Review article

Toxicity of inorganic arsenic to animals and its treatment strategies

Qian Su [a,1], Ying He [b,c,d,1], Hang Pan [a], Haiyan Liu [a], Khalid Mehmood [e], Zhaoxin Tang [a], Lianmei Hu [a,*]

[a] College of Veterinary Medicine, South China Agricultural University, Guangzhou 510642, China
[b] Guangxi Key Laboratory of Veterinary Biotechnology, Guangxi Veterinary Research Institute, Nanning 530001, China
[c] Guangxi Key Laboratory of Veterinary Biotechnology, Nanning, Guangxi, China
[d] Key Laboratory of China(Guangxi)-ASEAN Cross-border Animal Disease Prevention and Control, Ministry of Agriculture and Rural Affairs of China, Nanning, China
[e] Department of Clinical Medicine and Surgery, Faculty of Veterinary and Animal Science, The Islamia University of Bahawalpur, 63100, Pakistan

ARTICLE INFO

ABSTRACT

In nature, arsenic is mostly found in the form of inorganic compounds. Inorganic arsenic compounds have a variety of uses and are currently used in the manufacture of pesticides, preservatives, pharmaceuticals, etc. While inorganic arsenic is widely used, arsenic pollution is increasing worldwide. Public hazards caused by arsenic contamination of drinking water and soil are becoming increasingly evident. Epidemiological and experimental studies have linked inorganic arsenic exposure to the development of many diseases, including cognitive impairment, cardiovascular failure, cancer, etc. Several mechanisms have been proposed to explain the effects caused by arsenic, such as oxidative damage, DNA methylation, and protein misfolding. Understanding the toxicology and potential molecular mechanisms of arsenic can help mitigate its harmful effects. Therefore, this paper reviews the multiple organ toxicity of inorganic arsenic in animals, focusing on the various toxicity mechanisms of arsenic-induced diseases in animals. In addition, we have summarized several drugs that can have therapeutic effects on arsenic poisoning in pursuit of reducing the harm of arsenic contamination from different pathways.

1. Introduction

Arsenic, a naturally occurring metalloid substance, is widely distributed in nature in both organic and inorganic forms, and mostly exists in the form of trivalent arsenic (As^{3+}) and pentavalent arsenic (As^{5+}) (Jomova et al., 2011). The toxicity of arsenic is related to its chemical form and solubility. Simple arsenic is non-toxic, while arsenic compounds are toxic, and the toxicity of trivalent arsenic is stronger than that of pentavalent arsenic (Sodhi et al., 2019).

Arsenic circulates through natural and human activities, causing arsenic contamination of the human and animal habitat. Natural activities include rock weathering and geothermal activity. At the same time, human activities such as metal mining and smelting, fossil fuel combustion, and emissions of arsenic-based industrial wastes result in large amounts of arsenic entering the environment. Arsenic from natural and anthropogenic sources eventually sinks in the environment through biogeochemical cycles (Wang et al., 2023). With the rapid development of the global economy and industry, many countries in the world have serious water arsenic pollution problems (Sandhi et al., 2022; Xu et al., 2022; Yuan et al., 2022). The use of arsenic contaminated groundwater to irrigate crops will lead to arsenic contamination of soil and crops, thus affecting food security (Gillispie et al., 2015), threatening human and animal health. The main routes of exposure of humans and most animals to arsenic are diet and drinking water (Sattar et al., 2016). Animals can suffer from arsenic poisoning by drinking potable water containing excessive arsenic or accidentally eating seeds treated with arsenic, while poisonous rats containing arsenic have also become a major cause of acute arsenic poisoning in animals due to accidental ingestion. It is worth noting that arsenic residues in fruits and vegetables caused by arsenic-containing pesticide preparations also seriously threaten food safety (Bertin et al., 2013). At the same time, the problem of arsenic pollution in the ocean is becoming more and more serious, which poses a great threat to the marine ecosystem and also adds a danger to human animal food safety (Baeyens et al., 2019).

* Corresponding author.
E-mail addresses: sq@stu.scau.edu.cn (Q. Su), heying921@163.com (Y. He), 20222029013@stu.scau.edu.cn (H. Pan), 857479891@stu.scau.edu.cn (H. Liu), khalid.mehmood@iub.edu.pk (K. Mehmood), tangzx@scau.edu.cn (Z. Tang), hulianmei@scau.edu.cn (L. Hu).
[1] Qian Su and Ying He are co-first authors of the article.

People may suffer from acute poisoning if they eat a large amount of inorganic arsenic in a short period time. Long-term excessive intake of inorganic arsenic may damage the skin, cause chronic liver disease and cancer, etc. (Jomova et al., 2011). Similarly, inorganic arsenic can cause a variety of toxic damage when it enters the animal body in various ways. In animal experiments, long-term use of arsenic can cause hepatorenal toxicity in animals, which is related to oxidative damage and persistent inflammation caused by arsenic (Esfahani et al., 2022; Duan et al., 2022). In addition, arsenite, as a weak mutagen, can enhance the mutagenicity of other carcinogens (Costa, 2019). In known studies, arsenite can enhance the mutagenicity of various carcinogens in mammalian cells, such as X-ray and ultraviolet radiation (UVR) (Tam et al., 2020; Volk et al., 2022). At the same time, sodium arsenite can accelerate the testis aging of rats induced by D-galactose, leading to reproductive toxicity in animals (Akbari et al., 2022). Moreover, the cardiotoxicity, neurotoxicity and immunotoxicity caused by arsenic exposure have also been proved in different types of animal studies (Chen et al., 2022a; Rao et al., 2022; Wang et al., 2022).

For a long time, people have devoted themselves to looking for drugs that can treat arsenic poisoning. In many studies, it has been proved that curcumin has significant effects on various toxicity induced by arsenic exposure in animals, mainly by regulating oxidative stress, inhibiting autophagy and apoptosis, and alleviating inflammatory reaction (Wu et al., 2021a; Wu et al., 2021b). In addition, selenium, *N*-acetylcysteine, melatonin and other substances can also against arsenic toxicity (Adedara et al., 2019; He et al., 2021; Zhang et al., 2017). These studies put forward new ideas on how to alleviate the harm of arsenic to humans and animals from different aspects.

The types of toxicity caused by arsenic have been widely studied, but the specific mechanisms of its toxic effects are still in different degrees of research. So far, there is no more literature to integrate these mechanisms. In this review article, we introduced in detail various toxic mechanisms of arsenic induced animal diseases. In addition, we also summarized several substances that can effectively treat arsenic poisoning, to pursue different ways to reduce the harm of arsenic pollution.

2. Metabolism of inorganic arsenic

The methylation of inorganic arsenic is considered to be the main mechanism of arsenic metabolism. Many mammals can methylate inorganic arsenic on the body (Sattar et al., 2016). In most mammalian species, including humans, inorganic arsenic is widely biotransformed and excreted mainly as its metabolite. Fig. 1 demonstrates the process of arsenic metabolism in rats. Arsenic is initially absorbed into the blood through various channels and is absorbed by red blood cells (RBC), white blood cells (WBC) and other cells (Lau et al., 2013a). At the same time, inorganic arsenic is transformed in the organism from arsenate to arsenite, and then forms monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA). This process also requires the participation of

glutathione (GSH) and arsenic methyltransferase, while S-adenosylmethionine (SAM) is involved as a methyl donor (Ventura-Lima et al., 2011a). However, not all organisms can methylate arsenic. For example, in chimpanzees, marmosets and guinea pigs, arsenic will not be methylated (Bjorklund et al., 2020; Zwolak, 2020).

Research shows that the arsenic content in the liver, kidney, spleen and lung of most species increases after arsenic intake (Sattar et al., 2016). Among them, MMA is the main metabolite of kidney, DMA is the main metabolite of lung, and inorganic arsenic and DMA in the bladder and skin are roughly the same (Kenyon et al., 2008). In carp, on the other hand, after arsenic exposure in the water column, arsenic accumulation could be detected in their gills and was dominated by monomethylarsenic and dimethylarsenic levels (Ventura-Lima et al., 2011b).

Arsenic and its metabolites are mostly excreted in urine and bile. The main way of excretion of arsenic compounds in most mammals and humans is urine, which is mainly excreted in the form of DMA. The rats preferentially excreted arsenic and its metabolites into bile (Kenyon et al., 2008).

3. Toxicity mechanism

After exposure to the animal organism through various pathways, arsenic induces a variety of adverse reactions in the organism, causing changes in various signaling molecules and even genes. Abnormalities in organ functions of the animal organism due to arsenic exposure cause toxic damage to organs. Specifically, there are several mechanisms that produce toxicity as demonstrated below.

3.1. Induced oxidative stress

Induction of oxidative stress is a key pathway for inorganic arsenic toxicity, and one of the major sites of arsenic-induced oxidative stress is the mitochondria (see Fig. 2). Arsenic can directly damage mitochondria thereby leading to elevated reactive oxygen species (ROS). Arsenic mainly causes alterations in mitochondrial structural integrity, which leads to rapid deterioration of mitochondrial membrane potential, and altered membrane potential can lead to a significant increase in ROS (Lau et al., 2013a; Zargari et al., 2022). At the same time, disruption of mitochondrial membrane integrity activates downstream free radical substance cascade reactions, leading to a decrease in cellular oxidative stress defense molecules such as glutathione (GSH), Glutathione peroxidase(GPx) (Prakash et al., 2016).

ROS plays a key role in arsenic-induced oxidative stress, and it can trigger various transcription factors that lead to the transcription of genes involved in the oxidative stress response. In many studies, it has been shown that arsenic induces increased production of ROS, causing altered levels of oxidase and antioxidant enzyme activities, and increased lipid peroxidation products, leading to hepatotoxicity and nephrotoxicity in arsenic-exposed rats and ducks (Reddy et al., 2011; Panda et al., 2022), as well as gill toxicity and liver toxicity in carp
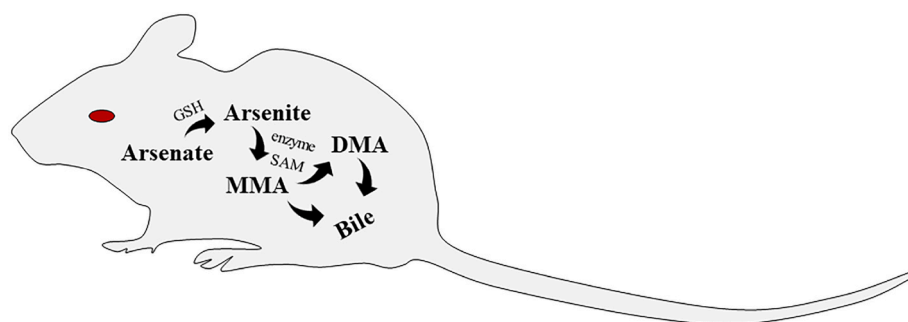

Fig. 1. After arsenate enters the body of rats, it forms arsenite under the action of glutathione, and then forms monomethylarsenic acid and dimethylarsenic acid after being supplied with methyl by S-adenosylmethionine under the action of arsenic methyltransferase, and finally is excreted through bile.
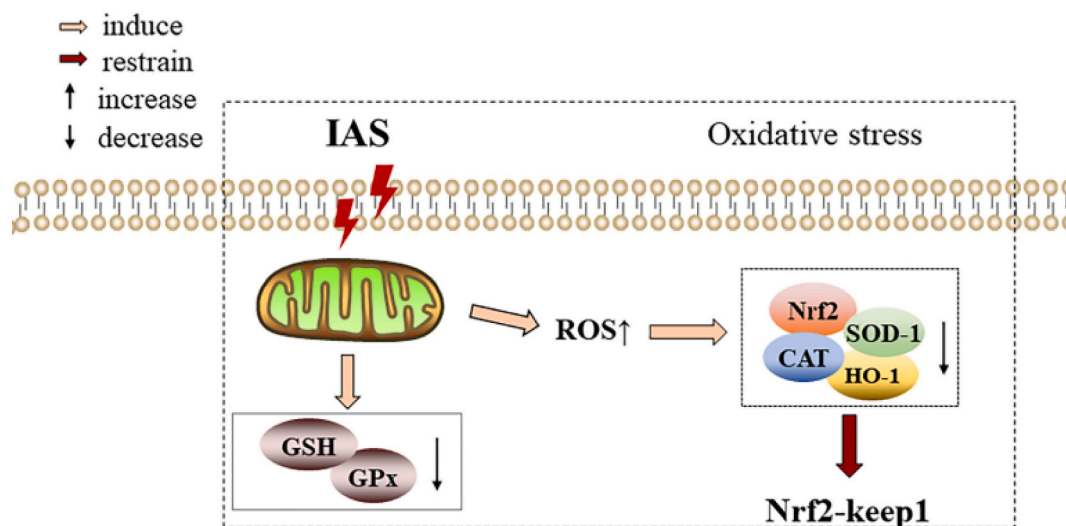
Fig. 2. Inorganic arsenic enters cells and attacks mitochondria, causing changes in mitochondrial membrane structure and function, resulting in increased production of reactive oxygen species (ROS) and decreased production of oxidative stress defense molecules glutathione (GSH) and glutathione peroxidase (GPx). ROS can affect the expression of various transcription factors, like downregulating the protein expression of Nrf2, HO-1, SOD-1 and CAT (all are important proteins on the Nrf2-keep1 pathway) as a way to inhibit the Nrf2-keep1 signaling pathway. Through the above pathways, inorganic arsenic induces oxidative stress in tissue cells.

(Ventura-Lima et al., 2009).

The Nrf2-keep1 pathway is a classical antioxidant response pathway. ATO induces a large production of ROS in the body, which can affect the expression of many genes and proteins in the Nrf2-keep1 pathway. For example, ROS can downregulate the mRNA and protein expression of Nrf2, HO-1, SOD-1, and CAT (Medda et al., 2021), inhibit the activation of the Nrf2 pathway, induce oxidative stress in the heart of ducks, and lead to cardiotoxicity of arsenic in ducks (Rao et al., 2022).

However, the complete molecular mechanism of arsenic-induced oxidative stress has not been fully understood.

3.2. Causing DNA damage

Arsenite is a weak mutagen that is known to enhance the mutagenicity of other carcinogens (Costa, 2019). In studies, arsenite enhances the mutagenicity of various carcinogens such as X-rays, ultraviolet radiation (UVR), and methyl methane sulfonate (MMS) in mammalian cells, this is because arsenic can inhibit the repair process of these carcinogen-induced DNA lesions (Tam et al., 2020; Volk et al., 2022). Arsenite can target interference with the base excision repair (BER) and nucleotide excision repair (NER) pathways by affecting the expression levels of DNA repair genes or the catalytic activity of DNA repair proteins (see Fig. 3 (Cooper et al., 2022; Holcomb et al., 2017)). NER is a critical and versatile DNA repair pathway, and studies have shown that arsenic primarily interferes with key NER participants by disrupting their gene expression levels and activity to interfere with NER (Muenyi et al., 2015).

DNA ligases play an important role in DNA replication, repair and recombination, and arsenite has been shown to inhibit the DNA ligation process (see Fig. 3). Studies have shown that mRNA, protein and enzyme
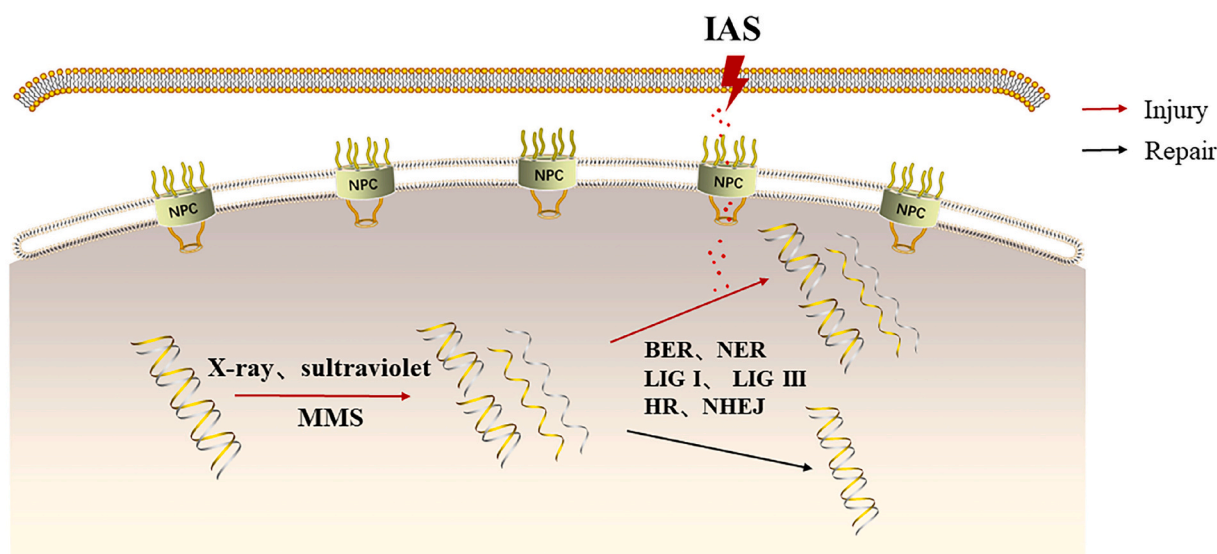

Fig. 3. Mutagenic agents such as X-rays, ultraviolet light, and methylmethane sulfonate (MMS) acting on DNA can cause DNA unhelicalization or breakage, and the body will initiate base excision repair (BER), nucleotide excision repair (NER), homologous recombination (HR), and non-homologous end joining (NHEJ) to repair damaged DNA to protect itself. But in the case of inorganic arsenic exposure, these several repair processes can be disrupted, resulting in DNA damage that cannot be repaired.

activity levels of DNA ligase I and DNA ligase III were significantly reduced in mammalian cells after exposure to inorganic arsenic (Tam et al., 2020). It was also shown that arsenite inhibits DNA ligation by interacting with the cysteine in DNA ligase III, thereby delaying the rejoining of DNA breaks in MMS-treated hamster cells (Tam et al., 2020; Li and Rossman, 1989).

Double-strand breaks (DSBs) is the most severe and threatening type of DNA lesions, leading to gene mutations, loss of heterozygosity and chromosomal rearrangements. If improperly repaired, DSBs can lead to cell death and cancer. In mammalian cells, DSBs repair occurs through both homologous recombination (HR) and non-homologous end joining (NHEJ) pathways, and it was found that exposure to arsenic inhibits DSBs repair of DNA and affects the selection of DSBs repair pathways by accommodating error-prone NHEJ repair while inhibiting the normally functioning HR pathway, leading to misrepair of DSBs and genomic instability (Sodhi et al., 2019; Li and Rossman, 1989).

In a study by Zheng et al. to assess arsenic-induced DNA damage in the kidney, comet assay (SCG) and immunohistochemistry were performed to examine the expression of 8-hydroxydeoxyguanosine (8-OHdG, an oxidative adduct produced by reactive oxygen radicals such as hydroxyl radicals and singlet-linear oxygen attacking the 8th carbon atom of the guanine base in the DNA molecule) and DNA strand in kidney tissue breakage in the kidney tissue. The results showed that comet 8-OHdG expression and comet number, tail moment, and tail length were significantly elevated in arsenic-poisoned mice (Zheng et al., 2017). It indicates that arsenic can cause nephrotoxicity in mice through DNA damage. While in the study by Ahmed et al. freshwater fish were exposed to three different concentrations of arsenic and liver, gill and blood tissue samples were collected after 48 h, 96 h and 192 h of exposure. The results showed that arsenic exposure could be observed to induce an increase in DNA comet tail in fish liver, gill and blood in a concentration-dependent manner causing DNA damage in all tissues (Ahmed et al., 2011).

3.3. Induction of inflammation and immune imbalance

Nuclear factor-kB protein (NF-kB) plays a key role in cellular inflammatory response, immune response, etc. Misregulation of NF-kB can cause autoimmune diseases, chronic inflammation, and many cancers. Studies have shown that acute arsenic exposure can activate the NF-kB signaling pathway and stimulate the production of inflammatory factors (TNF-α, IL-2, IL-4, IL-5, IL-10) (see Fig. 4), thereby inducing the development of inflammation in the spleen and thymus of mice (Yan et al., 2020). In addition, arsenic can impair the expression of anti-inflammatory genes and cause liver and kidney damage in ducks (Panda et al., 2022).

CD4 T cells are involved in the regulation of immune responses and inflammatory diseases and can be activated when encountering specific antigens, proliferate and differentiate into various effector T cell subsets such as T helper type 1 (Th1), Th2, Th17 and regulatory T cells (Treg cells). Studies have shown that arsenic exposure increased the expression of T-bet (the master transcription factor of Th1 cells), Foxp3 (the master transcription factor of Treg cells) expression, in contrast to arsenic, which strongly decreased the mRNA levels of RORγt (the master transcription factor of Th17 cells), and these results suggest that arsenic exposure can alter the subpopulation differentiation of CD4 T cells (Duan et al., 2017), thereby affecting immune regulatory processes. It was also shown that arsenic exposure can activate NLRP3 inflammatory vesicles and disrupt the Th1/Th2/Th17/Treg homeostasis in the hippocampus of mice, thereby inducing neuroimmunotoxicity in mice (see Fig. 4 (Jing et al., 2022)).

3.4. Disruption of the cell cycle

The cell cycle is the entire process that a cell undergoes from the completion of one division to the end of the next. Disturbances in the cell cycle can lead to cell death or carcinogenesis (Arjona et al., 2022; Navalkar et al., 2022), which induces the development of many diseases. Cell death can be induced by the stimulation of a harsh external environment, including apoptosis, cell necrosis, cell autophagy, iron death, and other modes of death (Tian et al., 2022; Ketelut-Carneiro and Fitzgerald, 2022). Cell carcinogenesis prevents cells from completing differentiation normally and turns them into malignant proliferating cells that are not controlled by the organism and undergo continuous division (Lau et al., 2013b).

In the experiment of Zhong et al. liver tissues of ducks attacked with ATO (8 mg/kg) could observe significant apoptosis under transmission electron microscopy (TEM), and the expression levels of genes and proteins associated with apoptosis (Caspase-3, Cytc, Bax and P53) were significantly increased (see Fig. 5). This demonstrates that ATO can affect the expression of apoptosis-related proteins and genes, leading to apoptosis (Zhong et al., 2021). Meanwhile, Arsenic trioxide can also
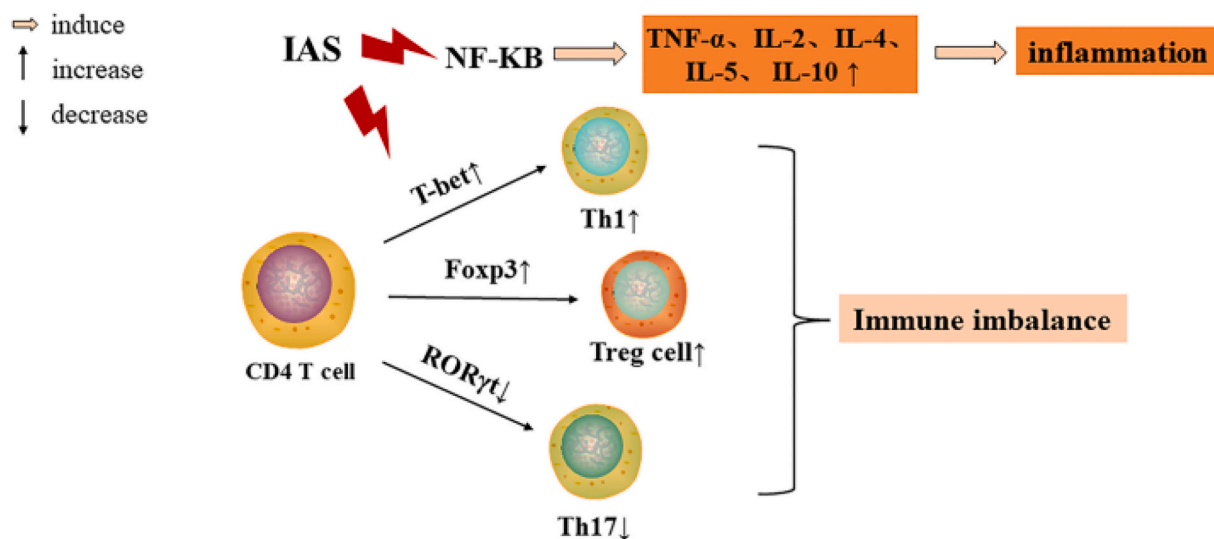

Fig. 4. Inorganic arsenic exposure can act on the NF-kB pathway, causing the production of multiple inflammatory factors and inducing inflammation. It also can act on the differentiation process of CD4 T cells, increasing the expression of T-bet (master transcription factor of Th1 cells) and Foxp3 (major transcription factor of Treg cells) and decreasing the mRNA level of RORγt (master transcription factor of Th17 cells), thus altering the subpopulation differentiation of CD4 T cells and causing immune imbalance.
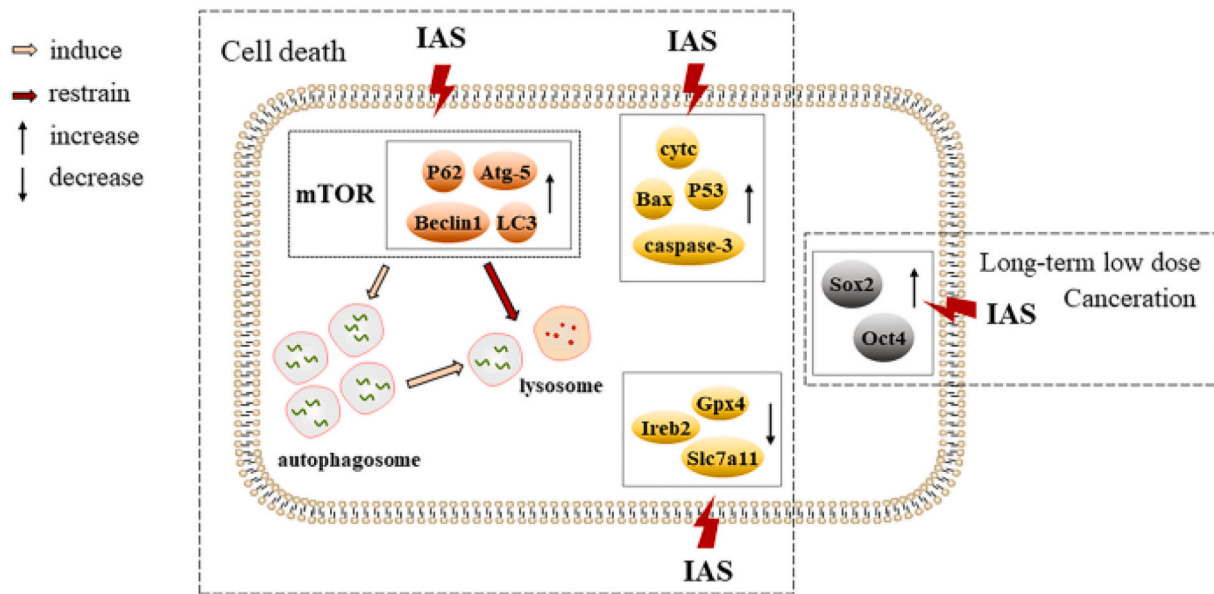
Fig. 5. Inorganic arsenic acts on cells can cause an increase in the expression of apoptosis-related genes and proteins. It also induces autophagy and inhibits autophagic flux through mTOR-dependent pathways and stimulation of autophagy and iron death-related protein and gene expression, causing cells to move toward death. But when acting on embryonic stem cells at low doses for a long period of time, it causes an increase in the expression of oncogenes Sox2 and Oct4, which inhibit cell differentiation toward carcinogenesis.

trigger apoptosis-induced cardiotoxicity in ducks through the Nrf 2 / cystathione 3 signaling pathway (Rao et al., 2022).

In addition, arsenic exposure inhibits autophagosome-lysosome fusion by triggering autophagy activation in an mTOR-dependent manner, while accumulating P62 (autophagy-associated protein) and inhibiting autophagic flux (Lau et al., 2013b). In a study by Wu et al., adult mice exposed to arsenic trioxide (ATO) showed a significant increase in the expression levels of autophagy and autophagy-related genes and proteins (including Beclin1, Atg-5, LC3, and p62) in their testicular tissues in vivo (see Fig. 5), indicating that ATO can induce testicular autophagy and inhibit autophagic flux in mice (Wu et al., 2021c), thereby causing reproductive developmental toxicity in mice. These suggest that arsenic induces excessive depletion of intracellular material through autophagy, leading to cell death.

Iron death is an iron-dependent, novel form of programmed cell death that is distinct from apoptosis, cell necrosis, and cell autophagy (Chen et al., 2022b). To investigate whether realgar (tetraarsenic tetrasulfide) causes iron death, the expression of proteins related to the iron death signaling pathway was examined in the kidneys of mice exposed to andrographis at moderate to high dose levels (1.0 and 2.0 g/kg). The results showed that glutathione peroxidase 4 (Gpx4), anticystine/glutamate anti-transport protein (Slc7a11) and iron response element binding protein 2 (Ireb2) showed a significant dose-dependent decrease (see Fig. 5). These suggest that andrographis can activate iron death-related signaling pathways that lead to iron death in the kidney and impair kidney function in mice (Zhang et al., 2022).

Interestingly, in arsenic-induced carcinogenesis, inorganic arsenic has been shown to interfere with cell cycle regulation, promote cell proliferation and inhibit apoptosis, thereby indirectly inhibiting DNA repair and allowing cells with DNA damage to multiply (Tam et al., 2020). Benjamin D. McMichael et al. incubated P19 mouse embryonic stem cells in six separate flasks exposed to 0 or 0.1-μM (7.5 ppb) arsenic in six separate flasks continuously for up to 32 weeks, and by comparing morphological differences between control and arsenic-exposed cells and analyzing the expression of genes (e.g., Sox2 and Oct4) in cells (see Fig. 5), the results showed that chronic low-level arsenic exposure impairs cell differentiation and that long-term low-level arsenic exposure reduces neuronal differentiation and keeps cells in a more pluripotent state (McMichael et al., 2021).

Thus, the effect of arsenic on cell death is often thought to be twofold.

4. Organ toxicity of arsenic to animals

After entering the animal organism, inorganic arsenic causes arsenic toxicity in animals by inducing oxidative stress, DNA damage, inflammation and immune imbalance, and cell cycle disorders, resulting in toxic damage to multiple organ systems (see Fig. 6).

4.1. Hepatotoxicity

As the main organ for metabolism of toxic substances, the liver is the main target of arsenic after it enters the body (Zhang et al., 2014a). In many experimental studies, arsenic can induce liver injury, leading to changes in biochemical indicators of liver function, such as elevated serum enzymes (Zhang et al., 2017). At the same time, arsenic can also cause severe histopathological changes in the liver, including steatosis, cell membrane rupture and mitochondrial swelling or dissolution (Zhang et al., 2017; Liu et al., 2020). A study on arsenic poisoning in ducks showed that arsenic exposure would reduce duck weight, increase liver coefficient, and cause arsenic concentration to increase in the liver and serum in a dose-dependent manner. The evidence of metabonomic analysis shows that arsenic exposure will interfere with the normal metabolism of liver cells and cause damage to liver structure (Zhong et al., 2021). Another study on zebrafish showed that arsenic exposure alters the expression of cell cycle and lipid metabolism genes in the liver of adult zebrafish, thereby inducing hepatotoxicity in zebrafish (Carlson and Van Beneden, 2014).

4.2. Nephrotoxicity

Studies have shown that subcutaneous injection of sodium arsenite (12.5 mg/kg) can increase the levels of serum urea nitrogen (BUN) and creatinine (CRE), urine NGAL (Early marker of renal injury, small molecule protein expressed in neutrophils and epithelial cells of renal tissue) and urine protein/CRE ratio in mice, thus causing renal insufficiency (Kimura et al., 2016). Under the action of ATO, the renal tissue of rats showed cortical edema, tubular cell swelling, interstitial edema,
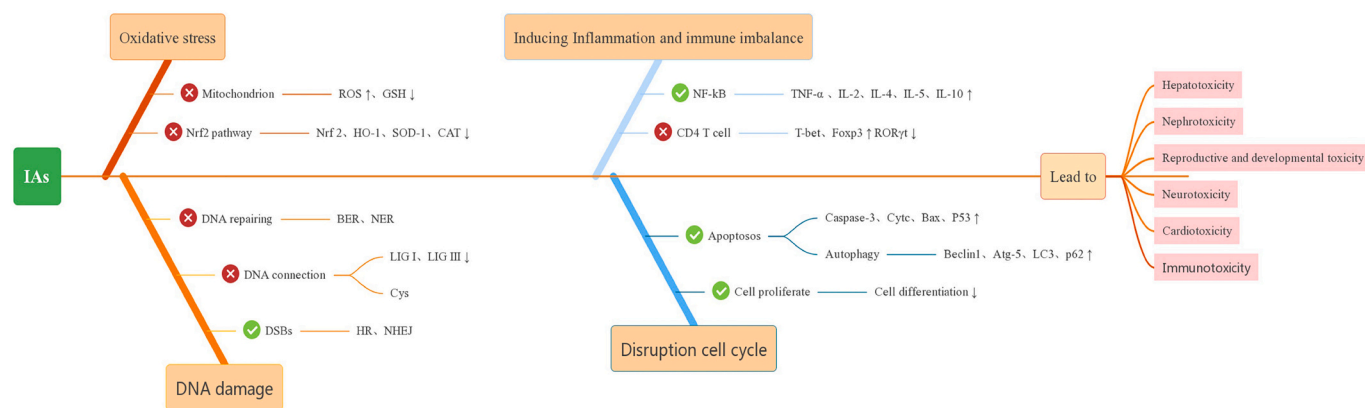
Fig. 6. Inorganic arsenic enters the animal organism and initiates a toxic mechanism that causes toxic damage to multiple organ systems.

glomerular expansion and congestion, severe necrosis of the glomerular nucleus, and tubular cell exfoliation (Zhang et al., 2014b). It can be seen that inorganic arsenic can cause nephrotoxicity in animals.

4.3. Neurotoxicity

Many pieces of evidence show that arsenic has effects on the nervous system of animals. Arsenic can enter the brain through the blood-brain barrier, thus affecting cognitive ability, concentration, speech learning and memory. Studies have shown that exposure of pregnant mice to sodium arsenite(NaAsO2) can increase the accumulation of arsenic in the brains of their offspring and damage the learning and memory processes (Ramos-Chavez et al., 2015). In addition, when mice are exposed to NaAsO2 before birth, their offspring will have behavioral disorders and abnormal formation of the frontal cortex (Aung et al., 2016).

4.4. Reproductive and developmental toxicity

Zeng et al. fed male mice (4 weeks old) with sodium arsenite (5 or 50 ppm arsenic) through drinking water for 180 days, and then evaluated the sperm count, biomarkers of oxidative stress, cell cycle progression and apoptosis of mouse testicular tissue. The results showed that arsenite seriously damaged the structure of the testis and reduced the number of sperm (Zeng et al., 2019). In female mice treated with As, abnormal meiosis of oocytes and impaired preimplantation development were observed. The cleavage rate of mouse-fertilized eggs was low, and the formation and development of morula and blastocyst were reduced (Wang et al., 2006).

4.5. Cardiotoxicity

Animal experiments confirmed that arsenic exposure could cause abnormal ECG, myocardial damage marker enzymes and cardiac histomorphology in rats. After acute arsenic poisoning, the heart tissue of mice showed pathological characteristics such as myocardial cell edema, death, myocardial fiber atrophy, interstitial vascular expansion, inflammatory cell infiltration, etc. (Zhao et al., 2020). On the other hand, mitochondrial swelling and mitochondrial membrane rupture were observed in the heart cells of arsenic-trioxide-treated mice (Han et al., 2022). All these indicate that arsenic can cause cardiac toxicity in animals.

4.6. Immunotoxicity

Studies have shown that subchronic exposure to arsenic trioxide induces thymus toxicity in chickens, because stimulation by arsenic trioxide alters the expression of inflammatory and immunomodulatory cytokines in chickens, inducing an inflammatory response and immune imbalance in the chicken thymus (Liu et al., 2018). In a goat experiments, lymphocyte degeneration was shown in arsenic-exposed spleen sections and associated lymph nodes. Erythrophilic activity of reticuloendothelial cells in the splenic red medulla appeared to increase, splenic trabeculae showed truncated thickening, and fibrous tissue replaced focal areas of necrosis (Patra et al., 2013). These results suggest that arsenic exposure has a damaging effect on the immune system of animals.

5. Treatment of inorganic arsenic poisoning

Induction of oxidative stress is the main pathway of inorganic arsenic toxicity to animals, and induction of DNA damage and cell death is also an important cause of arsenic poisoning, so the application of drugs with anti-oxidative stress, inhibition of DNA damage and cell death effects can effectively treat arsenic poisoning. The following drugs are hot drugs for the treatment of arsenic poisoning in research animals in recent years.

5.1. Curcumin

Curcumin is a natural compound, a natural phenolic antioxidant extracted from the rhizomes of *Curcuma longa*, *Curcuma longa*, and Yucca longa of the ginger family, with antioxidant and anti-inflammatory effects. Several studies have shown that curcumin (400 mg/kg) can significantly alleviate the neurotoxicity, nephrotoxicity, skeletal muscle toxicity, and spleen toxicity induced by ATO (8 mg/kg) exposure in ducks by modulating oxidative stress, inhibiting autophagy and apoptosis, and alleviating the inflammatory response (Wu et al., 2021a; Wu et al., 2021b; Lan et al., 2022; Tang et al., 2022). In addition, the reversal of arsenic exposure by curcumin has been demonstrated in humans, and studies have shown that curcumin can induce arsenic-inhibited DNA repair at the protein and genetic levels. Thus, curcumin intervention may be a useful approach to prevent arsenic-induced carcinogenesis (Roy et al., 2011).

5.2. Selenium

Selenium, one of the trace elements essential for normal growth and development in humans and animals. Selenium is involved in many biological functions, including enhancing antioxidant capacity, improving immunity, regulating metabolism, and antagonizing many toxic heavy metals. Studies have shown that the addition of 5 mg/kg or 10 mg/kg of selenium to the feed of arsenic-poisoned chickens can repair arsenic-induced impaired liver growth and fatty degeneration, increase the protein content in liver tissues, reduce the rate of hepatocyte apoptosis (Ren et al., 2021a), and increase the level of T-

lymphocyte acid α-naphthyl acetate esterase (ANAE), increase the hemoglobin content of broiler chickens, and promote red blood cell immunity (Ren et al., 2021b). This indicates that the addition of selenium reduced the toxic effects of arsenic on animals. Yang et al. showed that selenium treatment significantly attenuated ATO-mediated cardiotoxicity, as evidenced by increased body weight, reduced markers of myocardial injury and improved cardiac function in mice (Yang et al., 2022).

5.3. N-acetylcysteine (NAC)

NAC is a thiol-based antioxidant that plays an important role in the protection of cellular components from oxidative damage and the detoxification of many electrophilic reagents. Research shows that NAC can reduce arsenic-induced oxidative stress by reducing lipid peroxidation in the testis and activating antioxidant enzymes, thereby ameliorating arsenic-induced reproductive inhibition in male mice (Reddy et al., 2011).

5.4. Melatonin

Melatonin is an amine hormone produced mainly by the pineal gland in mammals and humans, which has several physiological functions such as sleep promotion, jet lag regulation, anti-aging, immune modulation, and anti-tumor etc. Sayanta Dutta et al. found that melatonin could attenuate arsenic poisoning by overcoming arsenic-induced oxidative stress, inhibiting inflammation, apoptosis and DNA damage, and restoring homeostasis of glucose metabolism (Dutta et al., 2018; Abdollahzade et al., 2021). Therefore, melatonin is considered to be a promising new drug against As poisoning.

5.5. Propolis

Bee propolis is a traditional natural medicine that has been used in Europe for more than 2000 years. Its main components are beeswax, resin and hive oil. It can enhance immunity, scavenge free radicals, antifatigue, antioxidant, kill and inhibit cancer cells, anti-tumor and slow down aging. In a study by Talas, ZS et al., carp were exposed to 0.01 mg/L arsenic and 10 mg/L propolis for seven days. The results of various hematological tests showed that propolis improved the biochemical and hematological functions of the carp blood after arsenic exposure (Talas et al., 2012). Similarly, in another investigation, in order to study the effect of propolis on biochemical parameters and histopathology of carp exposed to arsenic, carp were exposed to sublethal concentrations of arsenic and/or propolis for one week. Histopathological changes in the liver, gill and muscle tissues of the carp were examined by light microscopy and various oxidative and antioxidant parameters were examined, which finally demonstrated the important antioxidant effect of propolis on the toxicity of arsenic in all tissues of the fish (Talas et al., 2014).

6. Summary

Through nature and human activities, arsenic enters the environmental space where humans and animal bodies live, causing widespread arsenic contamination and transformation between abiotic and biotic organisms. Arsenic pollution is widespread around the world, especially water arsenic pollution has a huge impact on humans and animals. Arsenic intake through drinking water or diet can cause arsenic accumulation in animals, which can cause toxic damage to the organism and pose a threat to animal life safety. It is noteworthy that aquatic animals are at greater risk of arsenic exposure compared to terrestrial animals. Aquatic animals cannot live without water, and arsenic contamination of water is almost everywhere, which poses a great threat to the survival of aquatic animals. Likewise, through water and feed, arsenic can accumulate in human food animals such as chickens, ducks, cattle,

sheep, and fish, threatening animal food safety, which has to draw our attention.

Arsenic exposure activates different molecular mechanisms, which can affect the structure and function of different organs and systems, resulting in a variety of diseases. In this review, several specific mechanisms by which arsenic produces toxicity are summarized, including oxidative stress, DNA damage, induction of inflammation and immune imbalance, and interference with the cell cycle. In the basic arsenic toxicity mechanism studies, reactive oxygen species-mediated oxidative damage is considered as the common denominator for arsenic-triggered disease development. At the same time, arsenic-induced oxidative stress can cause further damage to the organism through cascade reactions that induce apoptosis and autophagy. However, the complete molecular mechanism of arsenic-induced oxidative stress and its effects on other toxicity mechanisms have not yet been fully investigated. Given the importance of oxidative stress in the process of arsenicosis, further studies are needed to elucidate its specific molecular mechanisms as a breakthrough point for the treatment of arsenicosis. Meanwhile, arsenic, as a weak mutagen, exerts great influence in causing cellular DNA damage in animal tissues, and research in this area has significant implications for arsenic-induced cancer in humans, but no more studies have yet contributed in this regard. In addition, the treatment of arsenic poisoning is under a lot of research. Many compounds have been shown to be effective in mitigating the effects of arsenic poisoning, but not many of them have been applied to actual production, some are due to the high price, and some are due to the inconvenience of feeding. What we need to do is to break through the limitations and find compounds that can effectively treat arsenic poisoning and can be used in actual production. All of these need our attention.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

Abdollahzade, N., Babri, S., Majidinia, M., 2021. Attenuation of chronic arsenic neurotoxicity via melatonin in male offspring of maternal rats exposed to arsenic during conception: involvement of oxidative DNA damage and inflammatory signaling cascades. Life Sci. 266, 118876.

Adedara, I.A., et al., 2019. Selenium abates reproductive dysfunction via attenuation of biometal accumulation, oxido-inflammatory stress and caspase-3 activation in male rats exposed to arsenic. Environ. Pollut. 254 (Pt B), 113079.

Ahmed, M.K., et al., 2011. Assessing the genotoxic potentials of arsenic in tilapia (Oreochromis mossambicus) using alkaline comet assay and micronucleus test. Chemosphere 84 (1), 143–149.

Akbari, S., et al., 2022. Sodium arsenite accelerates D-galactose-induced aging in the testis of the rat: evidence for mitochondrial oxidative damage, NF-kB, JNK, and apoptosis pathways. Toxicology 470.

Arjona, M.I., et al., 2022. Intracellular mechanical drugs induce cell-cycle altering and cell death. Adv. Mater. 34 (17), e2109581.

Aung, K.H., et al., 2016. Prenatal exposure to arsenic impairs behavioral flexibility and cortical structure in mice. Front. Neurosci. 10, 137.

Baeyens, W., et al., 2019. Arsenic enrichment in sediments and beaches of Brazilian coastal waters: a review. Sci. Total Environ. 681, 143–154.

Bertin, F.R., et al., 2013. Arsenic toxicosis in cattle: meta-analysis of 156 cases. J. Vet. Intern. Med. 27 (4), 977–981.

Bjorklund, G., et al., 2020. Arsenic intoxication: general aspects and chelating agents. Arch. Toxicol. 94 (6), 1879–1897.

Carlson, P., Van Beneden, R.J., 2014. Arsenic exposure alters expression of cell cycle and lipid metabolism genes in the liver of adult zebrafish (Danio rerio). Aquat. Toxicol. 153, 66–72.

Chen, Y.Q., et al., 2022a. Arsenic exposure diminishes ovarian follicular reserve and induces abnormal steroidogenesis by DNA methylation. Ecotoxicol. Environ. Saf. 241.

Chen, Y., et al., 2022b. Ferroptosis: a new strategy for Cancer therapy. Front. Oncol. 12, 830561.

Cooper, K.L., et al., 2022. Contribution of NADPH oxidase to the retention of UVR-induced DNA damage by arsenic. Toxicol. Appl. Pharmacol. 434.

Costa, M., 2019. Review of arsenic toxicity, speciation and polyadenylation of canonical histones. Toxicol. Appl. Pharmacol. 375, 1–4.

Duan, X., et al., 2017. Acute arsenic exposure induces inflammatory responses and CD4(+) T cell subpopulations differentiation in spleen and thymus with the involvement of MAPK, NF-kB, and Nrf2. Mol. Immunol. 81, 160–172.

Duan, X.X., et al., Arsenic induces continuous inflammation and regulates Th1/Th2/ Th17/Treg balance in kidney and liver in vivo. Mediat. Inflamm., 2022. 2022.

Dutta, S., et al., 2018. Melatonin attenuates arsenic induced nephropathy via the regulation of oxidative stress and inflammatory signaling cascades in mice. Food Chem. Toxicol. 118, 303–316.

Esfahani, P.P., et al., 2022. Betaine protects against sodium arsenite-induced diabetes and hepatotoxicity in mice. Environ. Sci. Pollut. Res. 30 (4), 10880–10889.

Gillispie, E.C., et al., 2015. Soil pollution due to irrigation with arsenic-contaminated groundwater: current state of Science. Curr. Pollut. Rep. 1 (1), 1–12.

Han, X., et al., 2022. Protective effects of 6-Gingerol on cardiotoxicity induced by arsenic trioxide through AMPK/SIRT1/PGC-1alpha signaling pathway. Front. Pharmacol. 13, 868393.

He, Z., et al., 2021. NAC antagonizes arsenic-induced neurotoxicity through TMEM179 by inhibiting oxidative stress in Oli-neu cells. Ecotoxicol. Environ. Saf. 223, 112554.

Holcomb, N., et al., 2017. Inorganic arsenic inhibits the nucleotide excision repair pathway and reduces the expression of XPC. DNA Repair 52, 70–80.

Jing, H., et al., 2022. Arsenic activates the NLRP3 inflammasome and disturbs the Th1/ Th2/Th17/Treg balance in the hippocampus in mice. Biol. Trace Elem. Res. 201 (7), 3395–3403.

Jomova, K., et al., 2011. Arsenic: toxicity, oxidative stress and human disease. J. Appl. Toxicol. 31 (2), 95–107.

Kenyon, E.M., et al., 2008. Tissue distribution and urinary excretion of inorganic arsenic and its methylated metabolites in C57BL6 mice following subchronic exposure to arsenate in drinking water. Toxicol. Appl. Pharmacol. 232 (3), 448–455.

Ketelut-Carneiro, N., Fitzgerald, K.A., 2022. Apoptosis, pyroptosis, and necroptosis-oh my! The many ways a cell can die. J. Mol. Biol. 434 (4), 167378.

Kimura, A., et al., 2016. Exaggerated arsenic nephrotoxicity in female mice through estrogen-dependent impairments in the autophagic flux. Toxicology 339, 9–18.

Lan, J., et al., 2022. Curcumin alleviates arsenic-induced injury in duck skeletal muscle via regulating the PINK1/Parkin pathway and protecting mitochondrial function. Toxicol. Appl. Pharmacol. 434, 115820.

Lau, A., et al., 2013a. Arsenic-mediated activation of the Nrf2-Keap1 antioxidant pathway. J. Biochem. Mol. Toxicol. 27 (2), 99–105.

Lau, A., et al., 2013b. Arsenic inhibits autophagic flux, activating the Nrf2-Keap1 pathway in a p62-dependent manner. Mol. Cell. Biol. 33 (12), 2436–2446.

Li, J.H., Rossman, T.G., 1989. Inhibition of DNA ligase activity by arsenite: a possible mechanism of its comutagenesis. Mol. Toxicol. 2 (1), 1–9.

Liu, J., et al., 2018. Impacts of simultaneous exposure to arsenic (III) and copper (II) on inflammatory response, immune homeostasis, and heat shock response in chicken thymus. Int. Immunopharmacol. 64, 60–68.

Liu, Y., et al., 2020. Protective effects of crocetin on arsenic trioxide-induced hepatic injury: involvement of suppression in oxidative stress and inflammation through activation of Nrf2 signaling pathway in rats. Drug Des. Devel. Ther. 14, 1921–1931.

McMichael, B.D., et al., 2021. Long-term arsenic exposure impairs differentiation in mouse embryonal stem cells. J. Appl. Toxicol. 41 (7), 1089–1102.

Medda, N., De, S.K., Maiti, S., 2021. Different mechanisms of arsenic related signaling in cellular proliferation, apoptosis and neo-plastic transformation. Ecotoxicol. Environ. Saf. 208, 111752.

Muenyi, C.S., Ljungman, M., States, J.C., 2015. Arsenic disruption of DNA damage responses-potential role in carcinogenesis and chemotherapy. Biomolecules 5 (4), 2184–2193.

Navalkar, A., et al., 2022. Oncogenic gain of function due to p53 amyloids occurs through aberrant alteration of cell cycle and proliferation. J. Cell Sci. 135 (15).

Panda, S.K., et al., 2022. Hepatorenal toxicity of inorganic arsenic in white Pekin ducks and its amelioration by using ginger. Biol. Trace Elem. Res. 201 (5), 2471–2490.

Patra, P.H., et al., 2013. Immunotoxic and genotoxic potential of arsenic and its chemical species in goats. Toxicol. Int. 20 (1), 6–10.

Prakash, C., Soni, M., Kumar, V., 2016. Mitochondrial oxidative stress and dysfunction in arsenic neurotoxicity: a review. J. Appl. Toxicol. 36 (2), 179–188.

Ramos-Chavez, L.A., et al., 2015. Neurological effects of inorganic arsenic exposure: altered cysteine/glutamate transport, NMDA expression and spatial memory impairment. Front. Cell. Neurosci. 9, 21.

Rao, G., et al., 2022. Arsenic trioxide triggers mitochondrial dysfunction, oxidative stress, and apoptosis via Nrf 2/caspase 3 signaling pathway in heart of ducks. Apr, 10.1007/s12011-022-03219-1 Biol. Trace Elem. Res. 2022.

Reddy, P.S., et al., 2011. Protective effects of N-acetylcysteine against arsenic-induced oxidative stress and reprotoxicity in male mice. J. Trace Elem. Med. Biol. 25 (4), 247–253.

Ren, Z., et al., 2021a. Effects of selenium on arsenic-induced liver lesions in broilers. Biol. Trace Elem. Res. 199 (3), 1080–1089.

Ren, Z., et al., 2021b. Effects of selenium on the immunotoxicity of subacute arsenic poisoning in chickens. Biol. Trace Elem. Res. 199 (11), 4260–4272.

Roy, M., et al., 2011. Curcumin prevents DNA damage and enhances the repair potential in a chronically arsenic-exposed human population in West Bengal, India. Eur. J. Cancer Prev. 20 (2), 123–131.

Sandhi, A., et al., 2022. Arsenic in the water and agricultural crop production system: Bangladesh perspectives. Environ. Sci. Pollut. Res. Int. 29 (34), 51354–51366.

Sattar, A., et al., 2016. Metabolism and toxicity of arsenicals in mammals. Environ. Toxicol. Pharmacol. 48, 214–224.

Sodhi, K.K., et al., 2019. Perspectives on arsenic toxicity, carcinogenicity and its systemic remediation strategies. Environ. Technol. Innov. 16.

Talas, Z.S., et al., 2012. Effects of propolis on some blood parameters and enzymes in carp exposed to arsenic. Iran. J. Fish. Sci. 11 (2), 405–414.

Talas, Z.S., et al., 2014. Antioxidant effects of propolis on carp Cyprinus carpio exposed to arsenic: biochemical and histopathologic findings. Dis. Aquat. Org. 108 (3), 241–249.

Tam, L.M., Price, N.E., Wang, Y., 2020. Molecular mechanisms of arsenic-induced disruption of DNA repair. Chem. Res. Toxicol. 33 (3), 709–726.

Tang, L., et al., 2022. Curcumin antagonizes inflammation and autophagy induced by arsenic trioxide through immune protection in duck spleen. Environ. Sci. Pollut. Res. Int. 29 (50), 75344–75355.

Tian, C., et al., 2022. Mitochondria related cell death modalities and disease. Front. Cell Dev. Biol. 10, 832356.

Ventura-Lima, J., et al., 2009. Effects of different inorganic arsenic species in Cyprinus carpio (Cyprinidae) tissues after short-time exposure: bioaccumulation, biotransformation and biological responses. Environ. Pollut. 157 (12), 3479–3484.

Ventura-Lima, J., Bogo, M.R., Monserrat, J.M., 2011a. Arsenic toxicity in mammals and aquatic animals: a comparative biochemical approach. Ecotoxicol. Environ. Saf. 74 (3), 211–218.

Ventura-Lima, J., Bogo, M.R., Monserrat, J.M., 2011b. Arsenic toxicity in mammals and aquatic animals: a comparative biochemical approach. Ecotoxicol. Environ. Saf. 74 (3), 211–218.

Volk, L.B., et al., 2022. Impacts of arsenic on Rad18 and translesion synthesis. Toxicol. Appl. Pharmacol. 454.

Wang, A., et al., 2006. Reproductive and developmental toxicity of arsenic in rodents: a review. Int. J. Toxicol. 25 (5), 319–331.

Wang, H., et al., 2022. TNF-alpha derived from arsenite-induced microglia activation mediated neuronal necroptosis. Ecotoxicol. Environ. Saf. 236, 113468.

Wang, N.X., et al., 2023. Arsenic occurrence and cycling in the aquatic environment: a comparison between freshwater and seawater. Water 15 (1).

Wu, S., et al., 2021a. The neuroprotective effect of curcumin against ATO triggered neurotoxicity through Nrf2 and NF-kappaB signaling pathway in the brain of ducks. Ecotoxicol. Environ. Saf. 228, 112965.

Wu, S., et al., 2021b. Protective effects of curcumin on ATO-induced nephrotoxicity in ducks in relation to suppressed autophagy, apoptosis and dyslipidemia by regulating oxidative stress. Ecotoxicol. Environ. Saf. 219, 112350.

Wu, S., et al., 2021c. Evaluation of toxic effects induced by arsenic trioxide or/and antimony on autophagy and apoptosis in testis of adult mice. Environ. Sci. Pollut. Res. Int. 28 (39), 54647–54660.

Xu, N., et al., 2022. Hydrogeochemical processes and potential exposure risk of arsenic-rich groundwater from Huaihe River plain, China. WATER 14 (5).

Yan, N., et al., 2020. Chronic arsenic exposure induces the time-dependent modulation of inflammation and immunosuppression in spleen. Cell Biosci. 10 (1).

Yang, H.B., et al., 2022. Selenium supplementation protects against arsenic-trioxide-induced cardiotoxicity via reducing oxidative stress and inflammation through increasing NAD(+) pool. Biol. Trace Elem. Res. https://doi.org/10.1007/s12011-022-03478-y.

Yuan, J., Li, Q.X., Zhao, Y.Q., 2022. The research trend on arsenic pollution in freshwater: a bibliometric review. Environ. Monit. Assess. 194 (9).

Zargari, F., et al., 2022. Arsenic, oxidative stress and reproductive system. J. Xenobiot. 12 (3), 214–222.

Zeng, Q., et al., 2019. Long-term arsenite exposure induces testicular toxicity by redox imbalance, G2/M cell arrest and apoptosis in mice. Toxicology 411, 122–132.

Zhang, Z., et al., 2014a. Resveratrol, a natural antioxidant, has a protective effect on liver injury induced by inorganic arsenic exposure. Biomed. Res. Int. 2014, 617202.

Zhang, W., et al., 2014b. Protective effect of resveratrol on arsenic trioxide-induced nephrotoxicity in rats. Nutr. Res. Pract. 8 (2), 220–226.

Zhang, Y., et al., 2017. Melatonin protects against arsenic trioxide-induced liver injury by the upregulation of Nrf2 expression through the activation of PI3K/AKT pathway. Oncotarget 8 (3), 3773–3780.

Zhang, S., et al., 2022. Realgar-induced nephrotoxicity via ferroptosis in mice. J. Appl. Toxicol. 42 (11), 1843–1853.

Zhao, Z., et al., 2020. Ameliorative effects and mechanism of crocetin in arsenic trioxide-induced cardiotoxicity in rats. Mol. Med. Rep. 22 (6), 5271–5281.

Zheng, Y.H., et al., 2017. Protection of taurine against arsenic-induced DNA damage of mice kidneys. Taurine 10 975, 917–927.

Zhong, G., et al., 2021. Arsenic causes mitochondrial biogenesis obstacles by inhibiting the AMPK/PGC-1alpha signaling pathway and also induces apoptosis and dysregulated mitophagy in the duck liver. Ecotoxicol. Environ. Saf. 230, 113117.

Zwolak, I., 2020. The role of selenium in arsenic and cadmium toxicity: an updated review of scientific literature. Biol. Trace Elem. Res. 193 (1), 44–63.