has been illustrated in Figure 2.

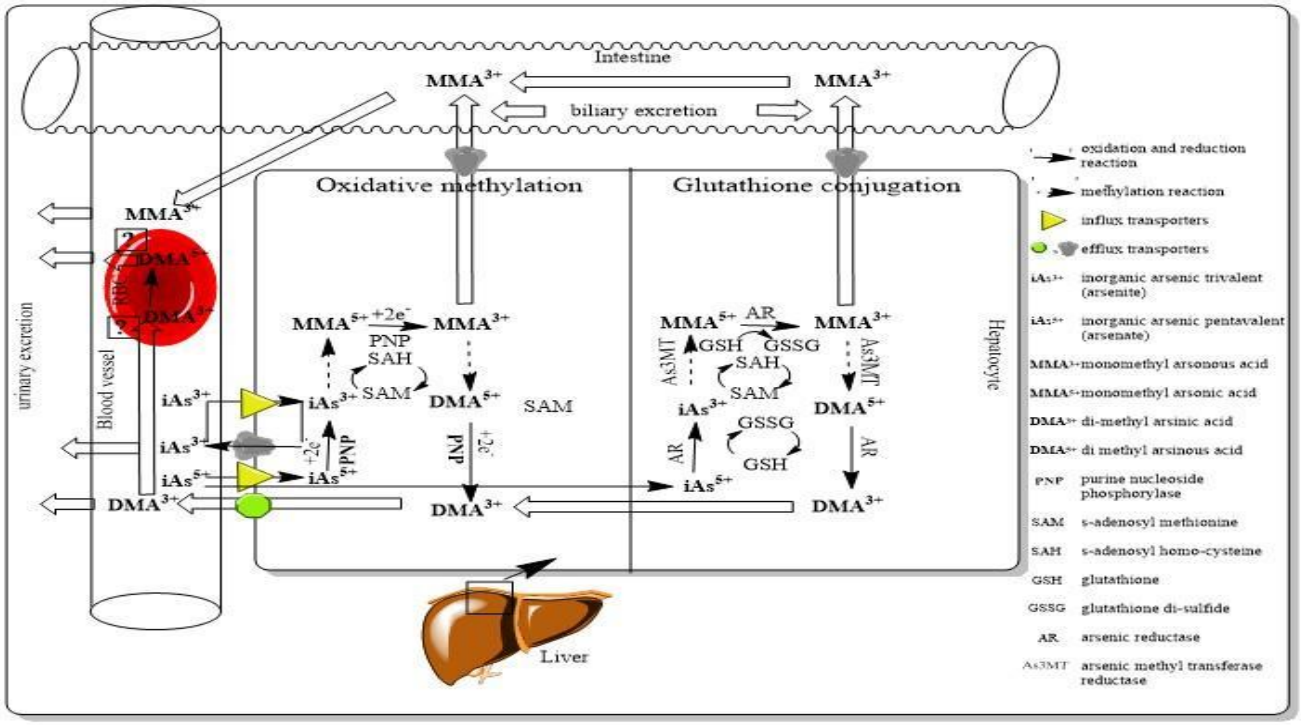

Figure 3: Intracellular metabolism and excretion of arsenic.

INTRACELLULAR METABOLISM OF ARSENIC

The toxicity caused by inorganic arsenic largely depends on its oxidation states (AsIII or AsV) and also on methylation levels (monomethyl, dimethyl and trimethyl) which occur in mammalian liver. Two mechanisms are proposed for the biotransformation of inorganic arsenic in the liver, namely 1) oxidative methylation and 2) glutathione conjugation (Figure 3). According to the first mechanism, inorganic arsenic mostly enters into the body in the form of arsenate and about 50-70% is absorbed. Absorbed arsenate is reduced to arsenite by the catalytic activity of arsenate reductase or PNP (purine nucleoside phosphorylase). The conversion of inorganic arsenic involves alternating steps of oxidative methylation and reduction. In this process, arsenite is methylated by the donor S-adenosylmethionine (SAM) to form mono-methyllarsonic acid (MMAV), which is then reduced to monomethylarsonous acid (MMAIII) before undergoing further methylation to dimethylarsinic acid (DMAV). The second theory proposes that the reduction and complex formation occur in two steps, firstly, arsenate is reduced to arsenite in the presence of 2 moles of glutathione followed by its conjugation with 3 moles of glutathione to form the glutathione-arsenite complex by its linkage with cysteinyl-sulfhydryl of glutathione. The biotransformation of inorganic arsenic occurs in the presence of two proteins, which are MMA reductase (MMAR) and arsenic methyl transferase-reductase (As3MTR).[6] This bio-methylation process can be considered as a possible detoxification mechanism as the end-products are less toxic (in the order MMAIII>arsenite>arsenate>MMAV=DMAV), less reactive and more easily excreted via urine than the inorganic forms. In contrary to other methylated derivatives, MMAIII is even more toxic than arsenite, which raises the question whether bio-methylation is truly a method of detoxification. The study has also raised the same question about the bio-methylation-dependent detoxification mechanism as a universal detoxification mechanism for arsenic. The report also states that some primates lacking methyl-transferase activity do not excrete methylated arsenicals as the end product.[6]

HEMATOLOGICAL ARSENICOSIS

Arsenic toxicity on erythrocytes

Arsenic toxicity, either acute, chronic or sub-chronic, is known to interfere with hematopoietic and immune systems. The first tissue that encounters arsenic in the body after its systemic absorption is blood, and probably for this reason, hematological manifestations are the most common features of arsenic poisoning, which is characterised by pancytopenia, i.e., reduction of the number of erythrocytes, leucocytes and platelets, associated with reduced haemoglobin content. The exposure of arsenic may lead to its accumulation in erythrocytes and cause anaemia. After entering the bloodstream, arsenic uptake by erythrocytes, probably through AE1 protein, takes place, followed by formation of a complex with the globin part of the haemoglobin.[7] Thus, as the most populous cellular species, erythrocytes appear to be the primary target of arsenic toxicity. The hematotoxic effects of arsenic exposure are commonly characterized by erythrocyte morphological response, haemolysis, impaired hematopoiesis, haeme biosynthesis, and leucopenia. Leucopenia and anaemia were found to be more frequent in the female patients who were underweight, thereby indicating that the poor nutritional status of the patients increases the complications of chronic arsenic toxicity. Prevalence of anaemia in pregnant women(a prevalence proportion ratio of 2.87 with respect to any anaemia) has also been reported.[8] Taken together, these finding suggests that women are probably more prone to arsenic-induced hematotoxicity.

Arsenic toxicity on leukocytes

Earlier, it has been reported that exposure to arsenic from drinking water leads to DNA methylation in whole blood (leukocytes) collected from adults.[9] Kile et al had shown that maternal exposure to arsenic leads to significant LINE-I methylation in cord blood. In utero exposure to arsenic is associated with altered development, activation, and proliferation of T cell population (both CD4+ T cell and CD8+ T cell) as well as cord blood leukocyte subpopulation.[9] It has been also been reported that arsenicosis distorts the balance of Th17/Treg cell in circulating peripheral blood mononuclear cell (PBMC) and it has been evident that there was an increase in Th17 cells in PBMC population, favouring and proinflammatory milieu in arsenicosis patients.[10] In addition, RORγt -mRNA and FOXP3- mRNA levels respectively increased and decreased in arsenicosis patients.[10]

At pharmacological concentrations arsenic trioxide (As_2O_3) leads to apoptosis of blood monocytes during the differentiation in the presence of granulocyte-macrophage colony stimulating factor (GM-CSF) and macrophage colony-stimulating factor. Another study showed that proliferation of T cells was decreased when PBMCs collected from individuals exposed to arsenic were stimulated with phytohemaglutinin (PHA).[11] Same study showed that PBMCs treated with sodium arsenite caused reduction in IL-2 secretion and proliferation of T-cell induced by PHA.[11] It has also been reported that non-cytotoxic concentration of sodium arsenite (0.25-2 μM) markedly decreased T cell proliferation by growing the share of non-dividing cells blocked in G1 phase.

Recently, it has been reported that total red blood cell (RBC) and white blood cell (WBC) count were decreased in arsenic nano-particles (AsNPs) treated Labeo rohita. Another study showed that there were significant decreases in total WBC, lymphocyte, and monocyte count in arsenic-treated Swiss albino mice, on the other hand neutrophil and eosinophil count were increased in arsenic arsenic-treated group when compared with the control group. Effect of arsenic toxicities on leucocytes cumulatively presented in Figure 4.

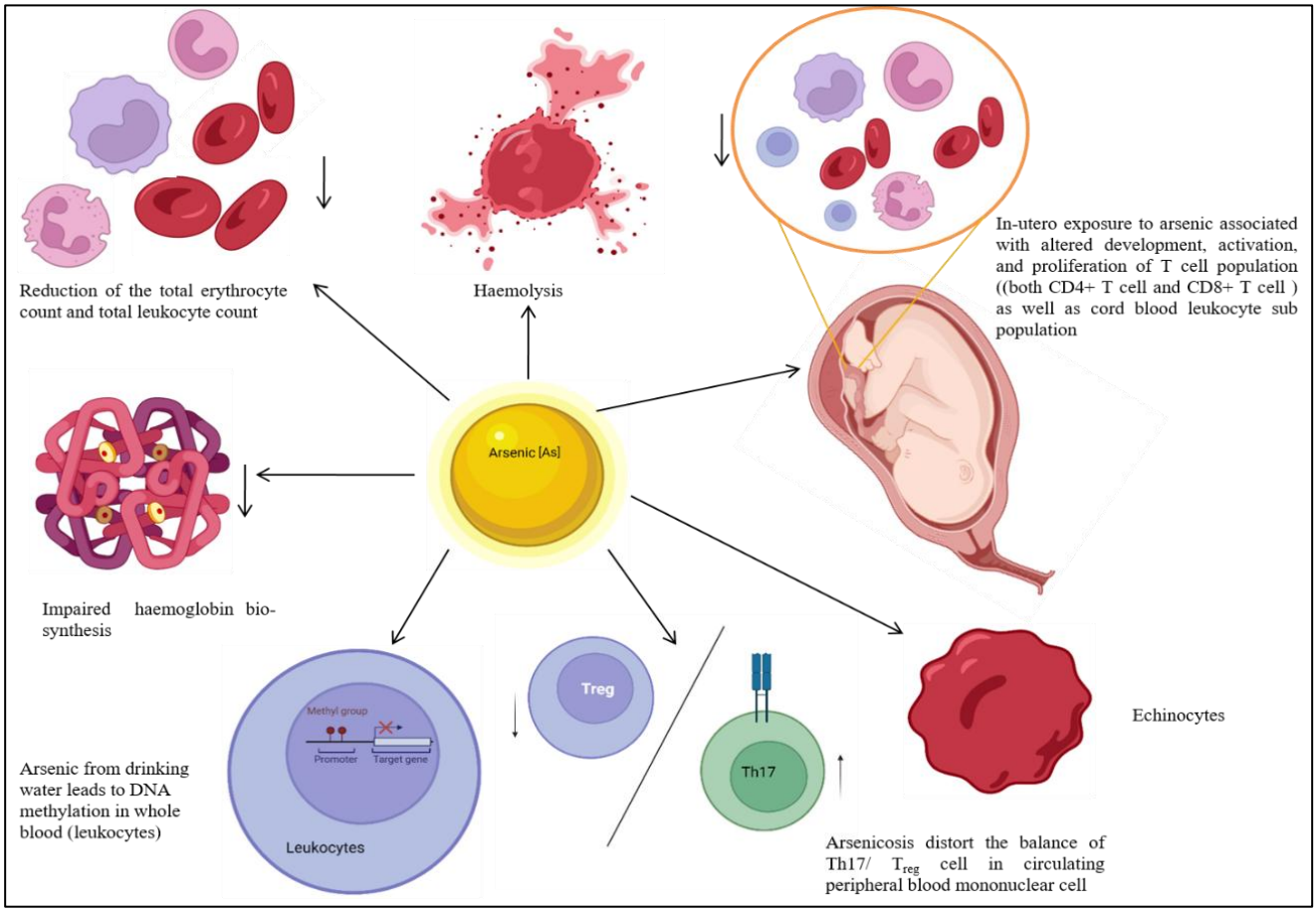

Figure 4: Arsenic induced hematological alterations in arsenicosis.

MECHANISM OF HEMATOTOXICITY

Mechanism of arsenic induced erythrocyte damage

Arsenic intoxication in erythrocytes is manifested as a change in the morphology or deformability of cells. Morphological aberrations of erythrocytes due to chronic inorganic arsenic exposure are associated with loss of membrane integrity, which often leads to microvascular occlusion and related peripheral vascular effects. Erythrocytes, when targeted by inorganic arsenic, undergo morphologic changes, converting discocytes into echinocytes, a form with invaginated spicules. The spicules then bud off, forming extracellular vesicles that form a spherical form called spheroechinocytes. Arsenate appeared to be more toxic to erythrocytes than arsenite, as it results in the formation of irreversible spheroechinocytes while the latter form restricts the damage to the formation of stage 2 echinocyte. The main attributes of arsenic-induced haemolysis include ATP depletion, cell shrinkage along with morphological alterations, increased membrane rigidity, increased deformability, loss of lipid asymmetry, which exposes phosphatidylserine on the outer leaflet of erythrocyte membrane, stimulating eryptosis.[12] This morphological deformity may lead to increased osmotic fragility, disturbances in peripheral circulation, and, ultimately, anaemia, as supported by epidemiological studies on arsenic intoxication, also mentioned earlier that arsenate and arsenite have different effects on erythrocytes and cause toxicity by separate mechanisms. The more toxic arsenate form causes toxicity by a process called 'arsenolysis' by replacing phosphate as a phosphate analogue followed by inhibition of ATP synthesis, whereas arsenite binds with sulfhydryl groups and inhibits the pyruvate dehydrogenase multienzyme complex and mitochondria-based citric acid cycle.

Delnomdedieu et al have found that the most important binding site for arsenite is free sulfhydryls in erythrocytes, and in this regard, apart from intracellular glutathione, haemoglobin, having 8 -SH groups, is another site of arsenic conjugation.[13] Sulfhydryl groups play an important role in maintaining the shape and motility of the erythrocyte membrane, and a reduction in their content is thus deleterious to the cell. The gaseous form, i.e. arsine gas (AsH_3), has also deleterious effects on erythrocytes. It has been observed that it also reacts with the sulfhydryl groups and Na+ K+ATPase pump present in the membrane resulting in cell swelling and

lysis. The binding induces oxidative stress by reducing reduced glutathione levels, but unlike arsenites, they do not interfere with ATP levels. Arsine toxicity results in haemoglobin oxidation and denaturation, and this disrupts the normal functioning of erythrocytes.[14] The other concomitant effects include loss of cell volume control, potassium efflux, sodium influx, and an increase in hematocrit. These changes are followed by disturbances in membrane ultra-structure. Such events cause haemolysis, which appears to depend on membrane disruption. Although arsine is a reducing agent, it has been postulated that it damages cells through oxidative mechanisms, possibly by forming hydrogen peroxide (H_2O_2) and inhibiting catalase. Arsine causes hemachrome and methaemoglobin formations, while H_2O_2 treatment results in the formation of ferrihaemoglobin. Catalase and glutathione peroxidase, two major peroxide scavenging enzymes, have little effect on the initial haemoglobin -O_2 changes caused by AsH3. The following equation demonstrates possible reactions involving AsH_3 and HbO_2,

H_2-As-H+HbO_2=H_2As+HbO_2-H=met-Hb+H_2As-OOH

Alternatively, the reaction may produce H_2O_2 and arsenic adduct, such as arsine-haemoglobin (H_2As-Hb) or arsine-haeme (H_2As-haeme), which has not yet been identified.[15]

Mechanism of arsenic-induced leucocyte damage

Arsenic-mediated carcinogenicity may be due to increasing the longevity of premalignant cells by elongation of telomere length.[16] Epidemiological studies showed that exposure to arsenic is significantly associated with elongation of telomeric length in peripheral blood leukocytes and up upregulates the expression of telomerase.[16] Arsenic toxicity leads to ROS generation and subsequent suppression of the cell's antioxidant activity. On the other hand, telomeres are vulnerable to the accretion of oxidative guanine lesions. Furthermore, the existence of oxidative DNA damage inhibits telomerase activity and prevents binding of TRF1, TRF2 and RAP1protein and also inhibits DNA repair by NHEJ (non-homologous end joining).[17]

Arsenic exposure is negatively associated with global 5-hmc (5-hydroxy methyl cytosine) and positively associated with percentage of 5-mc (5-methyl cytosine) percentage of 5-hmc in females and males, respectively. Another study showed that As_2O_3 leads to a decrease in DNA binding of p65 nuclear factor-κβ, along with this As_2O_3 was accountable for a decrease in protein level expression of X-linked inhibitor of apoptosis protein and FLICE-inhibitory protein. It has also been reported that genes that are responsible for the expression of MIP2, CCL19, CCL18, CCL1 chemokines, chemokine receptors such as CXCR5, CCR1, CCR2 and IL-10RB, IL-13RA2, IL-18R1 were downregulated in PBMCs, collected from arsenic-exposed individuals.[18] It has also been reported that the PBMC from arsenic-exposed individuals showed a marked up-regulation of BCL-xl, caspase-2, Bok, CD30, TNFRSF5 and TNFRSF10B when compared to the control group.[18]

EXPERIMENTAL EVIDENCES OF HEMATOLOGICAL ALTERATIONS IN ARSENICOSIS

The effects of arsenic exposure on blood trace element levels in rats reveal significant imbalances in essential elements such as iron and zinc. The study also noted sex-based differences in these alterations, suggesting that males and females may respond differently to arsenic exposure. Different animal models of experimental arsenicosis have been pursued to explore the extent of damage to blood cell components, which are critically analysed and summarised in Table 1 and Figure 3. Experimental model with radioactive labelled arsenite (As74) provides evidence of poor binding of arsenic to plasma proteins which results in retention of arsenic in blood cells rather than plasma. Cysteine residue at the 13th position of the α-chain of haemoglobin has also been identified as a binding site of trivalent DMAIII, suggesting that erythrocytes may serve as a major site for arsenic accumulation in blood.[19] Altered hematological responses were observed when mice were exposed to arsine, and the decrements were linear with increasing arsine concentration. In another study, oral arsine exposure to adult rats for 14 days showed a significant decrease in erythrocytes, hematocrit, lymphocyte and platelet counts, whereas mean corpuscular volume (MCV) and mean corpuscular cell haemoglobin concentration (MCHC) increased significantly.[20] Also, observation from another study claimed a significant reduction ($p<0.05$) in packed cell volume (PCV), haemoglobin concentration (Hb), and RBC after arsenic exposure in male Wistar rats, but total WBC count was elevated, and serum total protein, albumin, and globulin levels were insignificantly reduced.[21] The abnormalities manifested with the administration of arsenic to both mice and rats indicated the severity of arsenic-induced toxicity in the hematological system. Studies on the mouse model of arsenic toxicity show a reduction in counts of leucocytes and erythrocytes, along with a decrease in haemoglobin level, accompanied by damage to lymphocytes, which was distinctly observed.[22] Studies using rat model reported severe leucocytopenia with reduced ALAD and GSH levels, elevated zinc protoporphyrin (ZPP) levels, an indicator of iron deficiency, and ultimately haeme-biosynthesis impairment. Relatively altered activities of lipid peroxidation marker like TBARS along with other redox markers, i.e., SOD, GSH, etc. suggest that arsenic may alter the cellular metabolism by ROS generation in blood cells.[25] The increased lipid peroxidation and reduced GSH level in erythrocytes may be attributed to arsenic accumulation in erythrocytes.[26] Anaemia, leucocytopenia, thrombocytopenia, and lymphocytopenia associated with an increase in ZPP have been reported in several reports, which further attest to the previous studies using a similar

rodent model. A recent study further asserted the negative effect of arsenic on the bone marrow of mice, indicating disruption of cellular turnover and increased apoptosis in hematopoietic stem and progenitor cells, potentially impairing blood cell formation and immune function.[27]

Non-rodent animal models also confirm similar effects of arsenic exposure on hematological parameters. Fish model of arsenicosis using *Catla catla* showed a decrease of cell count, haemoglobin concentration, and hematocrit, though MCV, MCH and MCHC levels were increased.[28] Contradictory results like increased Hb, hematocrit (Hct) and leucocyte counts were also reported in *Catla* species.[29] In the experimental goat model, arsenic toxicity revealed morphological alterations along with significant differences in the counts of erythrocytes, leukocytes and haemoglobin concentration when compared with the control. Furthermore, while lymphocyte count has been found to be decreased, eosinophil and monocyte counts were increased, suggesting impaired bone marrow function.[30] Histopathological examination showed degeneration of lymphocytes and increased erythrophagocytic activity in the spleen, indicating the immunotoxic effects of arsenic. Increased expression of Caspase 3, and Terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) followed by fragmentation of DNA implies the genotxic impact of arsenic on bone marrow.[31] In the experimental Labeo rohita model, a significant drop in Hb concentration (from 10.2 to 8.7) and a comparable drop in hematocrit levels (32.5 to 28.1) were noted. The red blood cell count was significantly decreased (from 4.8 million/µl to 3.6 million/µl), which is a symptom of hematological damage brought on by arsenic.[32] Experiments on *Zebu* cattle in the arsenic-affected area, considered as the subclinical form of arsenic toxicity, showed a significant decrease in total erythrocyte count, packed cell volume, and total plasma protein concentration compared to the same values revealed from the cattle of the unaffected zone. The results also showed decreased superoxide dismutase and catalase activity in erythrocytes, followed by a reduction in plasma nitrite level and consequent elevation in lipid peroxidation and protein carbonylation, which led to altered hemato-biochemical parameters, and all these enzymatic and nonenzymatic alterations might be responsible for the hematological changes.[33]

Table 1: Details of animal models used and the effects of arsenic exposure by various routes on hematological parameters.

S. No.	Experimental design			Major effects	References
	Animal used	Arsenic species and route of exposure	Purpose, dose and duration		
1.	Mouse	Arsine inhalation	Acute toxicity; 5-26 ppm for 1 h	Hemolytic anaemia associated with increased reticulocyte count and osmotic fragility	20
2.	Swiss albino mouse	Sodium arsenite drinking water, orally	Chronic toxicity; 25 ppm for 12 months	Anaemia, leucopenia and increased platelet count associated with oxidative stress and reduced activity of serum ∂-δ-aminolevulinic acid dehydratase (ALAD)	25
3.	Mouse	Arsenic in drinking water, orally	Chronic toxicity; 30,150,300 ppm for 40 days	Anaemia and leucopenia	22
4.	Male Wistar rat	Sodium meta-arsenite in drinking water, orally	Sub-chronic toxicity; 20 ppm for 5 weeks	Reduced erythrocyte ALAD and SOD activities and GSH levels, associated with elevated TBARS	47
5.	Male Wistar rat	Sodium arsenite in drinking water, orally	Chronic toxicity; 25 ppm for 24 weeks	Anaemia, leucocytopenia, reduced MCH and MCHC and serum ALAD activity associated with increased serum ZPP level and platelet count	48
6.	Male Wistar rat	Sodium arsenite in drinking water, orally	Chronic toxicity; 20 mg/kg for 6 weeks	Increased lipid peroxidation and reduced GSH level in erythrocyte, increased concentration of arsenic in erythrocyte	26
7.	Male Sprague-Dawley rat	Sodium meta-arsenite, orally	Chronic toxicity; 5.5 mg/kg of body weight for 28 days	Anaemia, leucopenia and thrombocytopenia associated with decrease in total anti-oxidant capacity	49
8.	Rat and guinea pig	Arsenic (III) in drinking water, orally	Chronic toxicity; 10-25 ppm for 16 weeks	Anaemia, leucopenia associated with reduced ALAD activity, GSH levels, increased serum Zn protoporphyrin (ZPP)	23

Continued.

S.	Experimental design			Major effects	References
9.	Female Bengal goat	Sodium arsenite, orally	Chronic toxicity; 4 mg/kg body weight for 7 weeks followed by 5 mg/kg body weight for 8 weeks	Altered erythrocyte morphology, hemoglobin content associated with lymphocytopenia and increased monocyte, eosinophil and neutrophil count	30
10.	Catla catla	Sodium arsenate	Acute and chronic toxicity; 43.78 mg/L (lethal dose) for 96 h and 4.378 mg/L (sub-lethal dose) for 35 days	Anaemia with reduced Hb, Hct, erythrocyte count, associated with increased MCV, MCH and MCHC	28
11.	Catla catla	Arsenic trioxide exposed fingerling	Chronic toxicity; 2.041 ppm for 35 days	Increased Hb, Hct, leukocyte counts accompanied by reduced erythrocyte count	29
12.	Zebu cattle	Arsenic	Natural feeding in arsenic contaminated zone	Anaemia with decreased erythrocyte count, PCV, reduced total plasma protein levels	50
13.	Male Broiler chicks, Vencobb strain	Arsenic	Chronic toxicity; 100 ppm for 6 weeks	Anaemia with decreased erythrocyte count, Hct, Hb	51
14.	Broiler chicks	Inorganic arsenic salt in distilled water, orally	Chronic toxicity; 50 mg/kg body weight for 32 days	Anaemia with reduced erythrocyte count, Hct, Hb, leucocytopenia, reduced MCV, MCH and MCHC	52
15.	Human	Arsenic	Drinking water	Glutathione depletion, spherocytosis	53
16.	Human	Arsenic in drinking water	Drinking water	DNA methylation in maternal umbilical cord blood leukocytes	9
17.	Human	Arsenic in drinking water	Exposure to arsenic ≥6 months	Chronic arsenic exposure leads to DNA hyper methylation of promoter region of p53 and p16 gene	54
18.	Human newborns	In utero exposure to arsenic (Arsenic in maternal drinking water)	Drinking water	Arsenic exposure leads to DNA methylation in leukocyte sub-population in cord blood	55
19.	Arsenicosis patients	Arsenic in drinking water	Drinking water	Arsenic exposure alters Th17/ Treg cell balance in peripheral blood mononuclear cell (PBMC)	10
20.	Human monocytes (in-vitro experiment)	As_2O_3 in cell culture medium	6 days treatment	At pharmacological concentrations As_2O_3 leads to apoptosis of blood monocytes during the differentiation in the presence of granulocyte-macrophage colony stimulating factor (GM-CSF) and macrophage colony stimulating factor	56
21.	Human lymphocytes (in-vitro experiment)	$NaAsO_2$ in cell culture medium	2hr treatment	Arsenic leads to decrement of T-cell proliferation (in response to PHA stimulation) collected from PBMCs of arsenic-exposed humans	11
22.	Human lymphocytes (in-vitro experiment)	$NaAsO_2$ in cell culture medium	2hr treatment	Sodium arsenite (0.25-2μM) significantly decreased T cell proliferation by growing the share of non-dividing cells blocked in G1 phase	57

Continued.

S.	Experimental design			Major effects	References
23.	Swiss albino mice	$NaAsO_2$ at a dose of 0.0075 mg/ml in drinking water	8 weeks	Total WBC, lymphocyte, monocyte count were decreased in arsenic treated Swiss albino mice , On the other hand neutrophil and eosinophil count were increased in arsenic treated group and its amelioration by Allium sativum methanol extract	21
24.	Human	Arsenic in drinking water	-	Arsenic exposure through drinking water leads to elongation of the telomeric length	58
25.	Human	Arsenic in drinking water		Arsenic exposure is significantly associated with the elongation of telomeric length of PBMC	16
26.	Human	Arsenic in drinking water	-	Chronic arsenic exposure leads to an elevation of the human telomerase reverse transcriptase gene expression	59
27.	Human	Arsenic in drinking water	-	Arsenic exposure negatively connected with global % 5-hydroxymethylcytosine and positively connected with % 5-methylcytosine, in female and male respectively	60
28.	Human monocytes (in-vitro experiment)	As_2O_3 in cell culture medium	-	As_2O_3 leads to decrease in DNA binding of P65 nuclear factor-κβ along with this As2O3 was accountable for decrease in protein level expression of X linked inhibitor of apoptosis protein and FLICE-inhibitory protein	56
29.	Human	Arsenic in drinking water	-	Expression of MIP2, CCL19, CCL18, CCL1 chemokines, chemokine receptors such as CXCR5, CCR1, CCR2 and IL-10RB, IL-13RA2, IL-18R1 were downregulated in PBMCs, collected from arsenic-exposed individuals. On the other hand, up-regulation of BCL-xl, caspase-2, Bok, CD30, TNFRSF5 and TNFRSF10B in PBMC from arsenic-exposed individuals when compared to the control group	18
30.	Labeo Rohita	Arsenic in water	-	Haemoglobin concentration (from 10.2 to 8.7) and hematocrit levels (32.5 to 28.1) decrease. Erythrocytes exhibited irregular morphology and membrane damage. Oxidative stress, characterized by an increase in malondialdehyde (MDA) levels (3.2 to 8.1), is heightened in arsenic-exposed individuals, while superoxide dismutase activity decreases (15.8 to 10.5), indicating a dose-dependent response to oxidative stress	32

Table 2: Description of blood arsenic and associated diseases.

S. No.	Author	Arsenic level, Mean±SD/SE (µg/l)	Associated disease	CI (lower 95%)	Country
1.	Kumar 2021[34]	25.92±3.939	Leukemias	18.13	India
2.	Kumar 2021[34]	52.57±12.24	Lymphomas	28.33	India
3.	Dai 2020[35]	>3.69	Type II diabetes	3.01	China
4.	Tan 2021[38]	8.74	Oxidative stress	7.82	China
5.	Marciniak 2021[40]	≥0.85	Breast cancer	3.15	Poland, Latvia, Italy
6.	Arikan 2015[39]	4.22±9.42	Skin lesion	NF	Turkey
7.	Hall 2006[36]	23.1	Skin lesion	3.54	Bangladesh
8.	Kumar 2023[37]	52.28 ± 5.504	Gall bladder cancer	41.41	India

Table 3: Details of remedial measures assessed by using different ameliorating agents, dietary supplements in different animal models.

S. No.	Description of model			Major effects and probable mechanism	References
	Animal used	Arsenic dose and duration	Ameliorating agent used, dose and duration		
1.	Swiss albino mouse	Sodium arsenite at 25 ppm in drinking water fed orally for 12 months	MiADMSA at 0.2 mmol/kg body weight and quercetin at 0.2 mmol/kg body weight fed orally either alone or in combination for 5 days	Depletion of arsenic from blood, normalized serum ALAD activity, platelet counts, however, quercetin alone is ineffective	25
2.	Swiss albino mice	Sodium arsenite in drinking water at a dose of 0.0075 mg/mL for 8 weeks	Allium sativum methanol extract at 150, 300, and 500 mg/kg for 8 weeks	Total WBC, lymphocyte, monocyte count were increased in supplemented group along with decline in neutrophil and eosinophil count	21
3.	Male Wistar rat	Sodium meta-arsenite, 10 ppm in drinking water for 12 weeks	Cysteine, methionine, ascorbic acid, and thiamine at 25 mg/kg body weight	Reduced tissue accumulation of arsenic and associated oxidative stress, chelates arsenic, and the regime acts as antioxidant	61
4.	Male Wistar rat	Sodium arsenite 20 ppm in drinking water for 4 weeks	Centella asiatica extract 100, 200 and 300 mg/kg body weight/day	Restored leucocyte and platelet counts, MCV and MCH, serum ALAD activity, ZPP and GSH levels	47
5.	Male Wistar rat	Arsenic trioxide dissolved in saline, 4 mg/100 g body weight for 30 days	L-ascorbic acid	Regenerate glutathione, chelate inorganic arsenic and inhibit DNA damage	62
6.	Male Wistar rat	Sodium meta-arsenite in drinking water fed orally at 25 ppm for 6 months	Taurine at 100 mg/kg body weight given i.p. and MiADMSA at 50 mg/kg body weight fed orally	Restored MCH, MCHC, serum ALAD activity, GSH, ZPP and SOD levels	48
7.	Male Wistar rat	Sodium arsenite at 10 mg/kg body weight for 8 days	Pretreatment with hydro-alcoholic extract of Trichosanthes dioica root at 5 and 10 mg/kg body weight for 20 days	Normalized hematological parameters and restored redox balance	63

Continued.

S.	Description of model			Major effects and probable	References
8.	Male Wistar rat	Sodium meta-arsenite at 20 mg/kg body weight in drinking water fed orally for 6 weeks	Aqueous extract of Psidium guajava at100 mg/kg body weight	Reduced tissue accumulation of arsenic and erythrocyte lipid peroxidation	26
9.	Male Wistar rat	Sodium arsenite was fed orally at 4 mg/kg body weight for 63 days	Spirulina at 1 g/kg body weight and vitamin A at 2500 IU/kg body weight were fed orally for 63 days	Normalized erythrocyte and leucocyte counts and haemoglobin level, combined supplement has been found to be better than the single one	64
10.	Male Wistar rat	Arsenic in normal saline fed orally at 5 mg/kg body weight for 28 day	Diallyl trisuphide (DATS) at 20, 40 and 80 mg in corn oil/kg body weight 90 minutes before arsenic administration, ascorbic acid at 100 mg/kg body weight	Restored redox balance and ATPase activity, DATS at 80 mg has been found to be most effective	65
11.	Male Wistar rat	Sodium arsenite fed orally at 5.5 mg/kg body weight for 4 weeks	Hydro-alcoholic extract of Nasturtium officinale fed orally at 500 mg/kg body weight	Restored erythrocyte and leucocyte counts and Hct value, increased total antioxidant capacity	49
12.	Male Wistar rat	Arsenic trioxide at 3 mg/kg body weight per day for 28 days	Combination of vitamins C and E at 200 and 400 mg/kg body weight, respectively, for 30 days	Prevention of hematological abnormalities and erythrocyte morphological changes	66
13.	Male Wistar rat	Arsenic trioxide at 3 mg/kg body weight per day for 28 days	α-Lipoic acid at 25 mg/kg bw/rat/day for 28 days	Restoration of blood cell counts, other hematological indices and erythrocyte morphological damages, restoration of redox balance and reduces inflammatory changes	67
14.	Broiler chicks	Arsenic at 100 ppm for 6 weeks	Emblica officinalis at 500 ppm for 6 weeks	Normalized erythrocyte count, Hb, Hct values	51
15.	Broiler chicks	Inorganic arsenic salt at 50 mg/kg body weight in distilled water fed orally for 32 days	Ascorbic acid at 250 mg/kg body weight	Increased Hb concentration, erythrocyte count, normalized Hct, MCV, MCHC and MCH values, reduced tissue accumulation of arsenic	52
16.	Cyprinus carpio	Arsenic trioxide at 0.01 mg/L for 7 days	Propolis 10 mg/L for 7 days	Normalized blood cell counts, Hct, Hb, MCH, MCHC and MCV values	68
17.	Charles Foster rat	Arsenic (NaAsO2) at 1-10 mg/kg body weight in drinking water for 45 days	Ethanolic extracts of cumin seed and coriander leaves at a dose of 400mg/mL	Total blood cell count, liver enzyme's activity were restored in arsenic-treated 1563 Charles Foster rats exposed to ethanolic extracts of cumin seed and coriander leaves	41

Continued.

S.	Description of model			Major effects and probable	References
18.	Male Wistar rat	Arsenic ($NaAsO_2$) at 2.5 mg/kg in drinking water for 28 days	Lycopene 20 mg/kg	Lycopene was responsible for reversing hematological alterations in sodium arsenite treated male wistar rat	42
19.	Sheep	Arsenic ($NaAsO_2$) at 6.6 mg/kg body weight in drinking water for 133 days	Turmeric and P. foetida powder 500 mg/kg for the last 49 days	Turmeric and P. foetida powder significantly elevated ($p<0.05$) Hb content and total erythrocyte count (TEC) in arsenic treated sheep when compared to the control group	43
20.	Male Wistar rat	Arsenic (10 ppm) in drinking water for 14 days	Aspalathus linearis at 10 ppm for 14 days	Aspalathus linearis extract restored hematological parameter such as RBC count and PCV to normal level in arsenic treated rat	45
21.	Human	Arsenic in drinking water	Ginkgo biloba extract (GBE) containing flavonoid glycosides (19.2 mg) and terpenoids (4.8 mg) for 3 months of oral administration (3 tablets/day)	Administration of Ginkgo biloba extract to arsenicosis patients leads to up regulation the number of Treg cell and down regulation of the Th17 cell subpopulation	10
22.	Swiss albino female mice	Arsenic ($NaAsO_2$) in drinking water	$NaSeO_3$, 10 µM for 60 days	Sodium selenite significantly reduced neutrophil, eosinophil, lymphocyte, and monocyte counts, indicating a beneficial effect of selenium	69
23.	Female Wister rats	Sodium arsenate for 28 days	Spirulina at 600 mg/kg doses	Rats treated with 300mg/kg of spirulina showed a negligible increase in PCV, Hb, RBCs, and their markers (MCH, MCV, and MCHC), while 600mg/kg showed a significant increase	70

IN VITRO EFFECT OF ARSENIC ON ERYTHROCYTES

In vitro studies with human blood also support the above observations and show that treatment of human erythrocytes with arsine gas (1 mM) alters cell volume, increasing hematocrit values and ultimately leading to haemolysis within 30 min of exposure, associated with the formation of toxic haemoglobin adducts. In another study, Pernis et al have shown that a dose-dependent haemolytic activity of arsenic with a haemolytic set point of glutathione depletion to about 40% of the control. Discocyte-echinocyte transformation of human erythrocytes ultimately results into spherocytosis after arsenic treatment. Recent study on both *in vivo* and *in vitro* model ended up with an interesting observation regarding arsenic mediated anaemia. Arsenic interacts with the N- and C-terminal zinc finger motifs of GATA-1 which is mandatory for erythropoiesis. Interaction of arsenic with GATA-1 caused loss of zinc and inhibition of DNA and protein binding activities, leading to dyserythropoiesis and an imbalance of hematopoietic differentiation.

BLOOD ARSENIC AND DISEASE ASSOCIATION

For continuous and steady exposure, such as through contaminated drinking water, blood arsenic levels rapidly achieve a steady-state concentration, serving as a reliable indicator of the extent of exposure. Most of the arsenic species have a short half-life in blood, and it is also considered a difficult matrix for chemical analysis. Instead of this shortcoming, recent scientific evidence claimed blood arsenic as an important biomarker for disease risk conditions like diabetes, cancers, hypertension, skin lesions and oxidative stress.[34-36] A comprehensive study involving blood samples from 512 gallbladder cancer patients in Bihar unveiled a remarkably high prevalence of elevated arsenic concentrations within the population, with a peak concentration reaching 746 µg/l. Notably, 350 out of the 512 samples exhibited arsenic levels exceeding 2 µg/l, indicating that a substantial 68% of the cohort

demonstrated significant arsenic exposure.[37] A study from the same authors also claimed a strong correlation coefficient between blood arsenic levels and the occurrence of cancers in male and female patients from Bihar, India ($r=0.003$; $p<0.05$).[34] Among patients with elevated blood arsenic levels, the most frequently observed malignancies include leukaemias, lymphomas, gallbladder cancer, ovarian cancer, and head and neck cancers.[34] Higher incidence of oxidative stress was even associated with the presence of low blood arsenic amount, like 8.74 µg/l.[38] The levels of blood arsenic and its association with disease conditions are given in Table 2.[39,40]

Remedial measures

The primary measures against arsenic toxicity are to reduce the levels of arsenic species in drinking water and to implement the government's policies in this regard. A parallel thrust area in combating such toxicity is the identification and/or development of pharmaceutical/ therapeutic agents with the potential to prevent and/or cure arsenic-induced pathophysiological changes. The measures can broadly be classified into two groups: use of chelating agents, which can chelate free arsenic or arsenic derivatives, thus making them unavailable for causing any pathological consequences; use of nutrients/nutraceuticals as dietary supplements, which have the potential to prevent and/or cure arsenic-induced damages. DMSA (dimercaptosuccinic acid) and DMPS (sodium-2, 3 3-dimercaptopropane-1-sulphate), MiADMSA (Monoisoamyl DMSA), NAC (N-acetyl cysteine), ascorbic acid, α-tocopherol, lipoic acid and the extract of different parts of various plants, etc., are the ameliorative agents used for this purpose. The hemato-protective activities of these agents are presented in Table 3. These agents bring about the changes by normalizing hematological counts, haemoglobin content, restoring the redox balance and by quenching the free arsenic species in blood and tissues.

Earlier, it has been evident that blood cell count, liver enzymes' activity were restored in arsenic-treated Charles Foster rats exposed to ethanolic extracts of cumin seed and coriander leaves.[41] Another study showed that lycopene was responsible for reversing hematological alterations in sodium arsenite-treated male *Wistar* rats.[42] Turmeric and *P. foetida* powder significantly increased ($p<0.05$) haemoglobin content and total erythrocyte count in arsenic-treated sheep.[43] On the other *T. Cordifolia* reversed the oxidative damage at biochemical, histopathological and hematological levels in *Charles Foster* rats.[44] Recently, it has been reported that garlic extract was reasonable to restore SGPT, ALP, CRE, ALT, as well as WBC, lymphocyte, and monocyte to normal levels in arsenic-treated *Swiss albino* mice.[21] Another study showed that *Aspalathus linearis* extract restored hematological parameters such as RBC count and PCV to normal levels in arsenic-treated rats.[45] Stratification of vitamin D (vit D) exerts a significant impact on Th17 and IL-17A production in arsenic-exposed human.[46] Vitamin D level <20 ng/ml caused a decrease in the level of Th17. Researchers have theorized that the unusual interactions observed between arsenic (As) or its metabolic byproducts and vitamin D could be attributed to arsenic's substantial upregulation of T-cell receptor (TCR) pathways. This upregulation occurs through an increase in the protein tyrosine kinases Lck and Fyn. Consequently, vitamin D's influence on T-cell tolerance might elucidate this phenomenon.

CONCLUSION

Arsenic, a ubiquitous metalloid, poses a significant threat to global health, with its insidious impact on the hematopoietic system being a major concern. While this review is limited by its reliance on secondary data analysis and meta-analysis of hematological changes and remedial measure outcomes, it has highlighted the current status of knowledge on arsenic-induced hematological disorders, ranging from mild conditions like anaemia to severe and life-threatening malignancies such as leukaemia. The mechanisms underlying arsenic's toxicity are complex, involving oxidative stress, DNA damage, altered gene expression, and disruption of crucial cellular pathways. The prevalence of arsenic-related hematological issues varies geographically, with regions heavily reliant on contaminated groundwater, such as parts of Asia, facing the greatest burden. This is particularly concerning in developing countries, where the lack of affordable and effective arsenic filtration systems exacerbates the problem, limiting access to safe drinking water and water for irrigation. While the link between high-dose arsenic exposure and hematological malignancies is well-established, the effects of low to moderate exposure levels remain a subject of ongoing research. Emerging evidence suggests that even lower levels can contribute to subtle but significant hematological abnormalities, potentially increasing the risk of long-term complications. Given the challenges in eliminating arsenic from the environment, particularly in resource-limited settings, there is a growing need for interventions that can mitigate its toxic effects in exposed populations. This review has discussed the work carried out to date regarding the hematological aberrations caused by arsenic poisoning, and the probable mechanisms through which these changes occur. Recent research strongly suggests that dietary supplementation with specific nutrients or nutraceutical regimes may offer a promising avenue for reducing arsenic toxicity in both humans and animals. These interventions could represent a more immediate and cost-effective remedy in the face of widespread contamination. In conclusion, arsenic exposure remains a significant global public health challenge, with a wide spectrum of adverse effects on the hematopoietic system. A multi-pronged approach is essential to effectively address this issue. Primary prevention, through the provision of safe drinking water and the reduction of occupational exposure. Technological advancements in water filtration and

remediation offer promising avenues for mitigating arsenic contamination. For affected individuals, early diagnosis and intervention are crucial. While chelation therapy has limitations, it can be beneficial in acute cases. Supportive care, including blood transfusions and growth factors, plays a vital role in managing hematological complications. Further research is needed to delineate the exact mechanisms by which dietary supplements and other potential therapeutic agents counteract arsenic poisoning, and also which of the nutraceuticals have more potential to alleviate the toxicity. This will be crucial for developing more potent and targeted interventions in the future. By combining preventive strategies, improved diagnostic tools, and innovative therapeutic approaches, we can strive to reduce the burden of arsenic-induced hematological disorders, particularly in vulnerable populations.

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