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Amelioration of arsenic toxicity: A mini-review of current scientific literature

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Abstract
Every year millions of tons of heavy metal contaminants are produced and humans are vulnerable to them. The heavy metals that are toxic include lead, mercury, arsenic and cadmium. Heavy metals have adverse implications for both plants and animals. They may be found in nature anywhere, however their density varies by region. Arsenic, belonging to group XV elements of the periodic table, is a colorless, tasteless and odorless environmental contaminant classified as metalloid. Arsenic compounds are widely used in drug manufacturing, antifouling paints, pesticides, and wood preservation. Arsenic trioxide (As_2O_3) is prevalent in air and inorganic arsenates (AsO^{3-}) or arsenites (AsO^{2-}) are found in water, food and soil. On account of the widespread use of arsenic it has become a source of common heavy metal exposure leading to concern about the potential impact of arsenic on human beings. Elevated concentrations of arsenic are reported in carbonate spring waters (0.4–1.3 mg/L) of New Zealand, Romania, and the United States, in artesian wells (up to 1.8 mg/L) of Taiwan and China, and in-ground waters (up to 3.2 mg/L) in India. Occupational exposure occurs from metal smelting, pesticide usage, and fuel combustion, mainly from burning low-grade brown coal and mineral processing. Despite major governmental initiatives, absorption of arsenic poses a life - threatening issue in the living beings. This necessitates assessing the environmental contaminant –arsenic through the oral route as it may have a narrow period of sensitivity with implications for the human population.

Keywords: Arsenic, amelioration, antioxidants, nanostructures, phytochemical, microbes

Introduction
Since the 19th century, the medicinal uses and chronic toxicity of arsenic are prevalent in the world. Fowler's solution (1% As_2O_3 preparation) was an oral form of arsenic that was used to treat many cancers, including leukaemia, asthma, and leukaemia (Ho & Lowenstein, 2016) [29]. Arsenic can be found in wood that has been conserved, including telephone and power poles, residential docks, pressure-treated wood used to build playgrounds for kids, and decks found in homes (Costa, 2019) [15]. Plants, fruits and sea flora are well absorbed by arsenic-based insecticides like lead arsenate ($PbHAsO_4$) and sodium arsenate (Na_3AsO_4), which can either directly or indirectly impact people (Jang *et al*., 2016) [35]. Arsenic is absorbed rapidly and dispersed in the human body by accumulating in organs like the liver, kidney, lungs, and heart (Klaassen *et al*., 1996) [39] (Rodríguez *et al*., 2003) [68]. The absorption rate varies dramatically involving different exposure pathways where it undergoes chemical modification producing potential effects. Reports from human and animal data show that approximately 60-90% of ingested trivalent or pentavalent form of inorganic arsenic is absorbed from the gastrointestinal tract (Hall, 2002) [28]. Arsenic compounds are well absorbed and redistributed to organs like the liver, lungs, intestine, and spleen where they bind to the sulfhydryl (-SH) groups of proteins. Human urine samples contain arsenic metabolites such as monomethylarsonous acid (MMAIII) and dimethyl arsenous acid (DMAIII) (Le *et al*., 2000). Inorganic arsenic (As^{+5} > As^{+3}) and Arsine are more toxic than organic arsenicals (Kuivenhoven & Mason, 2022) [40]. Hyperpigmentation and keratosis are two dermatological alterations caused by arsenic. Arsenic exposure also causes an increase in HNO_3, O^{2-}, OH and ROS which cause DNA and protein damage as well as changes in cellular architecture, permeability, and cell viability (Hughes *et al*., 2011) [31] (Birben *et al*., 2012) [10]. Arsenic alters pathways meant for cell development, apoptosis and proliferation by activating numerous signaling cascades (Hughes *et al*., 2011) [31].

Oxidative stress causes lipid peroxidation, which then damages DNA and finally causes cell death (Mochizuki, 2019) [55]. Exposure to arsenic nanoparticles causes apoptosis and organelle impairment (Jahangirnejad *et al*., 2020) [32].

Since administering nephrotoxic medications is crucial in contemporary clinical practice, drug-induced nephrotoxicity is currently a major problem. Unbalanced lipid peroxidation causes endothelial dysfunction, as well as a decrease of plasma SOD and GPx activity which increases the risk of developing chronic kidney disease (Dennis & Witting, 2017) [16]. Arsenic inhibits GSH reductase and creates excessive ROS in renal tissue when it interacts with compounds containing sulfhydryl groups (Ghabaee *et al*., 2017) [23]. The kidney is the main organ targeted by arsenic because urine eliminates roughly 60% of the daily intake of arsenic (Thangapandiyan *et al*., 2019) [82]. Exposure to arsenic in the chronic phase has been linked to glomerular hypertrophy, nephritis and cellular vacuolation in the kidney (Waalkes *et al*., 2004) [84]. Arsenic-induced nephropathy and renal tubular cell death, which result in weight loss, are largely caused by oxidative stress (Sinha *et al*., 2008) [80]. Arsenic causes DNA damage brought on by oxidative stress and endothelial dysfunction in the kidneys, resulting in albuminuria and proteinuria (Ellinsworth, 2015) [18]. It has been concluded that arsenic metabolites are retained for longer when glomerular filtration rates are lower in *in-vitro*, preclinical, and clinical studies on arsenic (Robles-Osorio *et al*., 2015) [67]. Bladder cancer risk is enhanced as a result of arsenic's promotion of tumor suppressor genes, including those involving tumor protein P53 (TP53) (Kelsey *et al*., 2005) [37]. The risk of genotoxicity may increase due to interactions between different DNA repair proteins (Chen *et al*., 2010) [12]; (Banerjee *et al*., 2008) [5] (Cohen *et al*., 2013) [14]. Nucleotide excision repair, base excision repair, and mismatch repair can all be hindered by arsenic (Hossain *et al*., 2012) [30]. Centromeres frequently undergo chromosomal instability brought on by arsenic, which can lead to centromeric fusion between two chromosomes or the emergence of acentric chromosomes (Kesari *et al*., 2012) [38]. Chelation therapy and antioxidant therapy are two therapeutic strategies for arsenic-mediated toxicity (Susan *et al*., 2019) [81]. Tea extract (Akter *et al*., 2015) [4]; (Messarah *et al*., 2013) [52], as well as plants including *Phyllanthus emblica* (Sayed *et al*., 2015) [77] and *Syzygium cumini* (Barai *et al*., 2017) [7] have demonstrated ameliorative properties against arsenic toxicity. Biochanin A (BCA) and Ellagic acid are polyphenolic antioxidants that diminish arsenic's hepatotoxicity and cardiotoxicity, respectively (Jalaludeen *et al*., 2016) [33]; (Pace *et al*., 2017) [61]. Antioxidants have been shown to prevent arsenic-induced DNA damage (ROS) in a laboratory investigation (Liu *et al*., 2001) [46]. Vitamin E aids in the conversion of GSSG (oxidized glutathione) to GSH (reduced glutathione), which in turn aids in the conversion of mono and dehydroascorbic acid to ascorbic acid. It also increases the antioxidant capacity of the cell. Vitamin E also prevents the formation of disulfide from free or protein-bound sulfhydryls (Garg *et al*., 2005) [21]. All membrane lipids and unsaturated fatty acids are also guarded against oxidative degradation. Vitamin E supplementation increased active spermatogenesis in rats (Momeni *et al*., 2012) [57]. A 250 IU/kg meal dose of vitamin E supplementation decreased the accumulation of arsenic in tissues and shielded children from the oxidative stress caused by arsenic (Mohanta *et al*., 2015) [56]. As supplementary treatments assist in decreasing the harmful effects of arsenic, a high-protein diet and the prescription of vitamins, probiotics, polyphenols, or vital nutrients have also been recommended. The persistence and retention of metals in the environment, which has grown to be a significant research issue, is a significant global danger. Thus, emerging approaches that combine microbe-based remediation and nanoparticle-based formulations should be utilized to clean up the environment.

Methodology

This review provides background information and a thorough discussion of recent studies on the amelioration of detrimental processes brought on by arsenic. This study's objective was to look at the data available on ameliorative chemicals from major scientific databases. Terms like "Arsenic," "nephrotoxicity," "antioxidants," "carcinoma," "toxicity," "nanoparticles," and "therapeutics" were among the search terms. Research on humans and animals that includes acute and chronic arsenic exposure, harmful effects on body organs, and therapeutic drugs involved in healing the toxicity processes were searched in the literature. Unpublished data and letters to the editor were excluded.

Antioxidants in As toxicity

One of the key processes driving Arsenic-induced cell damage is oxidative stress. As a result, using various antioxidants as a therapeutic strategy to mitigate their toxicity in vivo is one of the therapeutic techniques. Ascorbic acid is a chemically characterized and well-described antioxidant that is frequently used as a standard for measuring antioxidative capacity. Furthermore, it is a natural chemical found in a variety of foods and beverages, and it has been shown to prevent reduced glutathione depletion and consequent cellular damage in rats following exposure to arsenic (Singh & Rana, 2010) [79]. After drinking water containing 100 ppm arsenic for 30 days, the albino rats showed signs of protein oxidation and double-strand DNA breakage.

Arsenic-induced damage was greatly reduced when antioxidants Vitamin C and Vitamin E were given together with arsenic (Kadirvel *et al*., 2007) [36]. Vitamin C had a positive impact on sperm morphology and DNA content in Teddy Goat Bucks exposed to Sodium arsenite for 12 weeks (Zubair *et al*., 2020) [90]. Vitamin C also restored GSH, SOD, CAT, Acid Phosphatase and Alkaline Phosphatase levels to normal in mice treated with arsenic trioxide (Banerjee *et al*., 2009) [6]. Folic acid is an antioxidant as well as a radical scavenger. Vitamin B12 and Folic acid minimized arsenic-induced cellular oxidative, inflammatory and toxic changes (Mukherjee *et al*., 2006) [59].

In a different experiment, Wistar rats received vitamin B12 and folic acid along with water contaminated with sodium arsenite for 24 days. Both of the antioxidants effectively reduced the effects of arsenic-induced altered liver function, increased ROS production, DNA fragmentation and poor histology of hepatic tissues (Chattopadhyay *et al*., 2012) [11]. Zinc also operates as an antioxidant. Administration of Zinc caused decrease in lipid peroxidation levels and an increase in the concentration of anti-oxidative markers (Kumar *et al*., 2010) [35]. In rat models of kidney injury brought on by cyclosporine and HgCl2, zinc increased the renal antioxidant status (Ghabaee *et al*., 2017) [23]. In rat kidney tissue, zinc supplementation throughout pregnancy and

lactation protected against arsenic-induced oxidative stress as seen by increased malondialdehyde (MDA) and GSH levels as well as histological changes (Bhardwaj & Dhawan, 2019) [8]. Chronic Arsenic poisoning in aquatic animals is alleviated by Zinc's hepatoprotective action (Zhao *et al*., 2019) [88]. Antioxidants and crucial nutritional trace elements, Selenium and Vitamin E, also ameliorate arsenic-induced toxicity. Selenium improved the hepatic damage indicators such as serum ALT, AST and antioxidant enzymes like SOD, GPX, CAT in arsenic-treated rats, showing less liver damage (Zhao *et al*., 2013) [89]. Vitamin E appeared to counteract sodium arsenite's detrimental effects on the amount of epididymal sperm and other morphometric characteristics of the adult rat testis (Momeni *et al*., 2012) [57]. In broiler chicks treated with 50mg/kg body weight arsenic for 30 days, vitamin E and selenium increased intracellular glutathione and superoxide dismutase which reduced free radical-induced lethal damage and checked upon lipid peroxidation (Mashkoor *et al*., 2013) [50]. Oral selenite supplementation in arsenic-toxicated rats decreased renal lipid peroxidation, regulated antioxidant enzymes, and protected kidney tissue against arsenite-induced histological alterations (Jalaludeen *et al*., 2015) [34]. Selenite given orally in drinking water was beneficial in avoiding teratogenic effects brought on by arsenic in female hamsters (Sampayo-Reyes *et al*., 2017) [73]. In another study, an organic form of selenium (SeMet) protected against arsenite-induced cell cytotoxicity and ROS generation in kidney (Chitta *et al*., 2013) [13]. Strong antioxidant silibinin has nephroprotective properties. In a rat model of arsenic-induced nephrotoxicity, silibinin prevented caspase-3-mediated tubular cell death, reduced upregulation of NF-κB, iNOS and NADPH oxidase in the kidney (Milton Prabu *et al*., 2012) [53]. Antioxidants have been thoroughly researched as therapies to counteract arsenic toxicity since it is widely known phenomenon that the cellular mechanisms underlying toxicity of arsenic and related illnesses heavily depends on the production of free radicals. As a result, antioxidants offer a strong foundation for reducing the negative outcomes of heavy metal toxicity in both humans and animals. They can also be employed in conjunction with chelating drugs to improve therapeutic outcomes (Table 1).

Nanostructured Materials

Long-term technologies for the protection of the environment and the well-being of people rely heavily on nanotechnology. Metal nanoparticles serve an important role in a variety of technologies, including catalysis, optoelectronics and biological diagnostic probes (Kumar *et al*., 2011) [42]. Nowadays, arsenic removal research utilizing biotechnological and Nanotechnological methods is gaining pace. Inorganic arsenic has been detected using a variety of nanostructured materials. Biosensor development is made possible by nanomaterials, which also significantly improve detection performance. As a result, extensive research has been done recently on sensors made up of nanomaterials and biosensors to detect arsenic in elemental form. Nano metal oxides are increasingly being utilized in biomedical applications to address this global challenge. Liposomes, polymeric micelles and phospholipids complexes are examples of emerging nanomaterials which act as potential therapeutic approaches to reduce arsenic toxicity (Edis *et al*., 2021) [17].

A study reported that nano-sheet layers have a high absorption capacity for both As (III) and As (IV) species and can successfully oxidize the extremely hazardous form of arsenic into less harmful form (Rosales *et al*., 2020). Arsenic can be detected quickly using biosensors, especially nanomaterial-based aptamer sensors, which have gained popularity for their ease of use, high sensitivity, and speed of response (Mao *et al*., 2020) [49]. A number of metal oxide nanoparticles have been used as nano-adsorbents to remove heavy metals from various sources (Pillai & Dharaskar, 2020) [63]. Prasad and co-workers studied the efficacy of nanoparticles on human lymphocytes treated with arsenic. Analysis of cell viability using DNA damage and MTT assay demonstrated that the manufactured selenium nanoparticles protected cells from DNA damage and cell death brought on by arsenic (Prasad & Selvaraj, 2014) [64]. Supplementation of selenium-encapsulated nanoparticles and riboflavin dramatically improved immunity, antioxidant status and specific growth rate of *Pangasianodon hypophthalmus* and also reduced bioaccumulation of arsenic along with reduced lipid peroxidation in the fish (Kumar *et al*., 2020) [43]. Nanoparticle-induced formulations also aid in reducing the genotoxic effects caused by arsenic. The therapy with silver nanoparticles significantly decreased the frequency of mutations brought on by arsenic exposure as well as the production of DNA double-strand break markers. In order to sustain the intracellular buildup of arsenic, silver nanoparticles inhibited the development of a specific arsenic-binding protein called Gal-1. Additionally, the activities of antioxidant enzymes were markedly boosted by the use of silver nanoparticles, which inhibited arsenic's ability to produce reactive oxygen species (ROS) (Wang *et al*., 2021) [85].

In a study, curcumin-encapsulated nanoparticles efficiently improved LPO levels by 78.3% and restored hepatic antioxidants. Additionally, it resulted in a considerable reduction in the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations in the blood as well as an increase in the antioxidative glutathione system (Sankar *et al*., 2015) [74]. Compared to free curcumin, encapsulated curcumin nanoparticles exhibit greater antioxidant and chelating properties (Sankar *et al*., 2013) [75]. Encapsulated curcumin nanoparticles provide considerable neurochemical and immunohistochemical protection, which supports the effectiveness of their neuroprotective properties (Yadav *et al*., 2012) [86]. An experiment was performed to investigate the role of morin encapsulated chitosan nanoparticles (MNCPs) against arsenic-induced liver damage in rats. Morin hydrate is a powerful flavonoid found in abundance in Moraceae plants and is regarded to be an important bioactive molecule that can help prevent a variety of diseases, including hepatotoxicity. The potent antioxidant, antiapoptotic, and anti-inflammatory capabilities of MCNPs make them a better hepatoprotective drug than free morin against arsenic-induced damage (Mondal *et al*., 2022) [58]. Riboflavin is a necessary ingredient for flavoprotein to function as an enzyme in the fish. The functional forms of riboflavin, flavin mononucleotide (FMN), and flavin adenine dinucleotide (FAD), are involved in a variety of oxidation and reduction reactions. Arsenic bioaccumulation and pollution were

dramatically decreased by supplementation with selenium nanoparticles and riboflavin. When they were added, the levels of acetylcholinesterase and ascorbic acid in the neuronal and cardiac tissue were dramatically increased, while stress biomarkers like lipid peroxidation, blood sugar, serum cortisol, and heat shock protein were significantly decreased (Kumar *et al*., 2020) [43].

A large class of chemical substances that exist naturally called polyphenols are identified by the presence of several phenol units. In the past, polyphenols have been used as dyes and tanning agents. These findings pave the way for more research into creating viable nano-medicines for arsenic toxicity that are both effective and safe. Nanotechnology's application in biomedicine is an emerging field with promising prospects for improving human illness diagnosis and therapy. A new era in pharmacotherapy where drugs or genes can be given to tissues or cells selectively is marked by the ability to combine medications or genes into a functionalized nanoparticle. The goal of using nanoengineering in ailment therapy is to help deliver drugs to specific tissues consistently and effectively while minimizing adverse complications and toxicity. Nanomaterials can be improvised based on the tissue specifications such as carbon-based, ceramic, metal nanoparticles, semiconductor nanoparticles, polymeric nanoparticles and lipid-based nanoparticles and can be given alone or in combination with antioxidants to suppress the detrimental effects of arsenic-induced toxicity (Table 2).

Plant extracts & phytochemicals

Due to their minimal adverse effects, medicinal plants are recently gaining potential as therapies in cases of toxic metal poisoning in scientific research (Mehrandish *et al*., 2019) [51]. Plants have been utilized to cure a variety of ailments since ancient times, and they continue to be a valuable source of novel medicinal substances for medical therapeutics. Literature findings suggest that certain properties of plant extracts and plant-derived compounds (anti-oxidant and anti-inflammatory) which help to counteract the oxidative stress-mediated harmful consequences of arsenic exposure have been used to alleviate arsenic-mediated toxicity. Arsenic intoxicated Wistar rats treated with methanol leaf extract of *Laportea aestuans* depicted restoration of serum protein concentration, decreased creatinine/urea concentration along with reduction in elevated serum alanine and aspartate aminotransferases activity. It also amelioarted the frequency of micronucleated polychromatic erythrocytes (Adetunji *et al*., 2021) [2]. When arsenic-treated mice were given *Mentha piperita* leaf extract, LPO content, ALP, SGOT, and SGPT activity significantly decreased, and body weight, liver weight, LDH, and GSH content significantly increased (Sharma *et al*., 2007) [78].

In an experiment, the ameliorative properties of *Syzygium cumini* leaf extract was investigated using Swiss albino mice. For a total of 12 weeks, the leaf extract was given daily to four groups of animals. The leaf extract decreased the arsenic-induced activation of the enzymes lactate dehydrogenase, alanine aminotransferase (ALT), alkaline phosphatase (ALP), glucose and uric acid (Barai *et al*., 2017) [7]. Apart from this, medicinal plants like *Coriandrum sativum, Ocimum basilicum, Triticum aestivum, Zea mays, Trichosanthes dioica, Nigella sativa, Azadirachta indica, Allium sativum, Camellia sinensis, Moringa oleifera* and *Ginkgo biloba* also have ameliorative potential in reducing arsenic toxicity (Table 3). Plant extracts generally have antioxidant qualities and may therefore have the ability to reduce oxidative stress brought on by metals by the production of free radicals (Bhattacharya, 2017) [9].

Microbial Treatment

Bacteria, fungus, ciliates, and other organisms may extract metals and metalloids from aqueous solutions. Phosphate transporters allow arsenate (V) to enter the bacterial cell, whereas aquaglyceroporin allows arsenic (III) to enter the cell. Arsenic (V) is then converted to arsenic (III) by the arsenate reductase enzyme found in bacteria using glutathione as a reductant (Yang & Rosen, 2016). *Exiguobacterium sp. strain As-9* was isolated from soil contaminated with arsenic and exhibited resistance to extremely high arsenic concentrations. By colonising the root surface, it also safeguarded the plants from the harmful effects of arsenic by limiting its uptake and transfer. Additionally, the presence of bacteria significantly reduced arsenic-induced oxidative stress (Pandey & Bhatt, 2016) [62]. Irrigation water polluted with arsenic and related agricultural soil included bacteria that promoted plant growth and were resistant to arsenic. The strains *Klebsiella pneumoniae* T22 and *Klebsiella oxytoca* N53 both showed the highest arsenic resistance (Qamar *et al*., 2017) [65]. Some scientists discovered new bacterial strain that provided resistance against arsenic toxicity. Minimum inhibitory values for the isolated strain, known as *Bacillus aryabhattai* AS6, were 100 mM for arsenate and 20 mM for arsenite, respectively (Ghosh *et al*., 2018) [26]. Another bacterial strain *Pseudomonas citronellolis* PC (KM594397) showed promising results in terms of arsenic (As^{+5} at 10-160 mg/kg) tolerance and enhanced plant growth-promoting activities under stress conditions in chickpea (Adhikary *et al*., 2019) [3]. Three arsenic-tolerant plant growth-promoting bacteria were found to exist: Acinetobacter species (GIS3), Bacillus *species* (GIS1), and MG203916, respectively (MG203917). These bacteria significantly absorbed arsenic and displayed tremendous potential for the bioremediation of arsenic contamination (Rahman *et al*., 2019) [66]. Rhizopheric interactions between plants and animals give rise to microbial activity can further reduce arsenic uptake up to many folds in living cells. Microbial treatment has the potential to cure heavy metal toxicity in both plants and animals. Therefore, it is comprehensible that combination treatments utilizing multiple approaches (microbes along with plant extracts) can have an additive impact on reversing detrimental effects caused by arsenic exposure in humans and animals.

Table 1: Therapeutic effects of Antioxidants in the treatment of arsenic-induced toxicity

Antioxidant	Dosage & Administration	Animal model/Cell Lines	Effects on As toxicity	References
Taurine	50 mg/kg, oral	Rat	IKK, p38, and JNK MAPK signalling pathways reduced NF-κB activation and decreased arsenic-induced myocardial pathophysiology.	(Ghosh *et al*., 2009) [24]
Alpha-Lipoic acid	35 mg/kg, gavage	Rat	ECG abnormalities in heart caused by As_2O_3 were eliminated	(Kumazaki *et al*., 2011) [44]
Silibinin	25, 50 & 75 mg/kg, intragastric	Rat	decreased the overexpression of NF-κB, iNOS, and NADPH oxidase in the renal tissue, and prevented the arsenic-induced caspase-3-mediated death of tubular cells	(Milton Prabu *et al*., 2012) [53]
Selenium	17 mg/L, oral	Rat	By changing the expression of oxidative stress-related genes to boost the activity of antioxidant enzymes, Na_2SeO_3 guards liver cells	(Zhao *et al*., 2013) [89]
Vitamin E	250 IU/kg, oral	Goat	controlled serum enzyme levels and lipid peroxidation, prevented deterioration of reduced glutathione, catalase, SOD and GST in erythrocytes caused by arsenic	(Mohanta *et al*., 2015) [56]
Biochanin A	10, 20 & 40 mg/kg, intragastric	Rat	demonstrated a substantial decrease in the indicators of oxidative and liver damage	(Jalaludeen *et al*., 2016) [33]
Omega-3 fatty acid	50 mg/kg, oral	Rat, cardiomyocytes	Significantly improved the Δψm, decreased LDH release, lipid peroxidation, and intracellular calcium concentration, and increased cardiomyocyte viability	(Varghese *et al*., 2017) [83]
Ellagic acid	20 & 40 mg/kg, oral	Rat	Total ROS generation is downregulated, and BAX, Bcl2, IL-1, TNF, and INF are altered	(Fakiha *et al*., 2018) [19]
Zinc	227 mg/L, oral	Rat	Restoration of antioxidant enzyme levels and total cell count in erythrocytes lysate of arsenic treated rats	(Bhardwaj & Dhawan, 2019) [8]
Vitamin C	200 mg/kg, oral	Goat	amelioration of adverse effects of arsenic on semen quality, hormones and histopathological lesions in testes	(Zubair, *et al*., 2020) [90]

Table 2: Therapeutic effects of Nanomaterials in the treatment of arsenic-induced toxicity

Nanomaterial	Dosage and administration	Animal model/Cell lines	Effects on As toxicity	References
Quercetin	8.98 µmol/kg orally	Rat	elevated reduced antioxidant levels caused by arsenic	(Ghosh *et al*., 2009) [24]
Encapsulated curcumin	15 mg/kg, orally	Rat	provided significant neurochemical and immunohistochemical protection against arsenic induced neurotoxicity	(Yadav *et al*., 2012) [86]
SJ loaded PLGA NPs	10 mg/kg, 20 mg/kg, gavage	Rat	PLGA encapsulated SJ (*Syzygium jambolanum*) nanoparticles provided reduction in arsenic induced hyperglycemia and stress	(Samadder *et al*., 2012b) [72]
Nano Insulin	0.5 mIU/g, 1 mIU/g, intraperitoneal	Mice	reduced arsenic-induced hyperglycemia by demonstrating positive regulation in mitochondrial signalling cascades and other downstream signalling components	(Samadder *et al*., 2013) [70]
Cur-NP	100 mg/kg, gavage	Rat	Cur-NP significantly caused reduction in chromosomal aberrations with 84% amelioration efficacy and decreased micronuclei formation by 81%; it also caused further reduction in the comet score by 60%	(Sankar *et al*., 2014) [76]
SeNP	0.01 µg/µl	Human lymphocytes	protective action against DNA damage and cell death brought on by arsenic	(Prasad & Selvaraj, 2014) [64]
SeNP & RF	5.5, 10.5 & 15.5 mg/kg, orally	Fish	Reduction in stress biomarkers such as lipid peroxidation and serum cortisol, reduction in bioaccumulation of arsenic	(Kumar, *et al*., 2020) [20]
Tannic acid + Vit E loaded PLGA NPs	40 and 80 mg/kg, intraperitoneal	Mice	Reduce inflammatory burden, prevented the production of reactive oxygen species, inhibited EGFR-AKT-STAT3 pathway and apoptosis to provide hepato-protection	(Nag *et al*., 2020) [60]
Ag-NP	0.3, 0.5, 2 and 4 µg/mL	Human-hamster hybrid AL cells	The production of phosphorylated histone H2AX and arsenic-induced mutation frequencies were both significantly reduced by Ag-NP; upregulated antioxidant enzyme activities, inhibited ROS generation	(Wang, *et al*., 2021) [85]
MCNPs	75, 150 & 300 mg/hykg, gavage	Mice	Inhibition of ROS generation and elevated MDA levels, enhanced antioxidant marker levels, suppressed arsenic-induced apoptotic effects	(Mondal *et al*., 2022) [58]

Table 3: Therapeutic effects of plant extracts in the treatment of arsenic toxicity

Plant extract	Part & Dosage	Animal model	Effect on As toxicity	References
Moringa oleifera	Seed powder, 500 mg/kg, oral	Mice	Significant increase in blood GSH, ALAD, restoration of antioxidant enzyme levels and a decrease in ROS, Metallothionein & TBARS levels	(Mishra *et al*., 2009) [54]
Quercetin (flavonoid)	8.98 µmol/kg, oral	Rat	Decreased oxidative injury in liver and brain, normalized changes in mitochondrial function, ROS formation, decreased hepatic As levels	(Ghosh *et al*., 2011) [27]
Pulsatilla nigricans	35 mg/kg, oral gavage	Mice	Significant arsenic-induced harmful effect in the testis was inhibited, and testis cells and sperm underwent less oxidative stress and death	(Samadder *et al*., 2012a) [71]
Syzygium jambolanum	Seed powder, 20 mg/kg, oral gavage	Mice	reduced blood sugar and amounts of glycosylated haemoglobin brought on by arsenic	(Samadder *et al*., 2012b) [72]
Camellia sinensis	Leaf, 10 mg/ml, gavage	Rat	DNA protection in arsenic-induced tissue necrosis/apoptosis is enhanced by robust SOD1 protection, a variety of radical-scavenging, and antimutagenic actions	(Acharyya *et al*., 2014) [1]
Emblica officinalis	Fruit, 500 mg in 0.1 ml drinking water	Rat	Restoration of antioxidant components, thiol levels and decrease in TBARS and conjugated dienes	(Maiti *et al*., 2014) [25]
Annona muricata	Leaf, 12.5, 25, 50 & 100 µg/ml	Human hepatic cells	hemolysis of erythrocytes was substantially prevented by 85%	(George *et al*., 2015) [22]
Phyllanthus emblica	Leaf, 50 µg/g, orally	Mice	decreased the enlargement of the liver, kidney, and spleen in arsenic-exposed mice and prevented a decrease in body weight gain	(Sayed *et al*., 2015) [77]
Syzygium cumini	Leaf, 50 µg/g, orally	Mice	Alkaline phosphatase (ALP), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), uric acid, and glucose elevations caused by arsenic were eliminated	(Barai, *et al*., 2017) [7]
Laportea aestuans	Leaf, 200 mg/kg, orally	Rat	showed restoration of serum protein concentration, decreased creatinine/urea concentration along with reduction in elevated serum ALT/AST activity	(Adetunji *et al*., 2021) [2]

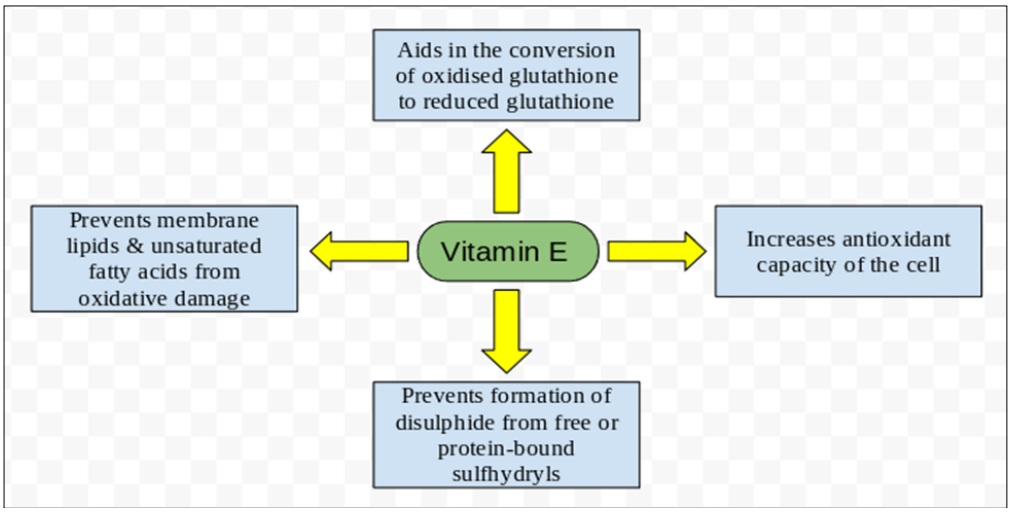

Fig 1: Mechanism of Vitamin E-mediated amelioration against arsenic-induced toxicity

Conclusion

This extensive analysis of arsenic toxicity concludes that humans will continue to come in contact with heavy metals from our environment. Therefore, adequate monitoring is implemented globally to prevent heavy metal pollution. Following poisoning, they have a well-known impact on the kidney, enabling antioxidant stress, competing with important metals such as zinc, selenium causing proteinuria, renal failure, mitochondrial impairment and apoptosis. Since chelation therapy has lethal side effects, concurrent treatment with combination therapy is favored than monotherapy, even at lower dosages. For its effectiveness and safety, drug delivery using nanoparticles is now being regarded as a potential successor to traditional therapies. Several encapsulation techniques have been used in recent years to transform liquid components into solid particles and give a method for their controlled release (Mandžuka & Knez, 2008) [48]. Supercritical fluids-based techniques have been shown to effectively boost the durability of bioformulative substances and medicines, with expected rise in their usage in near future (Fan & Anikeev, 2013) [20]. Nutritional factors are important for combating free radicals and enhancing arsenic methylation. A proper daily routine and the usage of nutritional additives like minerals and vitamins can help prevent arsenicosis-related damage and protect against chronic exposure. With further research and clinical trials, vitamins and minerals, as well as a powerful antioxidant generated from plants, may be utilized to treat acute exposure. Antioxidants found in plants and other supplements may play an important role in developing a novel treatment for heavy metal toxicity.

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Conflict of Interest
The authors declare that they have no conflicts of interest concerning this article.

References
1. Acharyya N, Chattopadhyay S, Maiti S. Chemoprevention against arsenic-induced mutagenic DNA breakage and apoptotic liver damage in rat via antioxidant and SOD1 upregulation by green tea (*Camellia sinensis*) which recovers broken DNA resulted from arsenic-H2O2 related *in vitro* oxidant stress. Journal of Environmental Science and Health, Part C. 2014;32(4):338-361.
2. Adetunji O, Olugbami J, Adegoke A, Gbadegesin M, Odunola O. Reno-Hepatoprotective and antidiabetic properties of Methanol Leaf Extract of *Laportea Aestuans* in Wistar Rats. Journal of Evidence-Based Integrative Medicine; c2021. p. 26.
3. Adhikary A, Kumar R, Pandir R, Bhardwaj P, Wusirika R, Kumar S. *Pseudomonas citronellolis*; A multi-metal resistant and potential plant growth promoter against arsenic (V) stress in chickpea. Plant Physiol. Biochem. 2019;142:179-192. 10.1016/j.plaphy.2019.07.006
4. Akter M, Islam NN, Sumit AF, Ahsan N, Hossain S, Ahmed M, Akhand AA. Tea Extract prevents arsenic-mediated DNA Damage and Death of Murine Thymocytes *in vitro*. Dhaka Univ. J Pharm. Sci. 2015;14;79-85. 10.3329/dujps.v14i1.23739
5. Banerjee M, Sarma N, Biswas R, Roy J, Mukherjee A, Giri AK. DNA repair deficiency leads to susceptibility to develop arsenic-induced premalignant skin lesions. Int J Cancer. 2008;123(2):283-287. 10.1002/ijc. 23478
6. Banerjee P, Bhattacharyya SS, Bhattacharjee N. Ascorbic Acid Combats Arsenic-Induced Oxidative Stress in Mice Liver. Ecotoxicology and Environmental Safety. 2009;72(2):639-649. 10.1016/j.ecoenv. 2008.07.005
7. Barai M, Ahsan N, Paul N, Hossain K, Rashid MA, Kato M, *et al*. Amelioration of arsenic-induced toxic effects in mice by dietary supplementation of *Syzygium cumini* leaf extract. Nagoya J. Med. Sci. 2017;79:169-179. 10.18999/nagjms.79.2.167
8. Bhardwaj P, Dhawan DK. Zinc treatment modulates hematological and morphological changes in rat erythrocytes following arsenic exposure. Toxicol Ind Health. 2019;35(9):593-603.
9. Bhattacharya S. Medicinal plants and natural products in amelioration of arsenic toxicity: A short review. Pharm Biol. 2017;55(1):349-354. 10.1080/13880209.2016.1235207
10. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organ J. 2012;5(1):9-19. 10.1097/WOX.0b013e3182439613
11. Chattopadhyay S, Deb B, Maiti S. Hepatoprotective role of vitamin B12 and folic acid in arsenic intoxicated rats. Drug and chemical toxicology. 2012;35(1):81-88.
12. Chen CL, Chiou HY, Hsu LI, Hsueh YM, Wu MM, Chen CJ, *et al*. Ingested arsenic, characteristics of well water consumption and risk of different histological types of lung cancer in northeastern Taiwan. Environ Res. 2010;110(5):455-462. 10.1016/j.envres.2009.08.010
13. Chitta KR, Landero Figueroa JA, Caruso JA, Merino EJ. Selenium mediated arsenic toxicity modifies cytotoxicity, reactive oxygen species and phosphorylated proteins. Metallomics. 2013;5(6):673-685. 10.1039/c3mt20213e
14. Cohen SM, Arnold LL, Beck BD, Lewis AS, Eldan M. Evaluation of the carcinogenicity of inorganic arsenic. Crit Rev Toxicol. 2013;43(9):711-752. 10.3109/10408444.2013.827152
15. Costa M. Review of arsenic toxicity, speciation and polyadenylation of canonical histones. Toxicol Appl Pharmacol. 2019;375:1-4. 10.1016/j.taap.2019.05.006
16. Dennis JM, Witting PK. Protective role for antioxidants in acute kidney disease. Nutrients; c2017. 10. 3390/nu9070718
17. Edis Z, Wang J, Waqas MK, Ijaz M. Nanocarriers-mediated drug delivery systems for anticancer agents: an overview and perspectives. International Journal of Nanomedicine. 2021;16:1313.
18. Ellinsworth DC. Arsenic, reactive oxygen, and endothelial dysfunction. J Pharmacol Exp Ther. 2015;353(3):458-464. 10.1124/jpet.115.223289
19. Fakiha F, Faraz ZM, Ehraz A, Masood A, Mohammad A. Ellagic acid attenuates arsenic induced neuro-inflammation and mitochondrial dysfunction associated apoptosis. Toxicology Reports. 2018;5:411-417. 10.1016/j.toxrep.2018.02.017
20. Fan M, Anikeev V. Supercritical Fluid Technology for Energy and Environmental Applications. Elsevier Science; c2013.
21. Garg MC, Chaudhary DP, Bansal DD. Effect of vitamin E supplementation on diabetes induced oxidative stress in experimental diabetes in rats. Indian J Exp Biol. 2005;43:177-180.
22. George VC, Kumar DR, Suresh PK, Kumar RA. *In vitro* protective potentials of *Annona muricata* leaf extracts against sodium arsenite-induced toxicity. Current Drug Discovery Technologies. 2015;12(1):59-63. 10.2174/1570163812666150602144154
23. Ghabaee D, Amiri FT, Moghaddam AE, Khalatbary AR, Zargari M. Administration of zinc against arsenic-induced nephrotoxicity during gestation and lactation in rat model. J Nephropathol. 2017;6(2):74.
24. Ghosh A, Mandal AK, Sarkar S, Panda S, Das N. Nanoencapsulation of quercetin enhances its dietary efficacy in combating arsenic-induced oxidative damage in liver and brain of rats. Life Sci. 2009;84(3-4):75-80. 10.1016/j.lfs.2008.11.001
25. Ghosh J, Das J, Manna P, Sil PC. Taurine prevents arsenic-induced cardiac oxidative stress and apoptotic damage: Role of NF-kappa B, p38 and JNK MAPK pathway. Toxicol Appl Pharmacol. 2009;240(1):73-87. 10.1016/j.taap.2009.07.008
26. Ghosh PK, Maiti TK, Pramanik K, Ghosh SK, Mitra S, De TK. The role of arsenic resistant *Bacillus aryabhattai* MCC3374 in promotion of rice seedlings growth and alleviation of arsenic phytotoxicity.

Chemosphere. 2018;211:407-419. 10.1016/j.chemosphere.2018.07.148
27. Ghosh S, Dungdung SR, Chowdhury ST, Mandal AK, Sarkar S, Ghosh D, *et al*. Encapsulation of the flavonoid quercetin with an arsenic chelator into nanocapsules enables the simultaneous delivery of hydrophobic and hydrophilic drugs with a synergistic effect against chronic arsenic accumulation and oxidative stress. Free Radical Biology and Medicine. 2011;51(10):1893-1902.
28. Hall AH. Chronic arsenic poisoning. Toxicol Let. 2002;128:69-72.
29. Ho D, Lowenstein EJ. Fowler's solution and the evolution of the use of arsenic in modern medicine. Skin med. 2016;14(4):287-289.
30. Hossain MB, Vahter M, Concha G, Broberg K. Environmental arsenic exposure and DNA methylation of the tumor suppressor gene p16 and the DNA repair gene MLH1: effect of arsenic metabolism and genotype. Metallomics. 2012;11:1167-1175. 10.1039/c2mt20120h
31. Hughes MF, Beck BD, Chen Y, Lewis AS, Thomas DJ. Arsenic exposure and toxicology: A historical perspective. Toxicol Sci. 2011;123(2):305-332. 10.1093/toxsci/kfr184
32. Jahangirnejad R, Goudarzi M, Kalantari H, Najafzadeh H, Rezaei M. Subcellular organelle toxicity caused by arsenic nanoparticles in isolated rat hepatocytes. *The* International Journal of Occupational and Environmental Medicine. 2020;11(1):41.
33. Jalaludeen AM, Ha WT, Lee R, Kim JH, Do JT, Park C, *et al*. Biochanin A ameliorates arsenic-Induced Hepato- and Hematotoxicity in Rats. Molecules. 2016;21(1):69. 10.3390/molecules21010 069
34. Jalaludeen AM, Lee WY, Kim JH, Jeong HY, Ki KS, Kwon EG, *et al*. Therapeutic efficacy of Biochanin A against arsenic-induced renal and cardiac damage in rats. Environ Toxicol Pharmacol. 2015;39(3):1221-1231. 10.1016/j. etap.2015.04.020
35. Jang YC, Somanna Y, Kim H. Source, distribution, toxicity and remediation of arsenic in the environment - a review. Int. J. Appl. Environ. Sci. 2016. p. 973-6077.
36. Kadirvel R, Sundaram K, Mani S, Samuel S, Elango N, Panneerselvam C. Supplementation of ascorbic acid and alpha-tocopherol prevents arsenic-induced protein oxidation and DNA damage induced by arsenic in rats. Hum Exp Toxicol. 2007;26:939-946.
37. Kelsey KT, Hirao T, Hirao S, Devi Ashok T, Nelson HH, *et al*. TP53 alterations and patterns of carcinogen exposure in a U.S. population-based study of bladder cancer. Int J Cancer. 2005;117(3):370-375. 10.1002/ijc.21195
38. Kesari VP, Kumar A, Khan PK. Genotoxic potential of arsenic at its reference dose. Ecotoxicol Environ Saf. 2012;80;126-131. 10.1016/j.ecoenv.2012.02.018
39. Klaassen CD, Gilman AG, Raw TW, Nies AS, Taylor P. Heavy metals and heavy-metal antagonist. *The* pharmacological basis of therapeutics, McGraw-Hill, New York; c1996. p. 1592-1614.
40. Kuivenhoven M, Mason K. Arsenic Toxicity. In Stat Pearls, Stat Pearls Publishing; c2022.
41. Kumar A, Malhotra A, Nair P, Garg M, Dhawan DK. Protective role of zinc in ameliorating arsenic-induced oxidative stress and histological changes in rat liver. J Environ Pathol Toxicol Oncol. 2010;29;91-100.
42. Kumar KP, Paul W, Sharma CP. Green synthesis of gold nanoparticles with Zingiber officinale extract: characterization and blood compatibility. Process Biochem. 2011;46:2007-2013.
43. Kumar N, Gupta SK, Chandan NK, Bhushan S, Singh DK, Kumar P, *et al*. Mitigation potential of selenium nanoparticles and riboflavin against arsenic and elevated temperature stress in Pangasianodon hypophthalmus. Scientific Reports. 2020;10(1):1-17.
44. Kumazaki M, Ando H, Sasaki A, Koshimizu TA, Ushijima K, Hosohata K, *et al*. Protective effect of α-Lipoic Acid Against Arsenic Trioxide-Induced Acute Cardiac Toxicity in Rats. J Pharmacol Sci. 2011;115(2):244-248. 10.1254/jphs.10280SC
45. Le XC, Lu X, Ma M, Cullen WR, Aposhian HV, Zheng B, *et al*. Speciation of key arsenic metabolic intermediates in human urine. Anal Chem. 2000;72(21):5172-5177. 1S0.1021/ac000527u
46. Liu SX, Athar M, Lippai I, Waldren C, Hei TK. Induction of oxyradicals by arsenic: implication for mechanism of genotoxicity. Proc Natl Acad Sci USA. 2001;98:1643-1648. 10.1073/pnas.98.4.1643
47. Maiti S, Chattopadhyay S, Acharyya N, Deb B, Hati AK. *Emblica officinalis* (amla) ameliorates arsenic-induced liver damage via DNA protection by antioxidant systems. Molecular & Cellular Toxicology. 2014;10(1):75-82.
48. Mandžuka Z, Knez Ž. Influence of temperature and pressure during PGSS™ micronization and storage time on degree of crystallinity and crystal forms of monostearate and tristearate. J Supercrit. Fluids. 2008;45:102-111.
49. Mao K, Zhang H, Wang Z, Cao H, Zhang K, Li X, *et al*. Nanomaterial-based aptamer sensors for arsenic detection. Biosensors and Bioelectronics. 2020;148:111785.
50. Mashkoor J, Khan A, Khan MZ, Abbas RZ, Saleemi MK, Mahmood F. Arsenic induced clinic-hemato-pathological alterations in broilers and its attenuation by vitamin E and selenium. Pak J Agric Sci. 2013;50:131-138.
51. Mehrandish R, Rahimian A, Shahriary A. Heavy metals detoxification: a review of herbal compounds for chelation therapy in heavy metals toxicity. J Herbmed Pharmacol. 2019;8(2):69-77. 10.15171/jhp.2019.12
52. Messarah M, Saoudi M, Boumendjel A, Kadeche L, Boulakoud MS, El Feki A, *et al*. Green tea extract alleviates arsenic-induced biochemical toxicity and lipid peroxidation in rats. Toxicol Ind Health. 2013;29(4):349-359. 10.1177/0748233711433934
53. Milton Prabu S, Muthumani M. Silibinin ameliorates arsenic induced nephrotoxicity by abrogation of oxidative stress, inflammation and apoptosis in rats. Mol. Biol. Rep. 2012;39:11201-11216. 10.1007/s11033-012-2029-6
54. Mishra D, Gupta R, Pant SC, Kushwah P, Satish HT, Flora S. Co-administration of monoisoamyl dimercapto-succinic acid and *Moringa oleifera* seed powder protects arsenic-induced oxidative stress and metal distribution in mice. Toxicology mechanisms and methods. 2009;19(2):169-182.

55. Mochizuki H. Arsenic neurotoxicity in humans. Int. J. Mol. Sci. 2019;20(14):3418. 10.3390/ijms20143418
56. Mohanta RK, Garg AK, Dass RS. Effect of vitamin E supplementation on arsenic induced alteration in blood biochemical profile, oxidant/antioxidant status, serum cortisol level and retention of arsenic and selenium in goats. Journal of Trace Elements in Medicine and Biology. 2015;29:188-194. 10.1016/j.jtemb.2014.08.013
57. Momeni HR, Oryan S, Eskandari N. Effect of vitamin E on sperm number and testis histopathology of sodium arsenite-treated rats. Reproductive biology. 2012;12(2):171-181.
58. Mondal S, Das S, Mahapatra PK, Saha KD. Morin encapsulated chitosan nanoparticles (MCNPs) ameliorate arsenic induced liver damage through improvement of the antioxidant system and prevention of apoptosis and inflammation in mice. Nanoscale Advances. 2022;4(13):2857-2872.
59. Mukherjee S, Das D, Mukherjee M, Das AS, Mitra C. Synergistic effect of folic acid and vitamin B12 in ameliorating arsenic-induced oxidative damage in pancreatic tissue of rat. J Nutr Biochem. 2006;17:319-327.
60. Nag S, Manna K, Saha M, Das Saha K. Tannic acid and vitamin E loaded PLGA nanoparticles ameliorate hepatic injury in a chronic alcoholic liver damage model via EGFR-AKT-STAT3 pathway. Nanomedicine (Lond). 2020;15(3):235-257. 10.2217/nnm-2019-0340
61. Pace C, Dagda R, Angermann J. Antioxidants Protect against Arsenic Induced Mitochondrial Cardio-Toxicity. Cardio-Toxicity. Toxics. 2017;5(4):38. 10.3390/toxics5040038
62. Pandey N, Bhatt R. Role of soil associated Exiguobacterium in reducing arsenic toxicity and promoting plant growth in Vigna radiata. Eur. J. Soil Biol. 2016;75:142-150. 10.1016/j.ejsobi.2016.05.007
63. Pillai P, Dharaskar S. Arsenic Removal Using Nanoparticles from Groundwater: A Review. Handbook of Solid Waste Management: Sustainability through Circular Economy; c2020. p. 1-15.
64. Prasad KS, Selvaraj K. Biogenic synthesis of selenium nanoparticles and their effect on As (III)-induced toxicity on human lymphocytes. Biological trace element research. 2014;157(3):275-283.
65. Qamar N, Rehman Y, Hasnain S. Arsenic-resistant and plant growth-promoting Firmicutes and γ-Proteobacteria species from industrially polluted irrigation water and corresponding cropland. J Appl. Microbiol. 2017;123(3):748-758. 10.1111/jam.13535
66. Rahman Md. Shahedur, Mostofa JAMH, Kumar BP, Mizanur RS, Priya SS, Kumar SS, *et al*. Arsenic Remediation in Bangladeshi Rice Varieties with Enhance Plant Growth by Unique Arsenic-Resistant Bacterial Isolates. Geomicrobiology Journal; c2019. p. 1–13. doi:10.1080/01490451.2019.1666938
67. Robles-Osorio M, Sabath-Silva E, Sabath E. Arsenic-mediated nephrotoxicity. Ren Fail. 2015;37(4):542-547. 10.3109/0886022X.2015.1013419
68. Rodríguez VM, Jiménez-Capdeville M, Giordano M. The effects of arsenic exposure on the nervous system. Toxicol Lett. 2003;145(1):1-18. 10.1016/s0378-4274(03)00262-5
69. Rosales M, Garcia A, Fuenzalida VM, Espinoza-González R, Song G, Wang B, *et al*. Unprecedented arsenic photo-oxidation behavior of few-and multi-layer Ti3C2Tx nano-sheets. Applied Materials Today. 2020;20:100769.
70. Samadder A, Das J, Das S, De A, Saha SK, Bhattacharyya SS, *et al*. Poly (lactic-co-glycolic) acid loaded nano-insulin has greater potentials of combating arsenic induced hyperglycemia in mice: some novel findings. Toxicol Appl Pharmacol. 2013;267(1):57-73. 10.1016/j.taap.2012.12.018
71. Samadder A, Das J, Das S, Khudabukhsh A. Dihydroxy-isosteviol-methyl-ester, an active biological component of *Pulsatilla nigricans*, reduces arsenic induced cellular dysfunction in testis of male mice. Environmental Toxicology and Pharmacology. 2012a;34(3), 743-752.
72. Samadder A, Das S, Das J, Paul A, Khuda-Bukhsh A. Ameliorative Effects of *Syzygium jambolanum* extract and its Poly (lactic-co-glycolic) Acid Nano-encapsulated Form on Arsenic-induced hyper- glycemic Stress: A Multi-parametric Evaluation. Journal of Acupuncture and Meridian Studies. 2012b;5(6):310-318. 10.1016/j.jams.2012.09.001
73. Sampayo-Reyes A, Tamez-Guerra RS, Bermudez de Leon M, Vargas-Villarreal J, Lozano-Garza HG, Rodriguez-Padilla C, *et al*. Tocopherol and selenite modulate the transplacental effects induced by sodium arsenite in hamsters. Reprod Toxicol. 2017;74:204-211. 10.1016/j.reprotox.2017.10.003
74. Sankar P, Gopal Telang A, Kalaivanan R, Karunakaran, V, Manikam K, Sarkar SN. Effects of nanoparticle-encapsulated curcumin on arsenic-induced liver toxicity in rats. Environmental toxicology. 2015;30(6):628-637.
75. Sankar P, Telang AG, Kalaivanan R, Karunakaran V, Suresh S, Kesavan M. Oral nanoparticle curcumin combating arsenic-induced oxidative damage in kidney and brain of rats. Toxicology and Industrial Health. 2013;32(3):410-421. 10.1177/0748233713498455
76. Sankar P, Telang AG, Ramya K, Vijayakaran K, Kesavan M, Sarkar SN. Protective action of curcumin and nano-curcumin against arsenic-induced genotoxicity in rats in vivo. Mol Biol Rep. 2014;41:7413-7422. 10.1007/s11033-014-3629-0
77. Sayed S, Ahsan N, Kato M, Ohgami N, Rashid A, Akhand AA. Protective effects of *phyllanthus emblica* leaf extract on sodium arsenite-mediated adverse effects in mice. Nagoya J. Med. Sci. 2015;77:145-153.
78. Sharma A, Sharma MK, Kumar M. Protective effect of Mentha piperita against arsenic induced toxicity in the liver of Swiss Albino mice. Basic & clinical pharmacology & toxicology. 2007;100(4):249-257.
79. Singh S, Rana S. Ascorbic acid improves mitochondrial function in the liver of arsenic-treated rat. Toxicol Ind Health. 2010;26(5):265-272.
80. Sinha M, Manna P, Sil PC. Arjunolic acid attenuates arsenic induced nephrotoxicity. Pathophysiology. 2008;15:147-156. 10.1016/j.pathophys.2008.03.001
81. Susan A, Rajendran K, Sathyasivam K, Krishnan UM. An overview of plant-based interventions to ameliorate arsenic toxicity. Biomed Pharmacother. 2019;109:838-852. 10.1016/j.biopha.2018.10.099

82. Thangapandiyan S, Ramesh M, Miltonprabu S, Hema T, Jothi GB, Nandhini V. Sulforaphane potentially attenuates arsenic-induced nephrotoxicity via the PI3K/Akt/Nrf2 pathway in albino Wistar rats. Environ Sci Pollut Res Int. 2019;26(12):12247-12263. 10.1007/s11356-019-04502-w
83. Varghese MV, Abhilash M, Paul MV, Alex M, Nair RH. Omega-3 Fatty Acid protects against arsenic trioxide-Induced Cardiotoxicity *In vitro* and In vivo. Cardiovasc Toxicol. 2017;2:109-119. 10.1007/s12012-016-9361-3
84. Waalkes MP, Liu J, Ward JM, Diwan BA. Mechanisms underlying arsenic carcinogenesis: hypersensitivity of mice exposed to inorganic arsenic during gestation. Toxicology. 2004;198:31-38. 10.1016/ j.tox.2004.01.017
85. Wang X, Nie Y, Si B, Wang T, Hei TK, Du H, *et al*. Silver nanoparticles protect against arsenic induced genotoxicity via attenuating arsenic bioaccumulation and elevating antioxidation in mammalian cells. Journal of Hazardous Materials. 2021;413:125287.
86. Yadav A, Lomash V, Samim M, Flora S. Curcumin encapsulated in chitosan nanoparticles: a novel strategy for the treatment of arsenic toxicity. Chemico-Biological Interactions. 2012;199(1):49-61.
87. Yang HC, Rosen BP. New mechanisms of bacterial arsenic resistance. Biomedical journal. 2016;39(1):5-13.
88. Zhao H, Wang Y, Yang X, Fei D, Mu M, Guo M, *et al*. Zinc alleviates arsenism in common carp: varied change profiles of cytokines and tight junction proteins among two intestinal segments. Fish Shellfish Immunol. 2019;94:761-768. 10.1016/j.fsi.2019.09.069
89. Zhao X, Zhou W, Jian-Jun L, Chen C, Ping-Chuan Z, Lu D, *et al*. Protective effects of selenium on oxidative damage and oxidative stress related gene expression in rat liver under chronic poisoning of arsenic. Food and Chemical Toxicology. 2013;58:1-7. 10.1016/j.fct.2013.03.048
90. Zubair M, Ahmad M, Saleemi MK, Gul ST, Ahmad M, Martyniuk CJ, Ullah Q, *et al*. Sodium arsenite toxicity on hematology indices and reproductive parameters in Teddy goat bucks and their amelioration with vitamin C. Environmental Science and Pollution Research, 2020;27(13):15223-15232.