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A REVIEW ARTICLE ON RECENT ADVANCEMENT IN ANTIOXIDANT AND PHYTOCONSTITUENTS FOR THE TREATMENT OF ARSENIC POISONING

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ABSTRACT
Arsenic is one of the most toxic heavy metal derived from the natural environment. The major cause of human arsenic toxicity is from contamination of drinking water from natural geological sources rather than from mining, smelting or agricultural sources (pesticides or fertilizers). Arsenic toxicity has been associated with numerous health effects affecting almost every organ system. These adverse effects have been identified to establish or facilitate various diseases manifestations. Treatment of arsenic-mediated disorders still remains a challenge due to lack of effective options. Chelating therapy has been the most widely used method to detoxify arsenic. As most of the adverse effects of arsenic arise due to induction of oxidative stress, anti oxidant therapy has emerged as an efficient strategy to counteract arsenic mediated toxic effects. It has been discovered that indigenous drugs of plant origin display effective and progressive relief from arsenic-mediated toxicity without any side-effects. Further, these phytochemicals have also been found to aid the elimination of arsenic from the biological system and therefore can be more effective than conventional therapeutic agents in ameliorating arsenic-mediated toxicity.

KEYWORDS: Arsenic, chelation, phytochemicals, Anti-Oxidant.

INTRODUCTION
The heavy metals are of great interest mainly from the toxicological point of view.[1] The most hazardous heavy metals that the human are exposed to are Arsenic. The metalloid arsenic is a natural environmental contaminant to which humans are routinely exposed in Water, air, food and soil.[2] It has been established that inorganic arsenic is extremely toxic, both acute and chronic. Initially it enters into the human body through inhalation, ingestion or skin absorption.[3]

All the heavy metals are cumulative and potentially toxic. They can cause widespread damage to various organs like the liver, the kidney and the gut.[1]

Arsenic is one of the **most toxic heavy metals** derived from the natural environment.[4] Arsenic is an element that raises much concern from both environmental and human health standpoints.[5] Arsenic is the most common causes of acute heavy metal poisoning in adults and is considered number one on the top Hazardous substances.[2]

Fig 1: Arsenic metal.

Arsenical compounds can be divided into:[1]

Inorganic arsenicals- used mainly as rodenticides, herbicides and insecticides and **Organic arsenicals** – This can be further subdivided into trivalent and pentavalent compounds.

The major cause of human arsenic toxicity is from **contamination of drinking water f**rom natural geological sources rather than mining, smelting or agricultural sources (pesticides or fertilizers). The

permissible limit of arsenic content in groundwater is 0.05mg/l.[5]

Arsenic toxicity has emerged as a global concern of prevalence especially in various Asian regions, highlighted with 130 million populations at risk in India and Bangladesh.[7]

Arsenic toxicity in the ground water has affected major parts of the Bengal basin covering Bangladesh and southern West Bengal as well as other parts of the world.[4]

The recommended limit of arsenic in potable water has been lowered to 0.01mg/l by the bureau of Indian standard.[4]

In industry arsenic is used to manufacture paints, fungicides, insecticides, pesticides, herbicides, wood preservatives and cotton desiccants. Gallium arsenide or aluminium gallium arsenide crystals are components of semiconductors, light emitting diodes, lasers and a variety of transistors.[4]

Sources of exposure

Arsenic is most commonly found in earth's crust, in the form of iron arsenide sulphide (FeAsS). It is also present in atmosphere in the form of arsenic trioxide dusts, a by-product of industrial smelting operations and through other anthropogenic activities.[7]

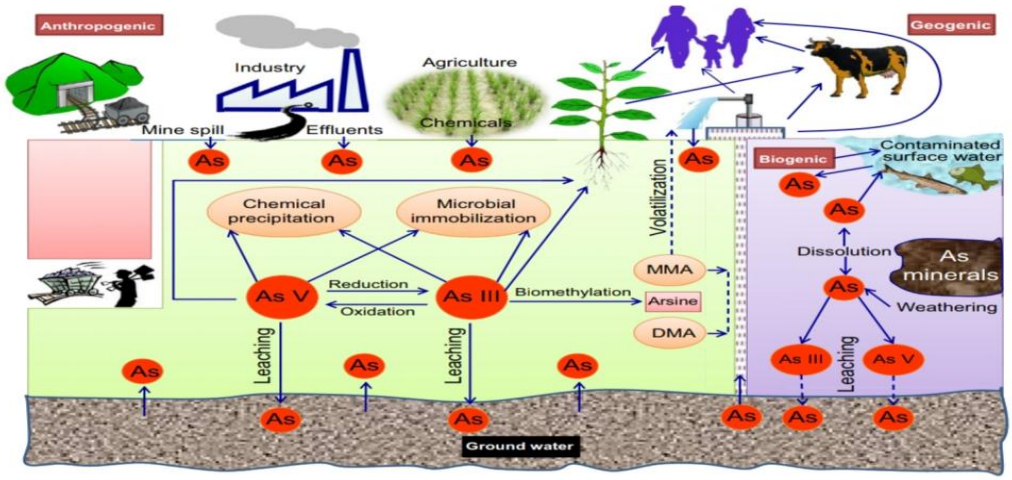


Fig –2: Various sources of exposure of arsenic in nature.

Drinking water: Exposure to contaminated drinking water by geological sources is the major causes for human toxicity rather than anthropogenic sources.[7]

Through the drinking water more than 200 million people globally are exposed to higher than safe level of arsenic. The area's most affected are **Bangladesh** and **west Bengal**. It is estimated that 6 million people in west Bengal and 25 million people in Bangladesh are exposed to arsenic – contaminated drinking water and groundwater.[8]

Food

In addition, another route of human exposure to arsenic toxicity is through dietary consumption of arsenic-contaminated food.[7] Agricultural sources like insecticides herbicides, wood preservatives, fertilizers and growth stimulants for plants and animals.[7]

Industrial processes

Arsenic is used industrially as an alloying agent, as well as in the processing of glass, pigments, textiles, paper, metal adhesives, wood preservatives and ammunition.[10]

Soil

Exposure to arsenic in soil can occur through multiple pathways. Compared with the intake of naturally occurring arsenic constitutes only a small fraction of intake.[9]

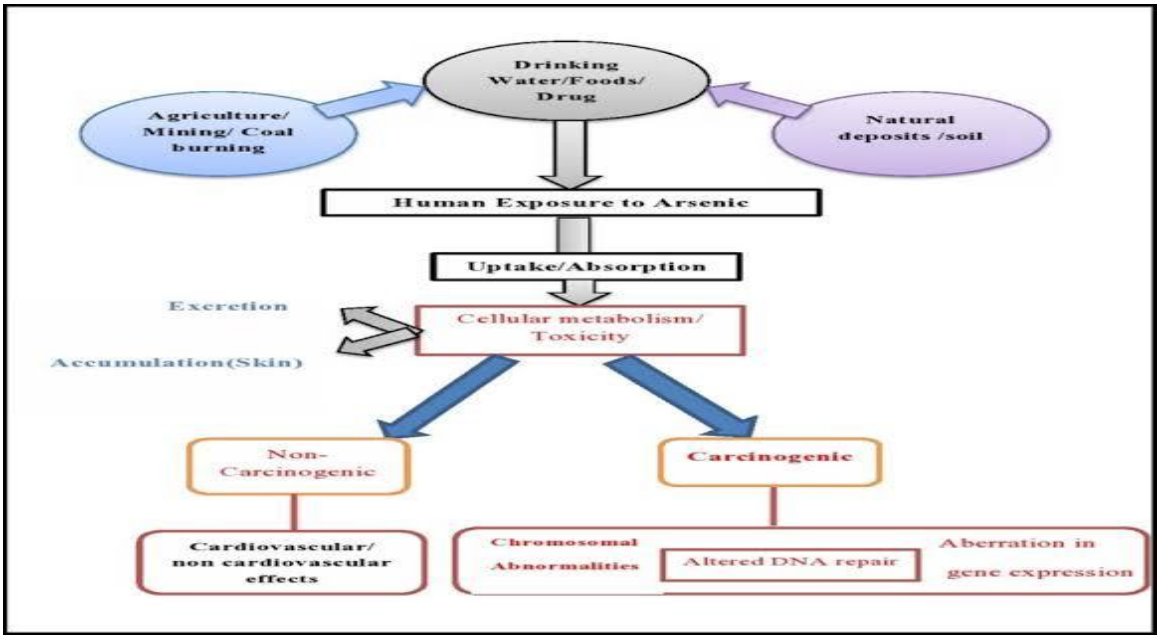


Fig-3: Sources and effect of arsenic on human.

Mechanism of action of arsenic toxicity

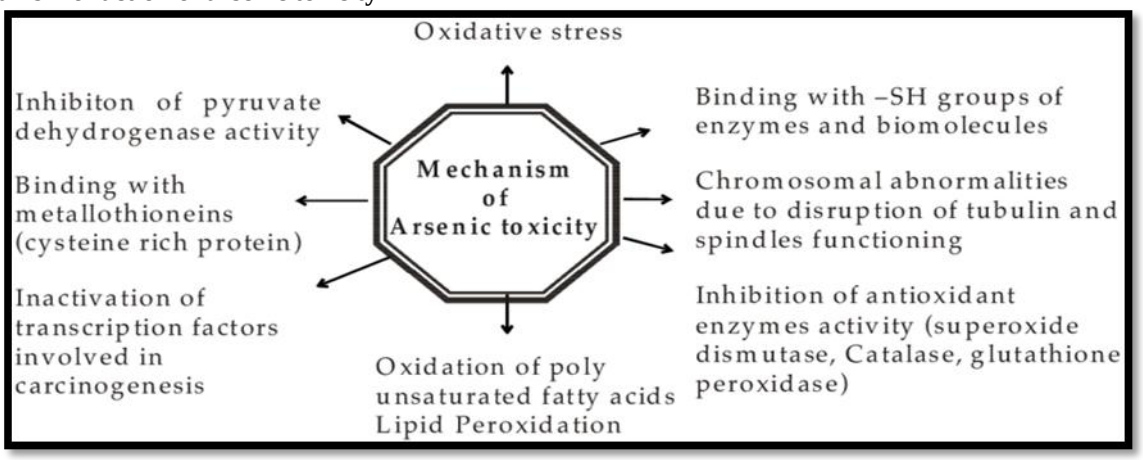


Fig - 5: Various mechanism of action of arsenic toxicity in human body.

In small pilot study of environmentally exposed children, arsenic altered monocyte superoxide anion production and inhibited nitric oxide production.[28]

Some studies report that arsenic causes gene amplification, chromosome damage, and inhibition of DNA repair as well as global DNA hypomethylation, decrease of DNA methyl transferase activity and proto oncogene activation.[11]

Oxidative stress is one of the proposed mechanisms of action for arsenic – induced toxicity and carcinogenesis. Reactive oxygen and nitrogen species are generated by several potential mechanisms in cell, animals, and humans that are exposed to arsenic. And can alter cellular redox status by depleting thiols such as glutathione and by modulating thioredoxin reductase. Also the reactive oxygen species are known to be able to alter signal transduction pathways that regulate gene expression.[12]

In an interesting paradox, arsenic trioxide (As_2O_3, a trivalent inorganic arsenical) is used therapeutically to treat acute promolytic leukemia. As_2O_3 is metabolized to mono and dimethylated arsenicals.[12]

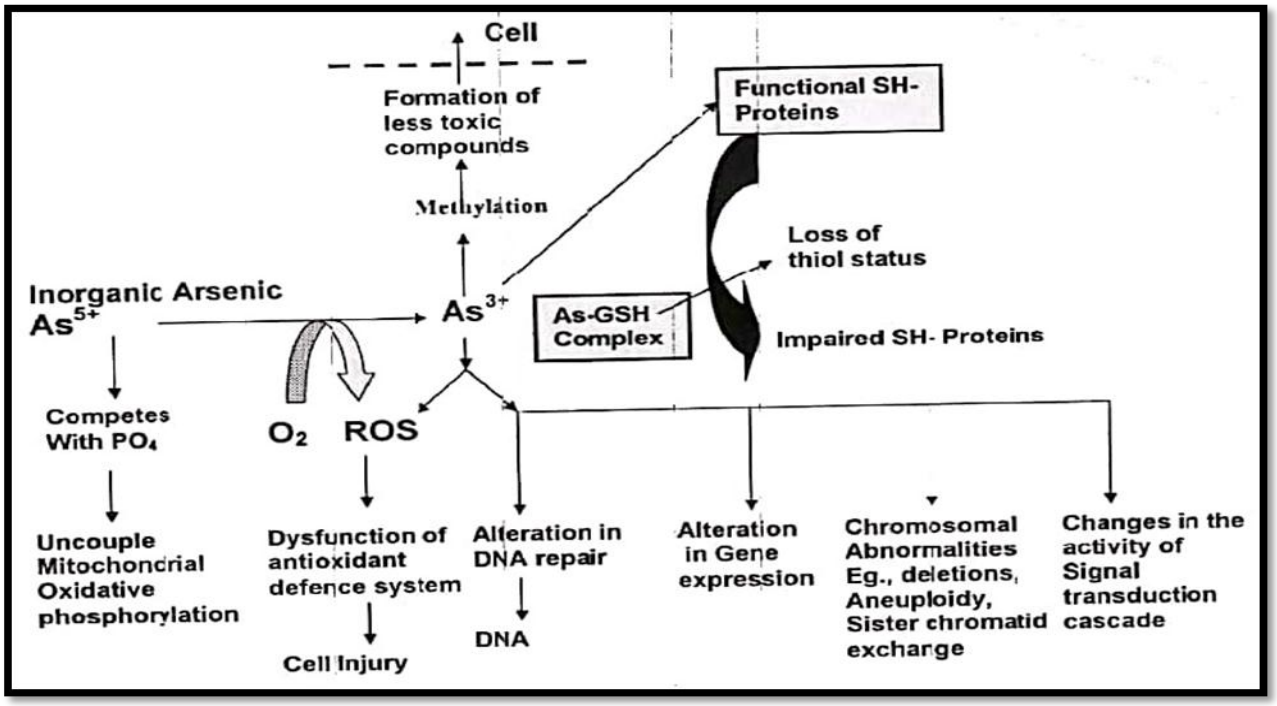


Fig – 6: Mechanism of arsenic poisoning.

Oxidative stress theory for arsenic carcinogenicity can also be explained by its ability to cause cancer at high rates in the lungs, bladder and skin. Human lungs may be an organ responsive to arsenic carcinogenesis because of high partial pressure of oxygen and the fact that demethylarsine, a gas is excreted via lungs. In addition, human bladder may be another organ responsive to arsenic carcinogenesis because of high concentration of DMA and MMA that is stored in the lumen of the bladder.[7]

Arsenic appears to inactivate endothelial nitric oxide synthase, leading to a reduction in production and bioavalaibility of nitric oxide. Chronic arsenic exposure also has been associated with inducing / accelerating atherosclerosis, increasing platelet aggregation and reducing fibrinolysis.[13]

Oxidative and nitrosative stress reduces the activities of complexes III, IV, and V of the respiratory chain, and decreases the level of ATP.[16]

Signs and symptoms

Acute arsenic poisoning

Symptoms of acute intoxication usually occurs within 30 minutes of ingestion but may be delayed if the arsenic is taken with the food.[5]

TABLE - 1

ACUTE POISONING SIGNS AND SYMPTOMS
Initially, a patient may have a metallic taste or notice a slight garlic odour associated with a dry mouth and difficulty in swallowing.[5]
Clinical features manifest in virtually all body system.
Cardiac manifestation includes acute cardiomyopathy, subendocranial haemorrhages and electrocardiographic changes.[5]
The most common changes on an electrocardiogram are prolonged QT intervals and non-specific ST- segment changes.[5]
It is also characterized by severe GI irritation, circulatory collapse and renal failure.[1]
Haematological abnormalities, respiratory failure and pulmonary oedema are common.[4]
Neurological manifestations include peripheral neuropathy or encephalopathy[4]. The peripheral neuropathy may lead to guillain- barre syndrome requiring mechanical ventilation.[5]
Drowsiness and confusion are often seen along with the development of a psychosis associated with paranoid delusions, hallucinations and delirium.[5]
Finally, seizures, coma and death usually due to shock.[5]

Chronic arsenic poisoning

Chronic arsenic poisoning is much more insidious in nature, often involving multiple hospital admission before the correct diagnosis is made.

TABLE - 2

CHRONIC ARSENIC POISONING SIGNS AND SYMPTOMS
The most prominent chronic manifestations involve the skin, lungs, liver, and blood system.
Excessive darkening of skin (hyper pigmentation) in areas that are not exposed to sunlight, exfoliative dermatitis, excessive formation of scaly skin on the palms and soles (arsenical keratosis), Arsenic- induced skin cancer (especially Dowen-disease, squamous cell carcinoma)
Transverse white bands of arsenic deposits across the bed of the fingernails (mee's lines)
Arsenic deposits in hairs
Sensory changes, numbness and tingling in a "stocking-glove" distribution (sensory peripheral neuropathy)
Headache, drowsiness, confusion.
Distal weakness of small muscles e.g. Hands and feet
Haemolytic anaemia (moderate), Leukopenia (low WBC count), Proteinuria (protein in urine), thrombocytopenia.
Peripheral vascular insufficiency
Increased risk of cancer of lung, liver, bladder, kidney and colon
Hepatic and renal damage are commonly present (multiorgan involvement)[14]
Obliterative arterial disease of the lower extremities (blackfoot disease)[14]

Toxicity of arsenic to humans

Effects of arsenic on respiratory system

Effect of arsenic on the human respiratory system has been reported from drinking water or occupational exposure source may lead to respiratory complications over time.[30]

Very high exposure to unprotected workers may manifest perforated nasal septum after 1-3 weeks of exposure[31] but such effects are minor or absent at exposure levels of 0.01-1 mg/m^3.[32] Chronic asthamatic bronchitis and asthma is a common complication of ground water arsenic toxicity.[34]

Effect of arsenic on cardiovascular system

It has been suggested by several epidemiological studies that chronic inhalation of arsenic trioxide can increase the risk of death in humans from cardiovascular disease.[35,36] Arsenic exposure results in oxidative stress resulting in decreased antioxidant mechanism causing hyper contraction in blood vessels.[15]

Effect of arsenic on hepatic system

Arsenic was the first chemical agent which liver disease was attributed in humans. Since the liver tends to accumulate arsenic with repeated exposure, hepatic involvement has been reported most commonly as a complication of chronic exposures over periods of months or years.[38] The analysis of blood sometimes shows elevated levels of hepatic enzymes.[39] On the other hand, increased activity of ROS following arsenic exposure may also induce lipid peroxidation and further causing hepatic cell damage and hepatic toxicity.[15]

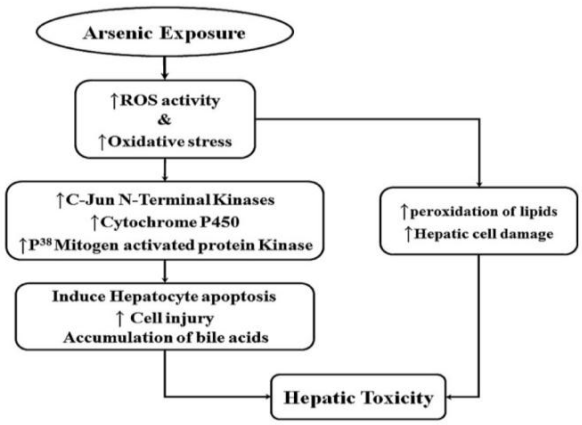


Fig – 7: Arsenic induced hepatic toxicity.

Effect of arsenic on renal system

The kidneys are the major route of arsenic excretion, as well as major site of conversion of pentavalent arsenic into the more toxic and less soluble trivalent arsenic. Site of arsenic damage in the kidney include capillaries, tubules and glomeruli.[40,16]

Mitochondrial damage is also prominent in tubular cells. Oliguria is a common manifestation, but if acute arsenic poisoning sufficiently severe to produce shock and dehydration, there is real risk of renal failure, although dialysis has been effective in overcoming this complications.[41]

Arsine-induced hemolysis is likely because tubular necrosis with partial or complete renal failure, requiring hemodialysis for removal of the haemoglobin bound arsenic.[42]

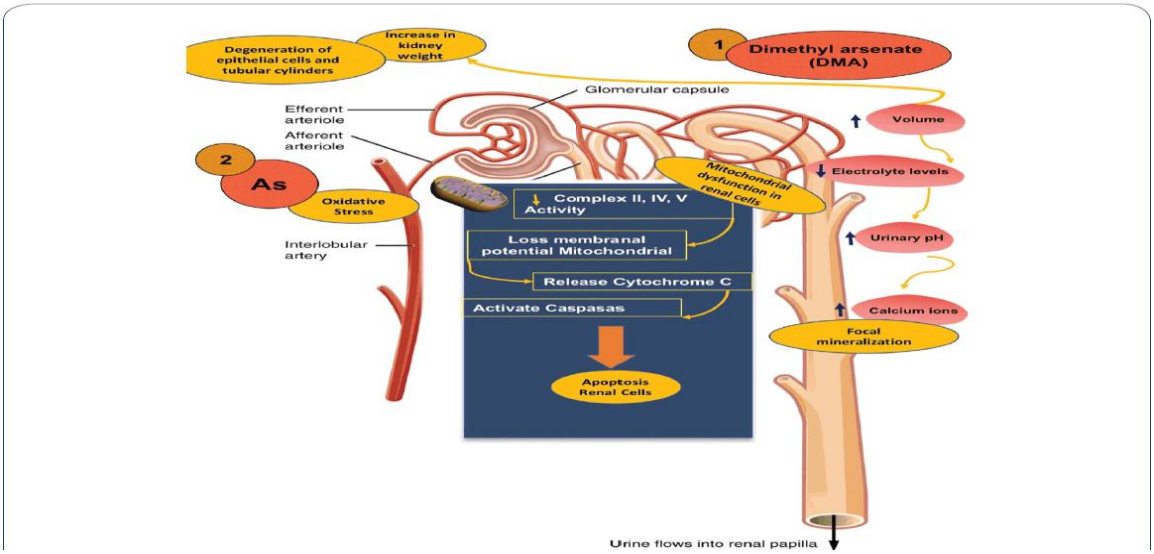


Fig – 8: Effect of arsenic on renal system.

Effect of arsenic on hematopoietic system

Anaemia and leukopenia are common effects of poisoning and have been reported as resulting from acute and chronic oral exposures.[43]

These effects may be due to a direct haemolytic or cytotoxic effect on the blood cells[44] and a suppression of erythopoies.[45] Relatively high doses of arsenic have been reported to cause bone marrow depression in humans.[46] Majority of the arsenic primarily binds to haemoglobin and accumulates in the erythrocytes inducing hemolysis.[49] Anaemia is one of the most common symptoms in arsenic exposed population.[50] Morphological changes in erythrocytes could affect microcirculation and capable of developing circulatory disorders, extensively elucidates various mechanism involved in chronic arsenic induced erythrophagocytosis and hemolysis.[51]

Carcinogenic effect

One of the most severe adverse manifestations of chronic arsenic poisoning appears to be cancer.[82]Arsenic-induced cancer has been extensively investigated and oxidative stress appears to be one of the most convincing mechanism underlying the etiology and progression of disease.[5]

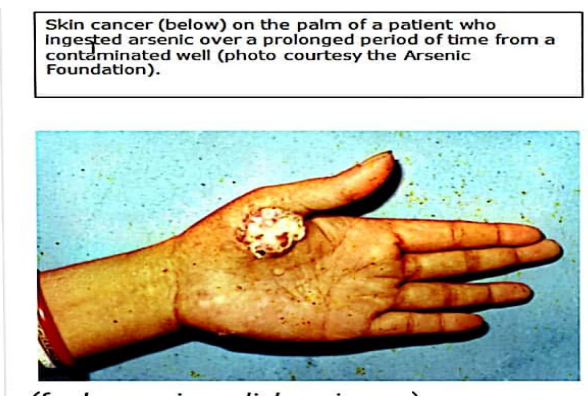


Fig – 9: Arsenic induced skin cancer.

Dermatological effect

Dermatological changes are a common feature and the initial clinical diagnosis is often based on hyperpigmentation, palmar and solar keratosis.

The keratosis may appear as a uniform thickening or as discrete nodules.[47] It is emphasized that both palmar and solar keratosis are a significant diagnostic criterion. Hyperpigmentation occurs as diffuse dark brown spots, or less discrete diffuse darkening of the skin, or has a characteristic "rain drop" appearance.[47]

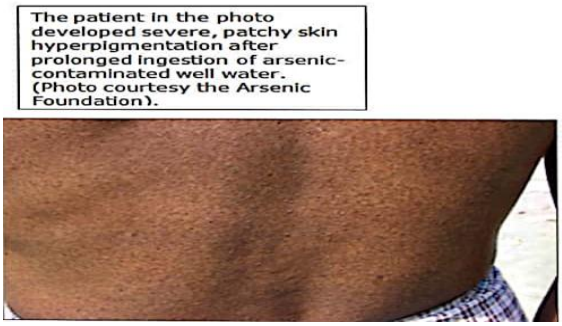
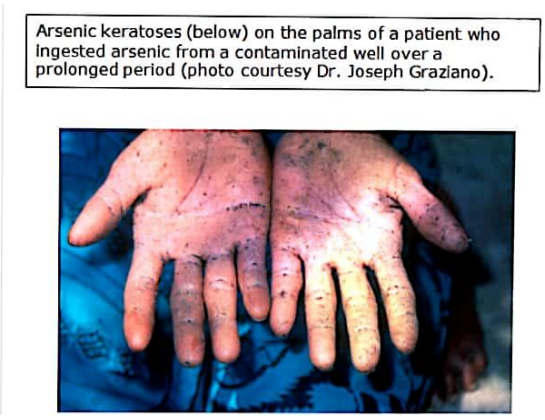


Fig – 10: Patchy skin hyper pigmentation.



Fig– 11: Arsenic Keratosis on the palm.

Another manifestation due to arsenic deposition in keratin- rich areas are prominent transverse white lines in the finger- nails and toenails called **Mee's lines**[5]

Fig – 12: Mee's line due to arsenic deposition.

Diagnosis of arsenic poisoning

Analyses of blood, urine, and hair samples are used to quantify and monitor exposure. Levels between 0.1 and 0.5 mg/kg on a hair sample indicate chronic poisoning while 1.0 to 3.0 mg/kg indicates acute poisoning.[5]

However the diagnosis of arsenic toxicity has two stages:[14]

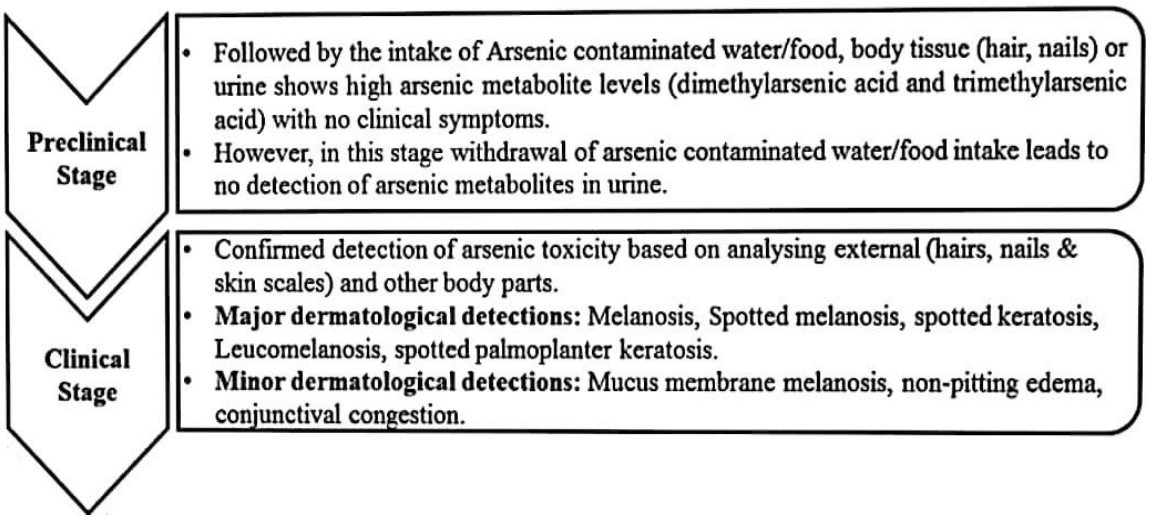


Fig – 13: Stages of arsenic poison diagnosis.

Laboratory testing

Complete blood count: Microcytic hypochromic anemia is common; with arsine exposure, acute hemolytic anemia is common.

Urine analysis: Urine spot test for arsenic and 24-hour urine collection for total arsenic excretion; patient must not have consumed seafood for at least 3 days prior to urine collection; laboratory must "speciate" the arsenic into organic and inorganic moieties, because the inorganic form is responsible for symptoms and signs of arsenic toxicity.[14]

Urine pregnancy test[14]

Serum acetaminophen levels[14]

Other studies

Abdominal x-ray: May reveal radio-opaque densities; may resemble an upper GI series[14]

Nerve conduction studies: May confirm peripheral neuropathy[14]

Electrocardiography: May reveal cardiac arrhythmias/failure from arsenic toxicity[14]

Management of arsenic poisoning

Supportive care

It is the most important aspect of the management of poisoned patients.[52] The initial management of the patient should be on the basis of (ABCD's) of the poisoning treatment which include;[17]

- **A**irway support
- **B**reathing
- **C**irculation
- **D**efinitive chelation therapy

Pharmacotherapy

Once the diagnosis of arsenic toxicity is confirmed and once the source is determined and eliminated, treatment is considered. The aim of treatment is relief of symptoms, reduction of body stores of arsenic and reduction of the complications, particularly dermatitis, neuropathy, BFD, hepatic toxicity and cancer. The earlier the treatment is started, the better is the result. Chelating therapy is specific for arsenic toxicity.

Chelation therapy

Chelation is the formation of a metal ion complex in which the metal ion is associated with a charged or uncharged electron donor referred to as ligand. Chelators act according to a general principle: the chelator form a complex with the respective (toxic) ion and these complexes reveal a lower toxicity and more easily eliminated from the body

Various types of chelators used in arsenic poisoning

The following are the agents used for the chelation of arsenic[53]

- Dimercaprol (BAL- British anti-lewisite)
- Succimer (DMSA- Dimercaptosuccinic acid)
- Dimerval (DMPS – Dimercaptopropane sulphonate)

British anti-lewisite (bal)

2,3 – Dimercaprol or British anti-lewisite (BAL) was one of the first chelating agents to be developed as an antidote for war gas dichlorovinyl arsine (Lewisite) during the second world war. In the early eighties it was shown that some newer complexing agents like 2, 3-dimercaptopropane 1-sulfonate (DMPS) and meso 2, 3-dimercaptosuccinic acid (DMSA) were effective against arsenic poisoning. When compared to BAL these newer chelating agents were of significant lower toxicity and moreover they could be administered orally or intravenously.[48]

2.3 Dimercaptopropane –1 – Suplphonate (DMPS)

DMPS was first introduced in Soviet Union in the 1950s as 'Unithiol'. DMPS is mainly distributed in the extra cellular space; it may enter cells by specific transport mechanism.[18] DMPA appears to have the appropriate chelating property that forms the complexes with various heavy metals including the arsenic and hence reduces the toxicity.[19]

2.3 Dimercaptosuccinic acid

DMSA has been tried successfully in animal as well as in few cases of human arsenic poisoning. DMSA has been shown to protect mice due to lethal effects of arsenic. Patients treated with 30 mg/kg DMSA per day for 5 days showed significant increase in arsenic excretion and a marked clinical improvement. Number of other studies appeared in the recent past have recommended that DMSA could be safe and effective for treating arsenic poisoning.[48]

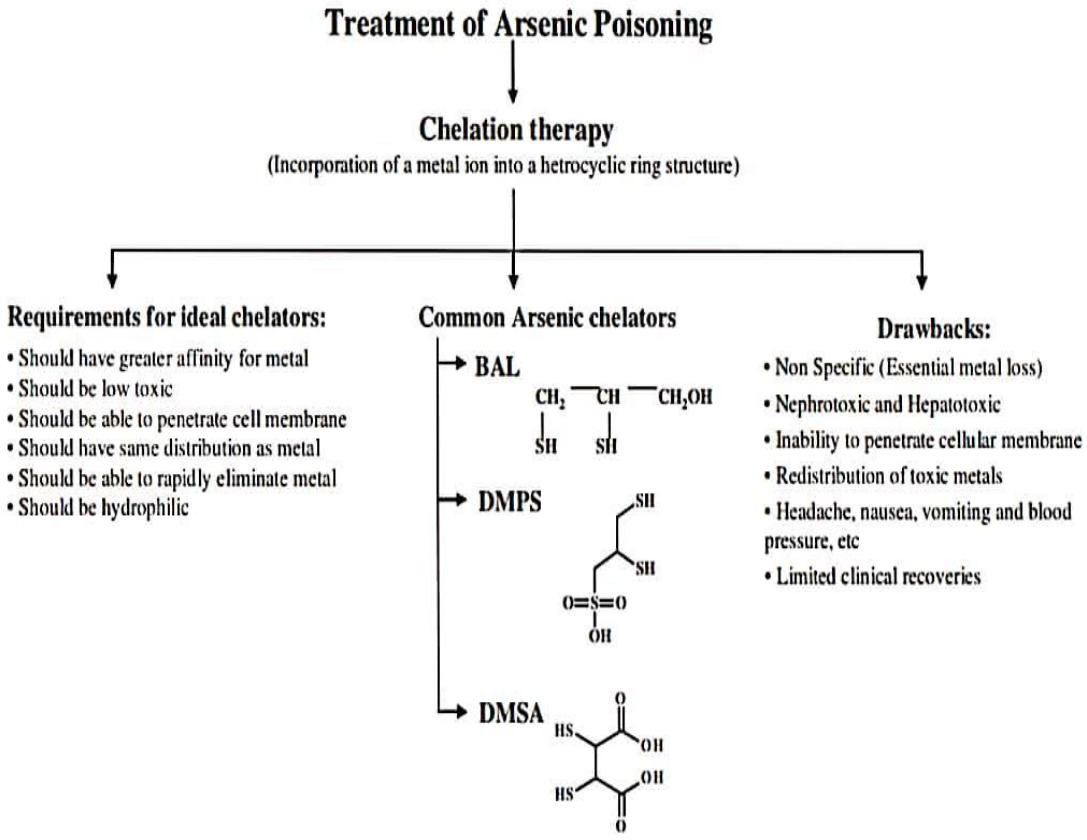


Fig – 14: Treatment of arsenic poisoning by chelation therapy.

Combination therapy

Monoisoamyl meso – 2,3 – Dimercaptosuccinic acid

A new trend in chelation therapy has emerged recently, which is to use of combination therapy with more than one chelating agent instead of mono therapy. It was observed that optimum effects of chelation therapy could be achieved by combined administration of DMSA and MiADMSA. It is evident from above that combination therapy is a new and a better approach to treat cases of metal poisoning.[6]

The metal chelators are given to increase the excretion of arsenic but unfortunately use of these chelators is comprised by number of drawbacks. These drawbacks open the search for new treatment which has no side effects and maximum clinical recovery in terms of altered biochemical variables because the total elimination of metals from the environment is not feasible.[6]

Recent advances in combination therapy with antioxidants

As most of the adverse effects of arsenic arise due to induction of oxidative stress, anti oxidant therapy has emerged as an efficient strategy to counteract arsenic mediated toxic effects. As arsenic affects the intracellular anti-oxidant machinery, exogenous supplementation of anti oxidants can counter the pro oxidant stress induced by arsenic.[54]

The most commonly used antioxidant which are used in the treatment of arsenic poisoning are as follows:

N-Acetyl cysteine (NAC): NAC is a thiol, a mucolytic agent and a precursor of L-cysteine and reduced glutathione. NAC is a source of sulphydryl containing antioxidant that has been used to mitigate various conditions of oxidative stress. Combined administration of NAC and succimer post arsenic exposure led to a significant turnover in variables indicative of oxidative stress and removal of arsenic from soft organs.[55]

Melatonin: Melatonin, N-acetyl-5-methoxy tryptamine, is a hormonal product of the pineal gland that plays many roles within the body. One major function of melatonin is to scavenge radicals formed in oxygen metabolism, thereby potentially protecting against free radical induced damage to DNA, proteins and membranes.[55]

Melatonin is found in mammals as well as in fruits, vegetables and grains have been found to scavenge free radicals and promote synthesis of glutathione peroxidase enzyme to counter the oxidative stress in brain tissue of arsenic administered animals.[56]

Vitamin E (α-tocopherol) and vitamin C: Various vitamins have been found to reduce the toxic manifestation of heavy metals. **Vitamin E**, which is a low molecular mass antioxidant, interacts directly with the oxidizing radicals and protects the cells from reactive oxygen species.[55]

Vitamin E supplementation alleviated the toxic effects caused by arsenic on serum alanine aminotransferase, aspartate aminotransferase and lipid peroxidation. It also prevented the depletion of reduced glutathione content and reduction in activity of catalase, superoxide dismutase and glutathione-s-transferase in erythrocytes resulted from arsenic intoxication.[20]

Vitamin C is a low molecular mass antioxidant that interacts directly with the oxidizing radicals and protects the cells from reactive oxygen species. Vitamin C scavenges the aqueous reactive oxygen species (ROS) by very rapid electron transfer that thus inhibits lipid peroxidation. administration of vitamin C or vitamin E when given in combination with succimer or its monoisoamyl derivative (MiADMSA) produced profound recoveries in sub chronically arsenic exposed rats.[55]

The anti-oxidant nature of **vitamin E** and its localization in the membrane that tends to reduce **membrane fluidity** and **lipid peroxidation** have been cited as major reasons for its therapeutic benefits[57]. The dual benefits of free radical scavenging and metal ion chelation have been attributed to the positive effects of vitamin C against arsenic-mediated toxicity.[58]

Taurine: a sulfur containing amino acid found in the biological system has been reported to ameliorate arsenic-mediated toxicity through scavenging free radicals and protecting the membrane from ROS-mediated damage by intercalating within the membrane bilayer.[57] Curcumin in the nanoparticulate form has demonstrated superior amelioration of arsenic-induced toxicity owing to its powerful anti- oxidant nature.

α – Lipoic acid (LA): It is a naturally occurring antioxidant and it functions as a cofactor in several multienzyme complexes. Its reduced form is dihydrolipoic acid (DHLA), has conatins two free sulfhydryl groups and the two forms LA/DHLA possess a great antioxidant potential. Both LA/DHLA have the ability to scavange some reactive species, can regenerate other antioxidant i.e. GSH, vitamin-C and vitamin-E and have metal chelating activity. Lipoic acid has been successfully used as an antidote in intoxication with arsenicals and mercurial.[55]

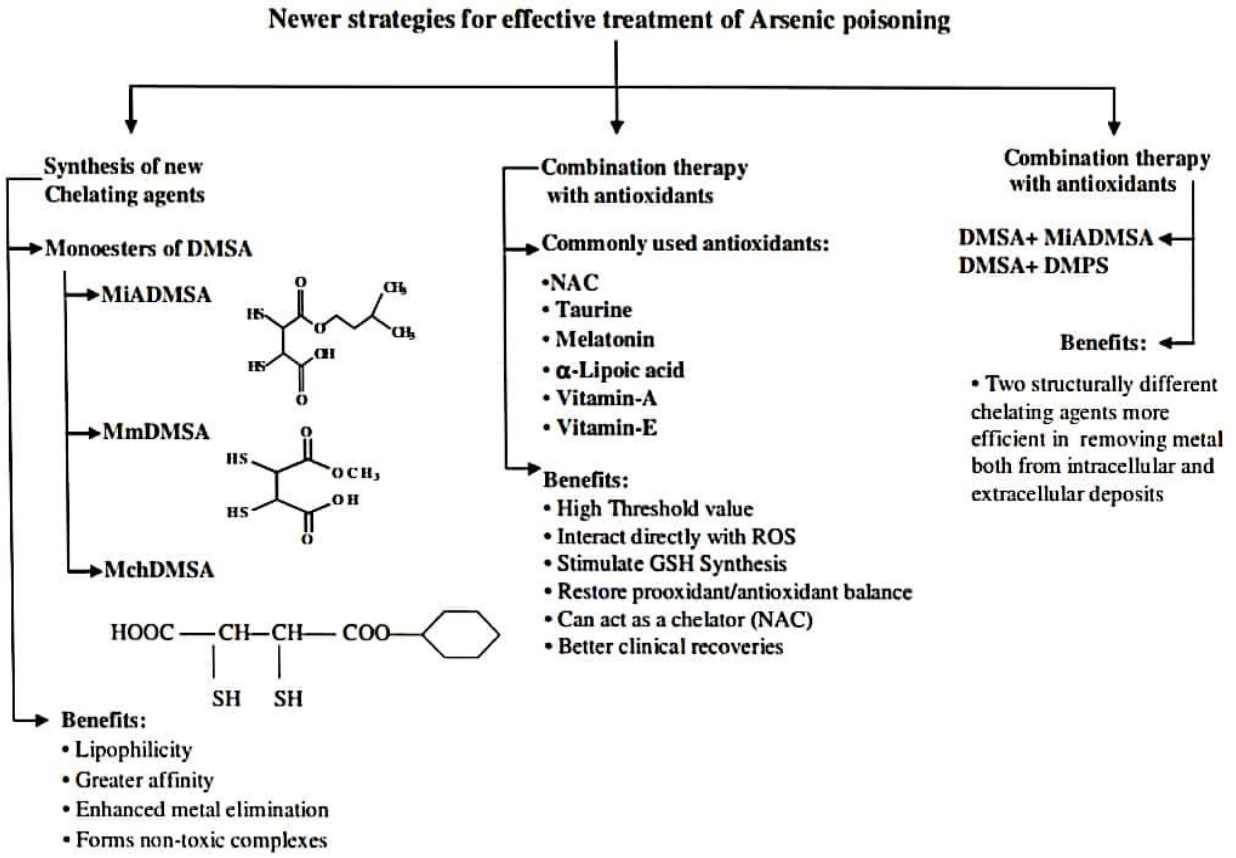


Fig – 15: Newer strategies For the treatment of arsenic poisoning.

Table – 3: therapeutic intervention against arsenic toxicity using synthetic chelators.

S.NO	CHELATING AGENT	PHARMACOLOGICAL EFFECTS
1.	2,3 Dimercaptosuccinic acid (DMSA) and monocyclohexyl DMSA (MchDMSA)	• Reduction in ROS • Restoration of mitochondrial membrane potential • Regulation of liver biomarkers
2.	DMSA and DL-α-Lipoic acid	• α- Lipoic acid increases the activities of superoxide dismutase, catalase, GSH • Reduces the ROS
3.	N- acetyl cysteine (NAC) and monoisoamyl DMSA	• DMSA reduces arsenic burden in cells • Reduction of arsenic content in blood and tissues • Combination therapy provides better protection against D-aminolevulinic acid dehydrase (ALAD) inhibition by arsenic and oxidative stress.

Recent advances of herbal products (phytoconstituents) as antioxidant in arsenic poisoning

Plants parts like wood, bark, stem, leaf and pod may be important source of natural antioxidants. Aloe vera has been reported to possess anti ulcer, anti diabetic, antioxidant and free radical scavenging activity. Centella asiatica improves learning and memory and possess antioxidant, anti ulcer, and radio protective activity. The whole plant of C. asiatica has been shown to be beneficial in improving alteration in arsenic induced oxidative stress besides it is also beneficial in depleting tissue arsenic, thus these herbal extracts when evaluated showed protection against arsenic-induced said manifestations.[13]

The **isoflavone biochanin found** in **soy and peanuts** was also demonstrated to possess anti oxidant property which was successfully employed to scavenge free radicals in arsenic exposed Sprague Dawley rats at a concentration of 40 mg/kg/day.[62] Similarly silibinin found in milk thistle (Silybummarianum) was reported to inhibit caspase 3 mediated tubular cell apoptosis, down regulate the expression of NADPH oxidase, iNOS (inducible nitric oxide synthase) and NF-κB (nuclear factor kappa B) in renal tissues and preserves the normal histological structure of renal tissues at a dose of 75 mg/kg against arsenic exposed rats.[62] Naringenin, another flavanone found in citrus plants was found to mitigate arsenic induced pathologic alteration in the liver and renal tissues. It also restored the liver biomarkers at

three different doses ranging between 20 50 mg/kg/day for 28 days in Wistar rats.[63]

Table-4: therapeutic action of flavonoids against arsenic toxicity.

S.NO	FLAVONOIDS	PHARMACOLOGICAL EEFECT
1.	Quercetin	• Reduces the ROS
2.	MiADMSA and quercetin	• Reduced arsenic levels in blood and soft tissues • Ameliorated oxidative stress
3.	Naringenin	• Restores hepatic serum biomarkers and antioxidant enzymes • Reverses the pathological changes due to arsenic intoxication in the liver and renal tissue
4.	Silymarin and naringenin	• Reduces the arsenic concentration in tissues
5.	Epigallocatechin-3- gallate (EGCG)	• Restores Superoxide (SOD), catalase, Glutathione(GSH) activity, Inhibits ROS • Mitigates sodium arsenite induced immune-suppression, inflammation and apoptosis in vitro.

It is proven recently that shelled **Moringaoleifera** seed powder has ability to remove cadmium and arsenic from the aqueous system. Fourier transform infrared (FTIR) spectrometery highlights protein/amino acid – arsenic interactions responsible for sorption phenomenon of seed powder of Moringaoleifera. Administration of the powdered seeds of **Moringa oleifera** in rodents after exposure to arsenic was found to restore the biochemical parameters as well as mitigate the deleterious effects of oxidative stress induced by arsenic. In addition, the arsenic levels from tissue were found to be reduced after treatment with **Moringa oleifera** indicating that the powder also contained several chelating agents apart from anti- oxidants that improve its therapeutic efficiency in combating arsenic-mediated toxicity.[71] Garlic has been reported to prevent arsenic-induced oxidative stress and apoptosis and reversing altered clinical variables.

Aloe vera (Aloe barbadensis) has been used in the traditional medicine but has been tried in a few limited studies against heavy metals/ metalloid particularly in reducing alteration in biochemical and physiological. The results however, suggest that it has got limited protective value against arsenic induced oxidative stress[20]

Cilantro and chlorella have also been proposed as a potent combination for chelation of toxic metals including arsenic.[59] Similarly, **turmeric and ginger h**ave been shown to enhance the elimination of arsenic in calves exposed to arsenic and ameliorate the adverse effects of arsenic poisoning. The beneficial effects of these extracts have been attributed to the anti-oxidant and chelating ability of their phytoconstituents.[60]

This may be attributed to the high content of sulfur containing compounds in garlic such as gamma-glutamyl cysteine, alliin, allicin, diallyl sulfide, diallyltrisulfide and diallyl disulfide which can effectively chelate with arsenic.[61]

A recent study has highlighted the therapeutic potential of the herb **Achyranthes aspera** whose aqueous extracts of leaf and root were in- dependently found to restore the imbalance in the hematological and immunological parameters caused due to exposure to sodium arsenate in mice models. The dose of the extracts administered for therapy was between 100–200mg/kg.[69]

Table – 5: phytochemicals used for the treatment of arsenic mediated toxicity.

S.NO	CHELATING AGENT	EXTRACTS	PHARMACOLOGICAL ACTION
1	Allicin, allyl cysteine, allin. Allyl disulfide	Garlic tuber extract	• Allicin scavenges superoxide ions • Allin, allyl cysteine and allyl disulfide scavange hydroxyl radicals.
2	Syzygium jambolanum	Ethanolic extracts of seeds	• Mitigates the arsenic induced hyperglycemia • Decreases ROS
3	Hippophae rhamnoids	Ethanolic extract	• Reverses arsenic toxicity when co-administered with arsenic
4	Diallyldisulfide	Garlic tuber extract	• Reduces ROS generation

5	Vitamin E & Spirulina	--	• Lipid peroxidation • Restores anti-oxidant defense mechanism
6	Phyllanthus emblica .	Leaf extract	• Reduces the arsenic content in blood, kidney, liver, lung and alters the biochemical parameters in liver • Ameliorate the adverse effects of arsenic when it is co-administered with sodium arsenite
7	Curcuma aromatica	Leaf extract	• Helps to reduce lipid peroxidation • Arsenic binds to thiol group of curcuma aromatica protein and consequently is detoxified

Plant extracts are rich in both anti-oxidant as well as chelating molecules and have been extensively explored to mitigate toxicity associated with heavy metal poisoning.[64,65] There are several plant species that have been investigated for their efficiency towards arsenic detoxification. The aqueous extract of **Trichosanthes dioica** fruit exhibited a prophylactic effect and was found to reduce aminolevulinic acid dehydratase (ALAD) activity and restore haemoglobin levels in wistar rats exposed to arsenic.[66] Another study reported that the extract restored normal levels of SOD, GST, GSH, GPx and Glutathione reductase (GR) in the liver and renal tissues of arsenic induced albino rats apart from rescuing the cells from DNA fragmentation and apoptosis.[67]

The ethanolic extract of **Syzygium jambolanum** seeds was investigated for its potential to mitigate arsenic-induced hyperglycemia using both in vitro and mice models.[68]

The hexane extract of the leaves from **Alchornea laxiflora**, a plant used in Nigerian traditional medicine was found to counter the adverse effects of arsenic mediated oxidative stress when it was pre-administered to rats at doses ranging from 5 mg/kg to 10 mg/kg body weight. The therapeutic efficiency of the extract was also investigated by administering various concentrations of the extract to rats exposed to arsenic for two days (post-treatment). The treated groups exhibited significant lowering of the liver enzymes that were elevated due to arsenic-induced hepatic damage. However, the pre-treatment with plant extract was found to be more effective when compared to the post-treatment group.[70] The aqueous extract of the water spinach **Ipomea aquatica** has also demonstrated protective effects against arsenic mediated toxicity both in vitro as well as in vivo.[72]

The Extracts from plants such as **Phyllunthus freternus,**[73] **Terminalia arjuna** (bark),[74] **Mentha piperita** (leaves),[75] **Hibiscus sabdariffa**(flowers),[76] **Withaniasomnifera** (roots),[73] **Pteris longifolia** (leaves)[73] and **Bauhenia variegate** (leaves),[74] have also shown significant alteration in lipid peroxidation and have helped in scavenging free radicals, reduce genotoxicity and exhibited hepatoprotective and nephroprotective effects. Arjunolic acid, a key constituent in Terminalia Arjuna has also shown a protective effect against arsenic-mediated oxidative stress in testes due to its antioxidant nature.[77]

Plants such as **Curcuma aromatic** have shown good results in combating arsenic-mediated toxicity in albino rats. It is also been proved that curcumin from Curcuma aromatica leaf extracts helps to reduce lipid peroxidation and normalize the levels of uric acid in serum.[79]

Previously reported individual beneficial efficacy of nanoparticle mediated administration of an antioxidant like '**curcumin**' and an arsenic chelator '**monoisoamyl 2,3-dimercaptosuccinic acid** (MiADMSA)' for the treatment of arsenic toxicity compared to bulk drugs.. The results demonstrated that co-treatment with nano-curcumin and nano-MiADMSA provided beneficial effects in a synergistic way on the adverse changes in oxidative stress parameters and metal status induced by arsenic.[78]

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The protective effect of **aqueous extract of Corchorus olitorius leaves** (AECO) against sodium arsenite-induced toxicity in experimental rats. Treatment with AECO at doses of 50 and 100 mg/kg body weight for 15 days prior to arsenic intoxication significantly improved hepatic and renal antioxidant markers in a dose dependant manner. AECO treatment also significantly reduced the arsenic-induced DNA fragmentation of hepatic and renal tissues.[80,83]

CONCLUSION

Arsenic poisoning leads to long-term implications that are detrimental to human health and such incidences through consumption of arsenic-contaminated water and food are well known. Arsenic affects almost all the cellular processes and organ functions in our body. The

oxidative stress can be partially implicated in arsenic toxicity, so a therapeutic strategy to increase the antioxidant capacity of cells may fortify the long term effective treatment of arsenic poisoning. Since the ancient times, the plants have been used to treat many disease and hence extracts of the plants (phytochemicals) can be generally employed as dietary supplement to prevent any adverse effects that may occur due to arsenic intoxication or as an adjuvant along with chelators for the treatment of arsenic- induced toxicity.

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