

Environmental toxicology of arsenic: current understanding of toxicity, detection, and remedial strategies

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Abstract

Arsenic toxicity is an important worldwide health problem of humans and animals due to environmental and occupational exposure through arsenic polluted water, air, soil and food items. It has a multifaceted health impact on animals, human beings, and the environment. Therefore, various experimental and clinical studies were undertaken and had been undergoing to understand its pathogenesis, identify the key biomarkers, medical and economic impact on the affected populations, timely detection and amelioration. However, despite these long-investigated studies, no conclusive information is available for prevention and control of arsenic toxicity, mainly due to complex epidemiology, scattered approach, and repetitive work. Hence, there is a need for literature that exclusively brings information on epidemiology, pathogenesis, and ameliorative measures of arsenic toxicity, which can help researchers and policymakers for effective future planning research and community control programs. In the above view, this article presents an extensive review on the current understanding of arsenic toxicity, detection methodologies, epidemiology, and remedial measures for the benefits of researchers, academicians, and policy makers in controlling arsenic eco-toxicology and direction for direction futuristic research.

1. Introduction:

The presence of inorganic arsenic (As) from geological sources is very common in water drawn from very deep wells in plain, hilly and mountain areas and even shallow wells from endemic regions. Arsenic is present in three common forms, e.g., inorganic salt, organic salt (monomethyl arsenic, common in aquatic food sources), and gaseous form (arsine) (Kuivenhoven et al., 2021). So, human exposure is very common through the soil, air, water, and food in different parts of the world, leading to arsenic toxicity (Sanyal et al., 2020). The global arsenic pollution scenario has changed with the discovery of new locations and more and more people being affected. Further, exposure to other metal and environmental toxicants along with arsenic is also an important public concern due to strong interaction and complex pathogenicity, especially with fluoride and lead in polluted groundwater (Kumar et al., 2020; Mondal and Chattopadhyay 2020).

The other important source of arsenic exposure is the anthropogenic origin, like agrochemicals, wood preservatives, mineral processing, acid mine drainage, burning of fossil fuels, etc. (Kumari et al., 2017; Bundschuh et al., 2021). A recent report revealed that natural exposure to arsenic from groundwater is one of the foremost concerns human and animal health in more than 103 countries, including Bangladesh, India, Vietnam, Taiwan, China, Thailand, Pakistan, Iran, Australia, Argentina, Brazil, Chile, Bulgaria, Canada, Czech Republic, Egypt, parts of USA, etc. (Sanya et al., 2020; Shaji et al., 2021). Moreover, arsenic presence in drinking water is imperceptible, tasteless and odorless (Viscusi et al., 2015). Therefore, excessive prolonged exposure of inorganic arsenic from drinking water and food is inevitable to a large population consuming untreated water, causing endemic arsenicosis (Sanyal et al., 2020; Oza et al., 2021).

A range of studies revealed that human and animal exposure to different levels of arsenic causing acute, sub-acute and chronic toxicity in animals (Bharti and Srivastava 2009; Bharti et al 2012a; b) and humans and affects their body physiology and health (Tchounwou et al., 2019; Alvarado-Flores et al., 2019). The latest global number of people infected with arsenicosis, which exceeds the World Health Organization's (WHO's) safe standard for drinking water by 10 ppb, is around 230 million, which has increased dramatically in a decade (Shaji et al., 2021). Arsenic toxicity affects animals and humans differently, depending on their species, age, geographical region, the form of arsenic, feeding habits, etc. (Sanyal et al., 2020). So, the environmental toxicology of arsenic is not just applied science, focusing only on toxicity testing; it is an experimental science that includes basic cell and developmental biology targeting the molecular mechanisms by which arsenic interact with cells and other physiological systems. Recent reports revealed that continued exposure to arsenic also significantly increases the risk of illness and death from cancer and heart, lung, kidney, and liver disease (Rahman et al., 2019). The association between arsenic exposure and abnormal obstetric effects like spontaneous abortion, stillbirths, embryonic death, pregnancy hypertension, and gestational diabetes has also been observed in many developing countries (Amadi et al., 2017). Further, chronic arsenic exposure may affect adult cognitive function in a dose-dependent manner (Wang et al., 2021a). In addition, it is an independent risk factor for cognitive impairment. Therefore, there is a need to establish a proper epidemiological database for effective preventive and control measures of arsenic toxicity.

Literatures are available on arsenic toxicity, pathogenesis in various species, and ameliorative measures; however, specific epidemiology of arsenic exposures, detection mechanism, and remediation are poorly understood (Sage et al., 2017). Therefore, in this review paper, the current state of sources of arsenic exposure, health effects, pathogenesis, modern techniques of arsenic removal, therapeutic agents, and critical areas for future research are comprehensively reviewed.

2. Abiotic Sources Of Environmental Exposure To Arsenicals:

Arsenic (As) is a toxic metalloid element of the earth's crust and is present abundantly in the air, water, and soil in different valence states viz. As(0), As(III), As(V) and arsine gas (-3 oxidative state). The abiotic sources of arsenic in the environment include geogenic (underground water, minerals and geothermal processes) and anthropogenic like mining operations, industrial processes, agricultural activities, etc. (Nadiri et al., 2018; Sanyal et al., 2020; Palma-Lara et al., 2020; Nadiri et al., 2021). Arsenic contaminated soil is a major source of arsenic exposure in humans by consuming plant-based food cultivated on these soils (Dahlawi et al., 2018). These contaminated soils also contribute arsenic to groundwater and surface water resources through leaching and runoff mixed with the river, pond, etc. The geogenic contamination can be further extended by unintended human and industrial activities (Nadiri et al., 2018, 2021). So, polluted groundwater for drinking and other household activities is a major source of arsenic exposure to humans.

High arsenic level equal to or greater than 50 µg/L in groundwater has been reported, especially in Southeast Asia and parts of India and Bangladesh, which is alarming for society (Chakraborti et al.,

2018). Other studies indicated that the outside Asia population is also affected by arsenic exposure through groundwater (Shahid et al., 2020; Shaji et al., 2021). Interestingly, Bharti et al. (2017), Giri et al. (2017, 2019, 2020) reported that water from high-altitude is also contaminated with arsenic along with other heavy metals. River sediment is another important source of arsenic to the ground and river water (Shaji et al., 2021). These reports indicate widespread arsenic contamination in water resources from high-mountain to plain areas, irrespective of industrialization and other anthropogenic sources.

To regulate water arsenic levels, earlier, the WHO has set 50 parts per billion (ppb) arsenic levels in drinking water throughout the exposure period but has been revised in 1993 to a lower level when it is considered to pose an unacceptably high risk of cancer death. The current WHO guideline value is temporarily set at 10 ppb due to arsenic detection and removal limits (Cheng et al., 2016), although this is still considered an unacceptably high health risk. So, every country should establish their own recommended level of arsenic in drinking water; so far, various countries have set from 50 ppb to less than 10 ppb (Altowayti et al., 2021).

The gaseous form of arsenic (arsine) is the most toxic form, and inhalation of over 10 ppm to 25 ppm is lethal even in less than an hour. The mining activities and burning of contaminated charcoal are causing air pollution with arsenic (Zhao et al., 2019a). Arsenic does not cause tissue irritation and is odorless, hence exposure to this arsine is unrecognizable. Hence, there should be regular monitoring of arsenic in different abiotic sources for better epidemiological study and control measures of arsenic toxicity and associated health hazards.

3. Arsenic Exposure Through Aquatic Food Animals:

The high concentrations of arsenic in fish, crabs, shrimps, bivalves and other seafood have also been reported (Liu et al., 2019). These food animals' products are the main sources of organic arsenic for humans (Feng et al., 2020). Several arsenic-based chemicals are used in the agricultural field, wood industry, pharmaceutical industry etc. which goes into the river, pond, lake, etc., and are exposed to aquatic animals (Kumari et al., 2017; Tuteja et al., 2021). These aquatic contaminations by arsenicals are further increased due to the high disposal of untreated sewage, posing widespread arsenic toxicity in aquatic organisms and bioaccumulation into their bodies. According to the international water quality standards, arsenic levels above 0.010 mg/L exposure result in bioaccumulation, mainly in the muscles, liver and kidney of freshwater organisms, including fish (Cui et al., 2021). One recent report observed very high biomagnifications up to 2.05 ± 0.30 mg Kg⁻¹ in freshwater fish, although water contained very low arsenic concentration 0.001 to 0.003 ppm (Alvarado-Flores et al., 2019). These findings indicate that aquatic animal-based food should be regularly monitored for arsenic concentration irrespective of harvesting or culture sources.

The presence of aquatic algal and flora biomass is another important source of arsenic to aquatic animals, as it retains arsenic, and so consumption of these algae and plants further magnify the arsenic bioaccumulation in aquatic foods (Hussain et al., 2021). Hence, increased algal biomass in ponds, lakes,

etc., is directly related to increased arsenic content in the aquatic animal. The other factors are the metabolic role of organs and their relationships with arsenic, which affect the concentration of arsenic in aquatic organisms (Juncos et al., 2019). Therefore, aquatic animals' products obtained from the arsenic-contaminated pond, river, etc., are an important source of arsenic to human consumers.

However, Juncos et al. (2019) reported that despite high arsenic levels in fish do not represent any health risk to consumers. Similarly, Liu et al. (2020) found less arsenic in Chinese mitten crab collected from different locations of China and said that intake of Chinese mitten crabs had not posed any appreciable danger to human health. These findings could be due to specific food habits of those human populations around the study areas and other dietary factors. Hence, more studies are required to correlate arsenic exposure to humans through aquatic animal origin food.

4. Arsenic Exposure Through Plant Origin Food:

Other routes of arsenic exposure include food from those crops irrigated with arsenic-contaminated water, as more arsenic is absorbed to plants irrigated with arsenic-contaminated water (Kaur et al., 2017; Allevato et al., 2019). So, plants are considered one of the most vulnerable matrices of short- and long-term exposure to arsenic (Navazas et al., 2020). The top layer of soil irrigated with arsenic-contaminated water acts as an arsenic reservoir which can affect plants for longer periods even after irrigation has stopped (Rehman et al., 2021). The contamination of vegetables and edible grains is considered a major exposure pathway by which this metalloid enters into the food chain of livestock and human beings (Kumar et al., 2019). So, agricultural fields should not be irrigated with polluted water to avoid entering arsenic into the food cycle through soil-water-plant interactions.

Now, it has been well known that arsenic is also toxic to plants (plant toxin) and higher soil arsenic level affects crop yield (Dahlawi et al., 2018). Zeng et al. (2021) investigated 157 crop varieties, including rice, vegetables, and corn, and their risk of arsenic accumulation in edible parts with the help of pot and field experiments. They found that rice has greater accumulation even in low concentrations of arsenic in soil (56.7mg/kg) but, green tender, cabbage, rapeseed and amaranth appeared with the risk of exceeding the limit for arsenic when the arsenic from the soil reached 238.3 mg/kg (serious contamination). However, he reported that corn and tubers or fruit vegetables had the lowest arsenic content in their edible parts, and sweet potatoes, peanuts, peppers, and potatoes had less variation in arsenic accumulation among varieties of the same crop. Paddy plant (*Oryza sativa* L.) is particularly effective in absorbing arsenic from the soil due to its unique mineral utilizing mechanism. So, flooded paddy fields may cause an increased accumulation of arsenic in rice and could become a new catastrophe for the population of Southeast Asia (Thielecke and Nugent 2018; Yan et al., 2021). Rasheed et al. (2018) found very high inorganic arsenic concentrations in Pakistan, which were $92.5 \pm 41.88 \mu\text{gkg}^{-1}$, $79.21 \pm 76.42 \mu\text{gkg}^{-1}$, and $116.38 \pm 51.38 \mu\text{gkg}^{-1}$ for raw rice, cooked rice and wheat, respectively. Thus, in addition to rice, many crops can also absorb arsenic and transport it to different ranges using similar transporters.

There are many reports on algae aggravated arsenic exposure to aquatic animals (Milan et al., 2021; Byeon et al., 2021), since algae additively acting with arsenic to increase arsenic uptake and assimilation in aquatic animals. Hence, water systems having high algae and arsenic are posing more bioaccumulation in aquatic animals.

5. Arsenic Exposure Through Livestock Origin Food:

Large amounts of arsenic have been reported in poultry and livestock origin foods such as milk, boiled egg yolks, egg whites, liver and meat (Das et al., 2021). Generally, animals are exposed to arsenic through drinking water, feed, grass, vegetables and other contaminated foliage. In endemic arsenic areas, irrigation with arsenic-contaminated water leads to soil contamination and subsequent transport of arsenic to forage grown on it and then to livestock, resulting in excessive bioaccumulation of arsenic in livestock products (Zubair et al., 2018; Das et al., 2021). A recent report revealed that bio-concentration of arsenic occurs more rapidly in water compared to rice straw, and when used as fodder, it manifests itself mainly in the excreta and tail hair of cattle (Das et al., 2021). Cow dung and tail hair are other obvious pathways for the biotransformation of arsenic in the environment (Rehman et al., 2021). So, arsenic-contaminated edible vegetables and grains are believed to be the main route of arsenic exposure into the food chain of livestock and humans (Kumar et al., 2019). Giri et al. (2016, 2020) studies on blood minerals status in dairy cattle and water quality at high-altitude have revealed the arsenic presence in blood, which could be due to high arsenic levels in fodder and water sources in that region. Therefore, contaminated fodder, grains, and drinking water are considered important sources of arsenic exposure to livestock population and livestock origin food, e.g. meat, milk, and eggs.

Various reports indicated higher estimated daily intakes from the recommended safe limits of arsenic from consumption of livestock origin food (Bala et al., 2018). Though chronic exposure to low levels of arsenic in livestock often shows no external signs or symptoms, although the concentration of arsenic (or its metabolites) in the blood, fur, hooves and urine of animals from contaminated areas remains high (Mondal 2017). Importantly, due to phosphoserine units in milk casein, arsenic in milk is mainly concentrated in casein (83%) (Das et al., 2021). The severity-adjusted margin of exposure (SAMOE) risk thermometer was calculated by Das et al. (2021) for the most commonly eaten foods in the region. It displayed human health risks in clear order: drinking water > rice grains > milk > chicken > eggs > lamb, from level 5 to level 1. Njoga et al. (2021) reported high level of arsenic (0.53 ± 0.10 mg/kg kidney, 0.57 ± 0.09 mg/kg liver and 0.45 ± 0.08 mg/kg muscle) in goat meat collected from Enuga state of Nigeria. The United States Environmental Protection Agency (USEPA) health risk assessment model shows that adults face a higher risk than children (Sheng et al., 2021) because eating animal protein foods that cannot be ignored in children has a continuing risk of serious health hazards. This arsenic-contaminated meat, milk, and eggs pose a threat to humans through the ingestion. Hence, livestock animals need to be provided with arsenic-free drinking water and nutritional supplements to affected populations to overcome the severe arsenic crisis in the human community.

6. Pathogenesis Of Arsenic Toxicity:

Investigating pathogenicity mechanisms is important in understanding arsenic-induced diseases and carcinogenesis, including identification of early diagnostic markers and drug development. As evident from the review of the previous section, arsenic is omnipresent in soil, water, air, and food chain and is considered a high-risk priority pollutant in various parts of the world, even at low concentrations. The Environmental Protection Agency (EPA) and the WHO has established less than 0.010mg/L the safe limit of arsenic in drinking water. In contrast, the National Institute for Occupational Safety Health (NIOSH) has recommended 2 $\mu\text{g}/\text{m}^3$ of air for no more than 15 minutes as a safe exposure limit (Marcotte et al., 2017). Therefore, a higher arsenic concentration than the recommended limit in drinking water and food leads to acute and chronic arsenic poisoning and adverse cellular metabolism changes in humans and animals (Sanyal et al., 2020). Various toxicologists, biochemists, cell biologists and other related scientists have been observing changes in physiological function and imprecise signaling pathways in response to arsenic (Wang et. al., 2019; Palma-Lara et. al., 2020; Cardoso et. al., 2020). Due to high arsenic exposure, these physio-pathological changes affect our body metabolism, reproductive health, embryonic development, cancer incidence, cognitive function, aging, immunity, and our symbiotic microbiome, summarized in an illustrative manner (Fig. 1).

Many toxicokinetic reports revealed that arsenic is highly toxic in its inorganic form than the organic form, especially the trioxide form (arsenite) than the pentoxide (arsenate). In contrast, inorganic (arsenite) and organic (monomethyl arsenic) forms are more toxic than the pentavalent compounds (arsenate). Aquatic animals, including fish, are the important source of organic arsenic exposure, whereas inorganic arsenic mainly enters through drinking water (Polak-Juszczak and Szlinder-Richert 2021; Raman et al., 2021). Total two-thirds absorption of ingested inorganic arsenic occurs through the gastrointestinal tract and is distributed in hepatic, kidney, muscle, skin, brain, and other parts of the body (Cui et al., 2020; Arbam et al., 2021). However, particulate form of arsenic is absorbed through respiratory routes and later mixed with blood, causing hemolysis and affecting oxygen transport to cells (Fig. 1). While dermal absorption is very less and not causing toxicity, however, caution should be maintained to avoid dermal exposure as it may pose chronic toxicity (Sohrabi et al., 2021).

Arsenic excretion from the body is very slow and primarily occurs through the renal system and depends upon valence state, the form of arsenic and body fat deposition. Arsenite is poorly excreted than arsenate and organic arsenic; therefore, arsenite is causing more toxicity (Sharma et al., 2020). Furthermore, the elimination of inorganic arsenic in urine can be monitored up to the first week of possible exposure, an important tool for epidemiology and clinical studies (Srivastava and Flora 2020). Serum arsenic concentration is not an effective or reliable indicator of arsenic toxicity due to the rapid removal of arsenic from the blood to tissues (Kuivenhoven and Mason 2021). Interestingly, arsenic is little excreted during breastfeeding, and studies have shown that breastfeeding exclusively reduces the risk of arsenic exposure in infants in pandemic regions. (Kuivenhoven and Mason 2021). However, arsenic is teratogenic and can cross the placenta and affects fetal development (Gangopadhyay et al., 2019).

All the absorbed arsenic are distributed to various tissues. After that, binding with the iron part of hemoglobin, interacting with serum and cellular minerals, sulphhydryl moieties of protein, phosphate molecules, and transcriptional factors. The metabolism of inorganic arsenic progress mainly through a sequence of repetitive reduction and oxidative methylation (Thomas 2021), the latter mediated by arsenic methyltransferase (CYT19) (Hayakawa et al., 2005). Arsenic-glutathione complexes are substrates for human CYT19. These cellular and molecular changes lead to cascades of various pathological changes, like impairment of cellular respiration, energy metabolism, protein synthesis, enzyme function, the oxygen-carrying ability of erythrocytes, aerobic respiration, DNA repair, cell cycle, etc. (Fig. 1). These above arsenic-induced pathological changes are flared up with other disease conditions, oxidative stress and deficiency of antioxidant system (Prabu and Sumedha 2014).

These pathological changes ultimately lead to increased cellular and tissue damage reported in various studies on arsenic toxicity. There may be relevant environmental co-exposures of arsenic with other inorganic compounds leading to a combined effect, with questions about the mechanisms involved. Therefore, the epidemiology of arsenic toxicity and its clinical signs is complex, which needs a multidimensional collection of information on disease history, food habits, environment, clinical laboratory reports, etc. This will help correct and timely diagnose arsenic toxicity, excluding other similar clinical conditions and proper control and preventive measures.

7. Experimental Advancement In Detection Of Arsenic Toxicity:

The animal models used in studying human disease by toxicants are often chosen because they are genetically, anatomically and physiologically similar to humans. Therefore, bio-medical research using laboratory animals like mice, guinea pigs, zebrafish and fruit flies has contributed greatly to many important scientific and medical advances (Norberg-King et al., 2018). Short-term in-vitro tests have been useful in screening for a wide variety of potentially toxic compounds of arsenic, safety assessment, and carcinogenicity testing (Tsuji et al., 2019). Additionally, animal models are generally preferred for research work for toxicology due to their ease of handling and test hypotheses about how a disease develops; however, an appropriate number of subjects should be used to test the experiment's outcome statistically (Smith 2020). These animal models have currently used in arsenic toxicological studies as indicators of human health problems and environmental monitoring. Hence, in this section, recent studies are reviewed to provide experimental advancement in detection of arsenic toxicity and mechanistic information to validate other alternative testing methods in a wide range of studies.

7.1. Aquatic animal model using fish:

Although it is widely recognized that aquatic ecosystems serve as the ultimate reservoir for many chemicals, including arsenic (Kumari et al., 2011b; Rand et al., 2020), water serves as the ultimate vehicle for exposure to many toxic substances. Fish is currently a well-known biological model for toxicological research (Denizeau 2018; Boudou and Ribeyre 2018) and can be used as a study model for arsenic toxicity to elucidate the molecular mechanism. Indeed, the establishment of zebrafish, medaka fish and

other schools of fish is probably at the forefront of biomedical research (Hirata and Lida 2018). Zebrafish have great potential for mechanistic study for arsenic and could be used more in the future.

Many biochemical processes have been studied in fish, including heterologous metabolism, DNA damage and repair induction, membrane transport, disruption of ion homeostasis, oxidative stress, metallothionein expression, and protein stress (Hugget 2018). The effect of foreign bodies on specific cellular functions, particularly those of immune cells and their response to estrogenic compounds, has also received some attention. This review has summarized the various studies on the effect of arsenic on different fish species, and how this information can be utilized for toxicological studies is presented in Table 1.

Arsenic has a high metabolic action in accumulation in various tissues and organs of different fish species such as *O. mykiss*, *S. trutta* and *Danio rerio* (Juncos et al., 2019; Wang et al., 2020). The toxic effects are dose-dependent and through various mechanisms (Mekkawi et al., 2020; Tuteja et al., 2021), being chronic exposures at low doses to the higher doses for acute exposure. Arsenic has a good effect at the extremely low amount (1-5ppb) (Kumari and Ghosh 2012a), while the same concentrations are lethal in other fish species. Acute arsenic exposure causes symptoms like increased mucus secretion, defects in gill epithelial and asphyxiation. In contrast, chronic exposure led to bioaccumulation and various histopathological changes, e.g. renal and hepatic degeneration, focal hepatic necrosis, bile duct obstruction, proliferation in parenchymal hepatocytes (Muneeb et al., 2020). Furthermore, the increased arsenic accumulation induces hyperglycemia, adverse changes in other biochemical and hematological parameters, down-regulation of antioxidant defense, inhibition of enzymatic activities, immune system dysfunction, and reduced breeding ability in fish (Kumari and Ahsan 2011b; Han et al., 2019; Prakash and Verma 2020; Mekkawi et al., 2020; Tuteja et al., 2021). Later it causes poor growth, behavioral changes and death in fish and other aquatic organisms. The other pathological markers of arsenic toxicity in fish are apoptosis of brain cells (Wang et al., 2021b), an indicator of arsenic as a neurotoxin.

Milan et al. (2021) observed that arsenic toxicity adversely affected the quality of rainbow trout (*O. mykiss*) fillets by inducing oxidative stress and affecting the level of antioxidant enzymes. In another study on *Clarias batrachus*, high blood glucose, and tissue glycogen levels low in muscles, liver and brain were observed (Kumari and Ahsan 2011a, 2011b; Kumari et al., 2012, 2015). The recent research by Han et al. (2019) and Mekkawi et al. (2020) also supported these findings that arsenic affects glucose levels. Effect of arsenic on fish's skin and their pigmentation has been noticed by Kumari et al (2013) when fish was exposed by arsenic for a week. Han et al. (2019; 2019a) reported the toxic effects of arsenic on *Platichthys stellatus* (*P. stellatus*), which were higher at the highest temperature. They observed a decrease in hematological and growth parameters with increasing arsenic concentration, while higher concentrations of the plasma components were detected. Kumari and Ghosh (2012b) observed the cellular damage in erythrocytes of fresh water fish. These results indicate that exposure to arsenic in water at high water temperatures may exert more toxic effects on growth, hematological parameters and plasma components

The arsenic contained in bottom sediments is biologically available to benthic fish and their food, and causing bioaccumulation. The body level of arsenic is positively correlated with the concentration of arsenic in sediment but not significantly related to water-soluble arsenic (Zhang et al., 2017b; Zhang et al., 2018). Although nutrition is an important means of uptake of arsenic in benthic fish, most studies of the toxicity and metabolism of arsenic in benthic fish have investigated how the absorption of arsenic contained in water through gills and consequences on their health (Hua et al., 2017; Juncos et al., 2019). The above review advocates that additional experiments are needed to study the toxicological effects and metabolism of arsenic in fish to identify vital signs that can be used as reliable and sensitive biomarkers of arsenic toxicity in environmental monitoring programs.

7.2. Small animal model using rodents:

Biologically, rats and mice are very similar to humans and undergo many similar physiological disorders and genetic expressions, so they can be genetically engineered to mimic any disease or human condition (Perlman et al., 2016). Rats and mice can be bred to produce genetically identical lines, and this uniformity allows us for more accurate and repeatable experiments (Zhang et al., 2019b). Hence, rodent species (rats and mice) are ideal animal models for experimental toxicology, including arsenic toxicity (Raydel-Tormanen et al., 2019; Smith 2020).

Arsenic's toxicity is partly due to its electrophilic nature, so when absorbed, it readily binds to the electronic sulfhydryl groups of proteins and then modulates the activity of the protein (Patel et al., 2020). There are various reports that observed a positive correlation between arsenic exposure level with arsenic accumulation in liver and kidney tissue (Patel et al., 2020; Garla et al., 2021). Arsenic exposure lowers the reduced glutathione (GSH), increasing kidney and liver function test parameters and histological abnormalities (Dkhil et al., 2020). The various histopathological changes are necrosis, the appearance of vacuoles, and degenerative nuclear changes in the experimental animals. So, the pathology of metabolically active organs like renal and hepatic tissues is a good experimental tool to study arsenic toxicity. Furthermore, arsenic is also responsible for damaging the male reproductive function in rats and mice and, after that, causing reduced spermatogenesis, sperm counts and motility (Liu et al., 2021; Souza et al., 2021). It also inhibits testosterone release, the function of the testicular enzyme and atrophy of male genital organs. Several experimental studies have been performed on arsenic exposure. Its effects on various parameters, such as physiology, biochemistry, genotoxicity, histopathology, etc. are presented in Table 2, which could be useful in designing experiments on arsenic toxicity for more data on regulatory and exploratory toxicology.

8. Recent Trends In Arsenic Toxicity In Humans:

Millions of people worldwide are exposed to arsenic from various sources regularly, mainly through drinking water. The human health risk comes from the (i) anthropogenic activities caused by unprecedented population growth, urbanization and industrialization (Zhai et al., 2017; Wang et al., 2019) and (ii) geogenic processes often resulting from long-term hydro-geochemical reactions (Beiyuan et al., 2017; Singh et al., 2018). Sarret et al. (2019) reported that in Latin America, millions of people are

chronically exposed to the high concentration of arsenic ($> 50 \mu\text{g/L}$ drinking water), with extremes up to $2000 \mu\text{g/L}$. Humans are primarily exposed to arsenic via contaminated drinking water, while inhalation and dermal absorption are secondary routes of exposure (Shih et al., 2019). The human health risks were also caused by eating plant origin food grown over soil irrigated with arsenic-contaminated water (Fig. 2).

There is a very rapid recent development in the diagnosis of arsenic toxicity and research into human environmental exposures and related arsenic induced diseases, which are highly relevant to public health in many countries. The various health effects of arsenic poisoning are keratosis, hyperkeratosis, melanosis, black foot disease, peripheral vascular disease, leuco-melanosis, dorsum, nonpetting edema, and gangrene (Altowayti et al., 2021). Keratosis and melanosis are the most common manifestations in affected people (Singh et al., 2021). Now a day, arsenic toxicity has become a global public health problem because of its association with various cancers and other pathological effects of vital organs through cytotoxicity and genotoxicity mechanism (Bjorklund et al., 2018; Zhao et al., 2018; Tchounwou et al., 2019; Tsuji et al., 2021). Exposure to arsenic can lead to various systemic diseases. The various experimental and clinical studies brought considerable evidence, which indicates that arsenic adversely affects the antioxidant defense system, apoptosis, and other physio-biochemical changes (Flora 2011; Giri et al., 2016) however, its specific mechanism is poorly understood. Recently, arsenic exposure has been implicated in the incidence of various skin cancer, gall-bladder, lung, and hepatocellular carcinoma (Fuijoka et al., 2020; Abdollahzade et al., 2021). The estimated lethal dose of inorganic arsenic for humans is 0.6 mg/kg , which leads to death within 1–4 days of ingestion (Kuivenhoven and Mason 2021).

However, long-term exposure to inorganic arsenic can cause various dysfunctions of vital organ systems such as the digestive system, respiratory system, cardiovascular system, hematopoietic system, endocrine system, kidney system, nervous system and reproductive system, and eventually lead to cancer (Palma- Lara et al., 2020). The various experimental and clinical researches brought numerous pieces of evidence and are presented in Table 3. Despite the magnitude of this potentially fatal toxicity, there is no effective treatment for the disease, so affected patients may not recover even after the restoration of arsenic-contaminated water. There is peripheral neuropathy which may disappear with the cessation of exposure (Kuivenhoven and Mason 2021). However, research data on absorption, distribution, metabolism and excretion (ADME) of arsenic species/compounds are lacking. Therefore, more studies are required on how age, sex, food habits, co-morbidity, etc., are affecting arsenic toxicity in humans.

9. Modern Technological Intervention In Arsenic Removal:

Arsenic contamination in drinking water is more important as compared to other sources, and their associated side effects are becoming more and more harmful with an increasing number of affected people and new sites being reported around the world. Hence, many analytical methods for arsenic detection have been developed in different samples to combat arsenic pollution and obtain a healthy environment and an ecosystem. In recent decades, many chemical methods and instrumental techniques have been identified for arsenic analysis. Basically, chemical approaches allow the

identification of arsenic in simple matrices. However, their low sensitivity and detection limit can satisfy the quantitative requirements of low-level analytes in many practical models (Xu et al., 2020). Therefore, arsenic removal studies using biotechnological and nanotechnological tools are gaining pace in arsenic removal. With the rise of nanotechnology development, many nanostructured materials have been investigated and used to detect inorganic arsenic. The introduction of nanomaterials not only enables the development of new sensors and biosensors but can also significantly improve detection performance.

For this reason, there has been active research on nanomaterial-based sensors/biosensors in recent years to determine inorganic arsenic (Table 4). Of these strategies, biosensors contain a major promise for the rapid detection of arsenic (Mao et al., 2020), especially the nanomaterial-based aptamer sensors that have drawn considerable attention due to their simplicity, high sensitivity and speedy action. According to Rosales et al. (2020), few-layer Mxene nano-sheets layers are capable of efficiently oxidizing the highly toxic As (III) to the less harmful As (V) and at the same time have remarkable absorption capacity for both species [approximately 44% for (III) and 50% for (V)]. In particular, few-layer Mxene nano-sheets layers are a promising candidate for effective arsenic suppression due to this toxic pollutant's unprecedented dual adsorption / photo-oxidation effect.

Biological treatment of arsenic-contaminated water with aquatic algae should be carried out, considering the effects on the entire ecosystem since algae enhance arsenic bioaccumulation in aquatic animals (Hussain et al., 2021). Some of the research findings have described the mechanisms of arsenic detoxification in microalgae, including cell surface absorption, intracellular As (III) oxidation, As (V) reduction and thiol (-SH) complexation, and vacuole sequestration (Huang et al., 2021). The role of microorganisms in the degradation and detoxification of arsenic-contaminated lands and water areas has become important in recent years under the process of bioremediation (Patel et al., 2021). Therefore, a multidisciplinary approach should be considered for bioremediation considering cross-taxon integrating behavioural and other effects of arsenic toxicity and after that restoration of aquatic and terrestrial ecosystems.

10. New Therapeutic Agents For Controlling Arsenic Toxicity:

In recent years, most *in-vivo* and *in-vitro* studies have shown that ROS generation, oxidative stress, DNA damage, mutations, and cytotoxicity are the important molecular changes in arsenic toxicity (Firdaus et al., 2018; Perker et al., 2019; Wu et al., 2019; Rahaman et al., 2020). This means that arsenic induces oxidative stresses and cytotoxicity in different cell lines through ROS generation, which triggers NADPH oxidation and leads to adverse cellular changes. Glutathione is an important antioxidant that maintains the antioxidant / pro-oxidizing balance and plays a vital role in protecting cells in oxidative stress (Rao et al., 2017). Hence, controlling oxidative stress and up-regulation of body antioxidant defense is an important strategy for controlling and treating arsenic toxicity.

Plant extract is rich in antioxidant content due to the presence of various flavonoids, alkaloids, trace minerals, etc., and so could be useful antioxidant based therapeutic agents in arsenic toxicity. Mohajeri et al. (2017) reported curcumin has beneficial effects against arsenic-induced toxicity without any side effects. Another study on the extract of *Ginkgo biloba* (GBE), obtained from leaves contains ginkgo flavone glycosides, terpene lactones, and other active components, which has shown beneficial effects through modulating antioxidant functions, anti-inflammatory effects, inhibition of platelet aggregation, and immune regulation (Xeng et al., 2021). Xia et al. (2020) observed that GBE has consequences for arsenicosis through the law of balance of pro-inflammatory and anti-inflammatory T cells, whereas the pathogenesis of arsenicosis induces an imbalance of pro-inflammatory and anti-inflammatory T cells. Yao et al. (2017) found that GBE can reduce the accumulation of arsenic in the liver and liver injury through ameliorating lipid peroxidation in rats. Recently, several reports (Rahman et al., 2018; Perker et al., 2019; Susan et al., 2019; Rahaman et al., 2020;) showed that Natural bioactive compounds exhibit antioxidant properties and effectively mitigate arsenic-induced toxicity by modulating the antioxidant defense system. These studies advocate that antioxidant treatment is comparatively safe and cost-efficient preventive therapeutics in arsenic toxicity and other human diseases and disorders. Numerous studies on different therapeutic materials to control arsenic toxicity are reviewed in detail and summarized in Table 5.

Although chelating therapy is also considered an effective and well-known treatment of arsenic's toxicity, however, it has shown several unwanted effects due to the limited safety of chelating agents (Nurchi et al., 2020). Further, it is suggested that arsenic is incorporated by cells in mammals and other organisms, after which it can be bio-transformed, and its metabolites also exert toxic effects (Hirano 2020). Thus, the inhibition of biotransformation of arsenic should be considered a prime pathway for arsenic bio-inactivation and reduction of arsenic toxicity in the body. This would be a vital point for the development of many future therapeutic agents.

Recently, nano metal oxides have been increasingly used to solve this global problem in various biomedical applications. The nanomaterials like liposomes, polymeric micelles, and phospholipid complexes have emerged as few promising therapeutic tools for reducing arsenic toxicity (Edis et al., 2021). These materials have a large surface area, specificity for their custom substrates and different shapes. Several metal oxide nanoparticles (NPs) such as iron (hydro) oxides, aluminium oxide, titanium dioxide, zinc oxides, and copper oxide have been used as nano adsorbents to remove heavy metals from various sources (Pillai and Dharaskar 2020). Naqvi et al. (2020) reported a better protective effect of solid lipid nanoparticles loaded with monoisoamyl-2,3-dimercaptosuccinic acid (NanoMiADMSA) compared to its volume of MiADMSA in the treatment of neurological and other biochemical abnormalities induced by arsenic. The results suggested that the size of NanoMiADMSA ranged between 100 and 120 nm has better chelating properties than MiADMSA in bulk. These findings encourage future investigation on identifying effective nanomedicine in arsenic toxicity having higher efficacy and safety.

11. Future Research And Policy Guidelines For Effective Control Of Arsenic Toxicity:

Arsenic toxicity requires multifaceted research interventions for development of sustainable technology and framing policy guidelines, following are the some important priority areas: i) Experimental pathogenesis studies in different species considering various developmental stages, age, sex, habitats, climates, and fat-muscle body mass index; ii) Histopathology of metabolic active organs like liver, kidney, skin, brain, lungs, and gonads for ascertaining tissues and cellular toxicities, metabolomics; iii) Identification of biochemical and molecular biomarkers of acute, sub-acute, and chronic toxicity; iv) Immunohistochemistry and initiation, promotion and progression of arsenic-induced cancer; v) Ameliorative measures targeting various sources of arsenic e.g. water arsenic removal, food fortification, chelating and neutralization techniques, nutraceuticals for animals and human, and specific community health preventive measures in endemic areas; vi) Intervention of biotechnology and nanotechnology tools for arsenic removal from various sources; vii) Epidemiological studies in-country and regional level along with other health program; viii) Evaluation of genetic and epigenetic factors affecting arsenic-induced health hazards; ix) Studies on the association of reproductive, embryonic developmental, and metabolic diseases in endemic arsenic areas; x) Regulatory studies and monitoring arsenic and other metals in water, soil, air, and food system at the community level. These are some important research areas where immediate interventions are required to develop better control and prevention strategies for arsenic toxicity.

Summary

The increase of arsenic in human bodies poses a serious global health risk to the human population. It is concluded that arsenic exposure has become common in the food chain, and therefore widespread toxicity is reported in various species of animals, including human beings. Since arsenic is a known human carcinogen and interacts with various cellular molecules, extensive epidemiological studies on arsenic-induced toxicity are extremely important. The experimental research on arsenic toxicokinetics, toxicodynamics, and mode of toxic action are high priority areas to address this issue. Nanotechnology and biotechnology-based ameliorative measures have proven good and promising in control measures of arsenic toxicity. So, arsenic epidemiology should focus on the dominance of different direct and indirect sources in the affected areas and then only control measures and implementation of public health policy could be successful.

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Conflict of Interests

Both authors have read the journal's policy and declare that they have no competing interests that might be perceived to influence the content of this article. Authors also declare that they have no proprietary, financial, professional, or any other personal interest of any nature or kind in any product or services and company that could be construed or considered a potential conflict of interest that might have influenced views expressed in this manuscript. Further, the views expressed in this article are those of the authors and do not necessarily represent the official views of their affiliated institutions.

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Consent for Publication

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Tables

Tables

Table-1 : **Arsenic toxicological research works on Fish** (arranged in chronological order). **As** indicating Arsenic; **iAs** – inorganic Arsenic; **As III**- Trivalent Arsenic; **AsV**- pentavalent Arsenic, **As₂O₃**- Arsenic tri-oxide; **NaAsO₂**- Sodium arsenite; **Cu**- copper

SN	Sp. Of Fish	Arsenic/ compound	Parameters	References
1	<i>Cyprinus carpio</i>	As	Hematological, biochemical and histomorphological	Tuteja et al 2021
2	<i>Danio rerio</i>	As	Alteration in stress marker and apoptotic gene	Mondal et al 2021
3	<i>Onchorhincus mykiss</i>	As	Oxidative stress	Milan et al 2021
4	<i>Gambusia affinis</i>	As III	Nucleotide polymorphism	Park et al 2021
5	<i>Clarias batrachus</i>	As ₂ O ₃	Behaviour and Morphology	Sahu & Kumar 2021
6	<i>Curassius auratus</i>	iAs	Biotransformation and bioaccumulation in muscles	Cui et al 2021
7	Twelve fish	As	Bioaccumulation	Raman et al 2021
8	<i>Scyliorhinus canicula</i>	As	Accumulation	Marques et al 2021
9	<i>Morone saxatilis + Esox lucius</i>	As	Lipid and protein level of muscles	Charette et al 2021
10	<i>Cyprinus carpio</i>	As	Apoptosis pathway	Wang et al 2021
11	<i>C. harengus,+S. fuegensis +P. dentatus</i>	As	As speciation	Polak Juszczyk and Richart 2021
12	Group of fishes		<i>In- vitro</i> Bio accessibility	Lin et al 2021
13	<i>Mystus vittatus</i>	As	Serum Biochemicals	Prakash & Verma 2020
14	<i>Curassius auratus</i>	i As	Biotransformation	Cui et al 2020
15	<i>Clarias garipenus</i>	As	Hemato- Biochemical	Mekkawi et al 2020
16	<i>Oryzias melastigma</i>	As	Physiological based pharmacokinetics model	Zhang et al 2020c
17	<i>Pangasianodon hypophthalmus</i>	As III	Stress biomarker	Kumar et al 2020
18	<i>Danio rerio</i>	As III & As V	Bioaccumulation and Biotransformation	Wang et al 2020
19	<i>Salmo trutta</i>	As	As in muscles tissue	Shakeri et al

20	<i>Clarias garipenus</i>	As	Hepatopathology	Muneeb et al 2020
21	<i>Clarias batrachus</i>	As ₂ O ₃	Biochemical	Pichhode & Gaherwal 2020
22	<i>Platichthys stellatus</i>	As	Growth and hematology	Han et al 2019
23	<i>O. mykiss</i> & <i>S. trutta</i>	As	Bioaccumulation	Juncos et al 2019
24	<i>C. carpio</i>	As	Bioconcentration	Ghadersarbazi et al 2019
25	<i>O. mykiss</i>	As	As speciation and accumulation	Erickson et al 2019
26	Six fish	As	As accumulation	Quintela et al 2019
27	<i>O. melastigma</i>	As	Bioaccumulation and antioxidant responses	Chen et al 2019
28	<i>Oryzias latipes</i>	As	Cytotoxic and genotoxic	Sayed et al 2019
29	<i>C. carpio</i>	As	Cardiotoxicity	Zhao et al 2019b
30	<i>Channa punctatus</i>	As	Genotoxicity	Singh et al 2019
31	<i>Mystus vittatus</i>	As	Lipid metabolism	Prakash & Verma 2019
32	<i>Anabas testidunes</i>	As	Digestive enzymes	Kole et al 2018
33	<i>D. rerio</i>	As	Neurobehavioral alteration	Dipp et al 2018
34	<i>O. mykiss</i>	As	Oxidative stress response	Kopp et al 2018
35	<i>Mugilogobius chulae</i>	As	Bioaccumulation of As in benthic fish	Zhang et al., 2017a
36	<i>Callionymus richardsonii</i>	As	Bioaccumulation & transformation	Zhang et al., 2017b
37	<i>Heteropneustes fossilis</i>	As + Cu	Hepatosomatic and Gonadosomatic index	Singh & Srivastava 2017
38	<i>Channa punctatus</i>	NaAsO ₂	Hematology	Amsath et al

				2017
39	<i>Labeo rohita</i>	As	Biomarker of Hepatoroxicity	Banerjee et al 2017
40	<i>S. trutta</i>	As	Bioaccumulation, oxidative stress and Antioxidant enzymatic defence	Greani et al 2017
41	<i>Heteropneustes fossilis</i>	As + Cu	Hepatosomatic and Gonadosomatic index	Singh & Srivastava 2017
42	<i>Heteropneustes fossilis</i>	As + Cu	Hepatosomatic and Gonadosomatic index	Singh & Srivastava 2017
43	<i>Oreochromis sp.</i>	As	Cortisol level	Thang et al 2017
44	<i>Channa punctatus</i>	NaAsO ₂	Hematology	Amsath et al 2017
45	<i>S. trutta</i>	As	Bioaccumulation, oxidative stress and Antioxidant enzymatic defense	Greani et al 2017

Table:2 : Arsenic toxicological works on Rat/mice. **As** indicating Arsenic; **As III**- Trivalent Arsenic;**AsV**- pentavalent Arsenic, **As₂O₃**- Arsenic tri-oxide; **Na₃AsO₄**- Sodium arsenate;

Table:3: Arsenic toxicity to Human. **As** indicating Arsenic; **As₂O₃**- arsenic tri-oxide; **NRF2**- Nuclear related Factor-2; **DNA**- Deoxyribonucleic acid; **DNMTs**-DNA methyltransferases; **miRNA**- Micro Ribonucleic acid; **mRNA**- Messenger RNA; **KRAS**- Kirsten rat sarcoma virus; **ROS**- Reactive oxygen species; **NF-κB**-nuclear kappa- light- chain- enhancer of activated B cells; **PBMC**- Peripheral mononuclear blood cells; **ROR**- Regulator of reprogramming.

S.N.	Affected organs	Analytical methods	Reference
1	Bladder/ Kidney cancer	DNA damage	Tsai et al 2021
2	Cancer risk assessment	Soil water analysis	Orosun 2021
3	Dermal / Oral hazards	As concentration in ground water	Patel et al 2021
4	Carcinogenesis	NRF2- mediated transcription and epigenetic regulator	Bi et al 2021
5	Skin	Modification of DNMTs gene	Chanda et al 2021
6	Breast cancer cell	Cell proliferation and gene expression	Kim et al 2021
7	Skin cancer	mi RNA and mRNA expression profile	Banerjee et al 2021
8	Gall bladder cancer	Immunological marker	Singh et al 2021
9	Lung cancer cell	<i>In vivo</i> & <i>In Vitro</i> Cell cycle genes	Sun et al 2021
10	Prostate cancer	KRAS-retroviral fusion transcripts and gene amplification	Merrick et al 2020
11	Bladder cancer	As level in drinking water & mortality rate	Lopez et al 2020
12	Bladder cancer	Clinico-pathological characteristics	Fernandez et al 2020
13	Lung cancer	As induced transformation	Chang et al 2020
14	Prostate cancer	ROS in the cytotoxicity of As ₂ O ₃ .	Dorosow and gaur 2020
15	Breast cancer	Attenuation of NF-κB signaling pathway	Nasrollahzadeh et al 2020
16	Skin cancer	immunological dysfunction and Histopathological analysis	Zeng and Zang 2020
17	Carcinogenesis	PBMC gene expression profile	Chen et al 2020
18	Growth factor, cancer related disease pathways	Transcriptome responses in blood	Rehman et al 2020
19	Liver cancer cell	Resistance of As ₂ O ₃ by Long non coding RNA ROR	Li et al 2020
20	Breast cancer	Immuno-histo-chemical	Lopez- Carillo et al 2020

Table: 4: Detection of Arsenic through nano-particles. **Au** indicates Gold; **Nps**- Nanoparticles; **AgNPs**- Silver nanoparticles; **Cu**: Copper; **SNPs**- Silica nanoparticles; **Pbs**- Lead; **SERS**- surface-enhanced Raman spectroscopy

SN	Nano Particle	Detection methods	Reference
1	Au NPs	SERS	Li et al 2021
2	Au NPs	Colorimetric assay	Pu et al 2021
3	Au NPs	Rapid colorimetric	Zheng et al 2021
4	Au NPs	Voltammetric detection	Sullivan et al 2021
5	Au NPs	Electrochemical detection	Sedki et al 2021
6	Au NPs	Ultra-sensitive Electrochemical detection	Jijana et al 2021
7	Au NPs	Selective and sensitive colorimetric	Harisha et al 2021
8	Au NPs	Absorption based detection	Karakuzu et al 2021
9	Au NPS	Voltammetric analysis	Salunke et al 2021
10	Cu ₂ O-Ag NPs	Chemometric SERS sensor	Barimah et al 2021
11	Prussian Blue NPs	Fluorescence Sensing	Pandey et al 2021
12	Au-Cu Nps	Electrochemical sensing	Fuletra et al 2021
13	Mn ₃ O ₄ NPS	Colorimetric chemosensor	Wang et al 2021
14	AuNPs	Voltammetric analysis	Bu et al 2020
15	Au NPs	Colorimetric	Shrivastava et al 2020
16	Zirconia NPs	Absorption based detection	Tokuyama et al 2020
17	Au-Cu NPs	Electrochemical aptanser	Mushiana et al 2019
18	Ag NPs	Colorimetric detection	Boruah et al 2019
19	Au NPs	Electrochemical	Gu et al 2018
20	Au NPs	Colorimetric detection	Yang et al 2018
21	Ag NPs	Electrochemical detection	Sonkoue and Tachekwajep 2018
22	S NPs	Sensor based	Taghdisi et al 2018
23	Ag Nps	Multimodal assay	Wen et al 2018
24	Pbs Nps	Absorption based	Priyanka et al 2017
25	AuNPs	Electrochemical detection	Idris et al 2017

Table: 5: Various therapeutic agents of arsenic toxicity. **DNA**- Deoxyribosenucleic acid ; **MiADMSA** – Monoisoamyl 2,3 dimercaptosuccinic acid ; **Chk1**– Checkpoint kinase 1; **p53** - 53 Kilodalpton protein product; **H3K18**- acetylation of histone H3 at the lysine-18 residue ; **JHDM2A**- JmjC-domain-containing histone demethylase 2A; **ERCC1** – Excision repair cross complementation group 1) and *ERCC2*-Excision repair cross complementation group 2)

SN	Treatment agent	Methods	References
1	N-Acetylcysteine (NAC)	Density Functional theory	Das et al 2021
2	Antibiotic cefoperazone	Blood chemistry	Roggenbeck et al 2021
3	<i>Ginkgo biloba</i> extract	DNA damage assay	Ding et al 2021
4	<i>Rosa roxburghii</i> Tratt (RRT)	hepatic oxidative damage assay	Xu et al 2021
5	<i>Ginkgo biloba</i> extract	Skin damage assay	Zheng et al 2021
6	melatonin	DNA damage, inflammation and apoptosis assay	Abdollahzade et al 2021
7	Lycopene	Kidney marker damage assay	Ramadan et al 2021
8	Epididymal vascular endothelial growth factor (VEGF)	Gene therapy	Dai and Gao et al 2021
9	Selenium	Assessment of oxidative damage and neurotransmitter-related parameters	Ren et al 2021
10	<i>Ginkgo biloba</i> extract	Chk1-p53 pathway assessment	Yang et al 2021
11	Spirulina and vitamin E	haematological parameters	Khatun et al 2020
12	acetylated histone H3K18	Chromatin immunoprecipitation (ChIP-qPCR) analysis	Zhang et al 2020a
13	Histone demethylase JHDM2A	DNA damage repair pathway	Zhang et al 2020b
14	Monoisoamyl dimercaptosuccinic acid (MiADMSA)	Chelation therapy	Sau et al 2020
15	BAL (dimercaptopropanol), DMPS (dimercapto-propane sulfonate)	Chelation therapy	Nurchi et al 2020
16	Turmeric and <i>Passiflora foetida</i> powder	Biochemical, haematological, antioxidant parameters	Maji et al 2020
17	Nano curcumin & nano MiADMSA	Chelation therapy	Kushwaha et al 2018
18	<i>Ginkgo biloba</i>	Liver function indices	Yao et al 2017

19	Hypermethylation of <i>ERCC1</i> and <i>ERCC2</i>	Methylight and bisulfite sequencing (BSP) assays	Zhang et al 2017
20	2,3-dimercaptopropane -1-sulphonate (DMPS)	Chelation therapy	Lu et al 2017

Figures

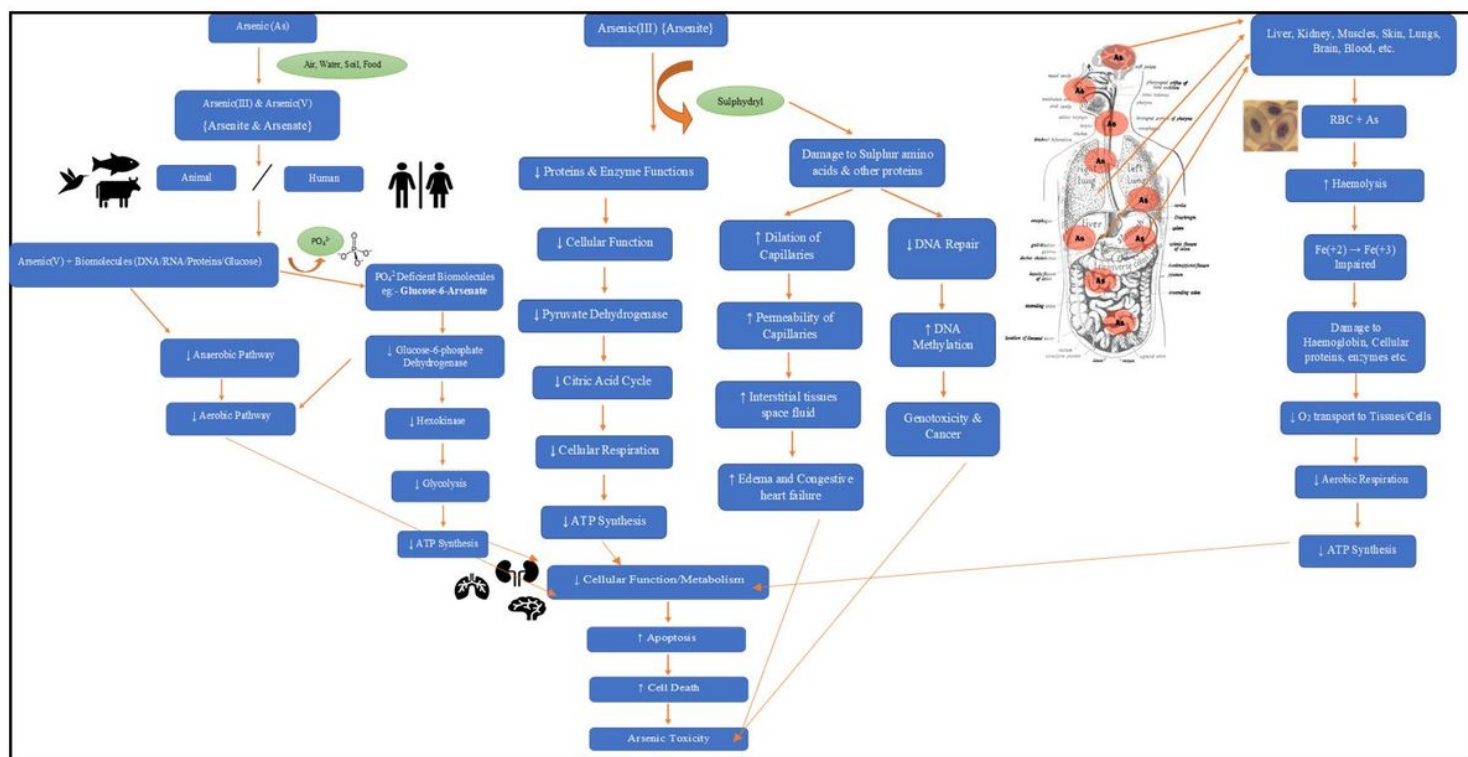


Figure 1

Schematic representation of pathogenesis of arsenic toxicity

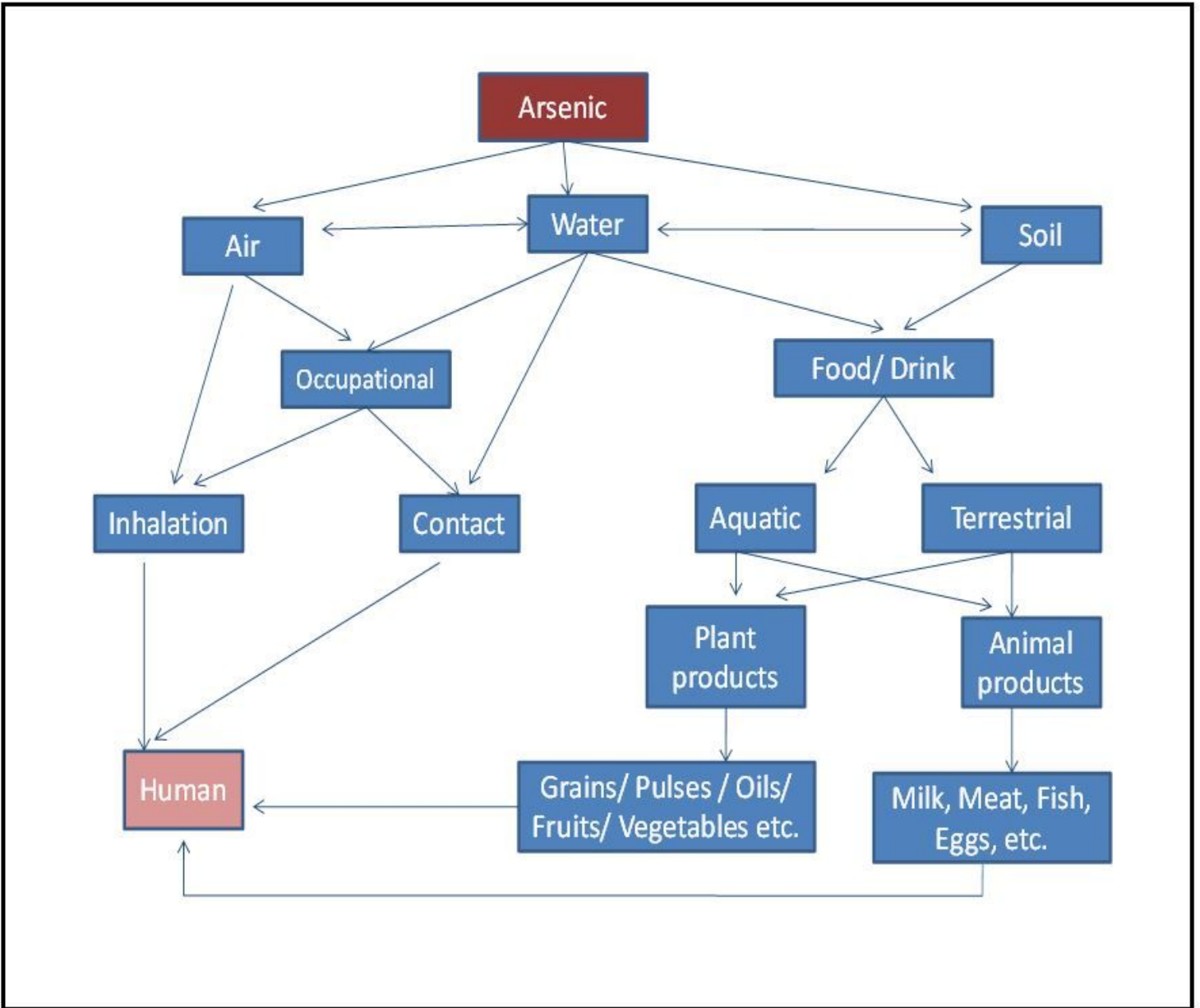


Figure 2

Various routes of exposure of Arsenic to Human