Austin Environmental Sciences

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Austin Publishing Group

Special Article - Arsenic Poisoning

Chemoprevention of Arseniasis-Past, Present and Future (Mini Review)

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Received: September 23, 2022; **Accepted:** November 12, 2022; **Published:** November 19, 2022

Abstract

Clinical management of arsenic poisoning has been a major concern especially in countries like Bangladesh., India., Taiwan., Chile, Hungary and Argentina. In recent past, therapeutic efficacy of chelating agents, vitamins, nutrients, antioxidants and hormones has been investigated in many laboratories. Whereas, arsenic can be chelated by several agents viz: British Anti Lewisite (BAL), unithiol (DMPS), succimer (DMSA), monoisoamyl dimercaptosuccinic acid (MiADMSA), monocyclohexyl dimercaptosuccinic acid (MchDMSA), co-administration of quercetin and MiADMSA and taurine and MiADMSA have been found to reduce arsenic burdeon more effectively than their individual treatments. There are convincing reports that non-enzymatic antioxidants i.e. ascorbic acid, alpha tocopherol, B carotene, N-acetyl cysteine, alpha lipoic acid, curcumin, GSH and selenium offer protection against arseniasis by reducing oxidative stress. Melatonin, a product of pineal gland being a strong free radical scavenger possesses immense therapeutic importance against arseniasis. Thyroid hormones too influence arsenic toxicity. All these studies made in experimental animals have been briefly described in this review. However, cohorts made in human population are insignificant. Suitable clinical trials using these therapeutic agents individually or in combination may lead to the discovery of a "magic bullet" against arseniasis.

Keywords: Arseniasis; Chelating agents; Antioxidants; Nutrients; Amino acids and hormones

Introduction

Arsenic is present in Earth's crust at an average concentration of 5 parts per million (ppm). It ranks 54th in abundance in Earth's crust. Arsenic is a component of 245 minerals associated most frequently with other minerals such as copper, gold, lead and zinc in sulfidic ores. The main ores of arsenic are arsenopyrites (FeAsS), realagar (As2S2), orpiment (As2S3) and arsenolyte (As2O3). Arsenic is usually not mined but is recovered as a by-product from the smelting of copper, lead, zinc and other ores. Natural processes such as weathering, biological activity and volcanic eruption disturb its geochemical cycle and it is released into the environment. Anthropogenic activities such as combustion of fossil fuels, mining ore smelting and well drilling also mobilize and introduce arsenic into the environment.

Although, most typical environmental exposures to arsenic do not pose a health risk, several countries are known to suffer the risk of arsenic poisoning. Over 140 million people worldwide consume arsenic contaminated drinking water that exceeds the World Health Organization (WHO) limit of 10ppb [1]. Highest concentration of arsenic are known to occur in the ground water of Bangladesh and West Bengal in India [2]. Human population of other countries that are suffering from arsenic poisoning include Taiwan [3-5], Argentina [6,7], Chile [8,9], India [10,11], Bangladesh [12,13], China [14] and inner Mongolia [15]. WHO declared arsenic poisoning as a global emergency. A strong association between exposure to high concentration of arsenic and prevalence of cancer of skin, lung and bladder has also been established [16]. Agencies like International Agency for Research on Cancer [17] and European Food Safety Authorty [18], have declared it as a human carcinogen. Agency for Toxic Substance and Drug Registry (ATSDR), has registered it as number one substance in the Comprehensive Environmental Response Compensation and Liability Act (CERCLA) priority list of hazardous substances [19].

In environment, arsenic exists in inorganic as well as organic forms and also in different valence or oxidation states. Elemental arsenic has a valence state (o). Arsine and arsenides have a valence state (III). All arsenic compounds may be classified into inorganic, organic and gaseous forms. The most common inorganic trivalent arsenic compounds are arsenic trioxide, sodium arsenite and arsenic trichloride. Pentavalent compounds are arsenic pentoxide, arsenic acid, arsenate (e.g. lead arsenate, calcium arsenate). Common organic arsenic compounds are arsanilic acid, monomethylarsonic acid, dimethylarsinic acid (cacodylic acid) and arsenobetaine [20].

Absorption of arsenic may occur through inhalation, ingestion and contact by skin. After absorption, arsenic is transported by the blood to other parts of the body. Two basic processes are involved in its biotransformation, (i) oxidation and reduction reactions that intervert As III and As V, and (ii) methylation reactions which convert arsenite to Monomethyarsanalic Acid (MMA) and Dimethylarsenilic Acid (DMA).

Research on the mechanism of arsenic toxicity has been ongoing for many years, yet precise mode of action (MOA) for many disease end points after exposure to arsenic are not fully understood. Trivalent arsenicals have been found to be more potent toxicants than

Citation: Rana SVS. Chemoprevention of Arseniasis-Past, Present and Future (Mini Review). Austin Environ Sci. 2022; 7(4): 1084.

pentavalent arsenicals. Several review articles have been published on its MOA [21-23]. These reviews indicate involvement of several mechanisms viz: altered DNA methylation, signal transduction, cell proliferation, Reactive Oxygen Species (ROS), oxidative stress and genotoxicity in its toxicity. Several of these mechanisms may be interdependent. Based on its MOA, attempts have been made to find out suitable drugs/antidotes against arseniasis.

Arsenic as a Medicine

Documented evidence showing that arsenic was used as a therapeutic agent dates back to 2000 BCE [33,34]. Ancient pioneering physicians e.g. Aristotle and Paracelsus reportedly used arsenic as medicine [35,36]. Hippocrates, the Father of Medicine is thought to have used arsenic paste to treat ulcers and abscesses [37,38].

Fowler's solution, that was discovered in 1786, is a 1% solution of potassium arsenite, used in the treatment of malaria, syphilis, asthma, cholera, eczema and psoriasis [39,40]. Paul Ehrlich discovered a new arsenic based drug called "salvarsan" which later became known as "magic bullet" for treating syphilis. It was used till penicillin became more popular in 1940s [38,41].

Pharmacological texts from 1880s described the use of arsenical pastes for the treatment of skin and breast cancer. It was found that Fowler's solution could be effective in lowering the white blood cell count in leukemia patients [42]. Later on the use of Fowler's solution declined due to its overt toxicity. More detailed understanding on the mechanisms of action of arsenic helped arsenic trioxide to emerge as an effective drug against Acute Promyelocytic Leukemia (APL) [43]. The treatment of other types of cancers with arsenic trioxide is still a matter of investigation [44,45].

Amelioration of Arsenic Toxicity

Sincere efforts have been made to develop methods to both enhance the efficacy of arsenic as well as to ameliorate the toxicity profile associated with different forms of arsenic. In recent past therapeutic efficacy of chelating agents, vitamins, nutrients, antioxidants and hormones has been investigated in many laboratories. Important developments are reviewed in the following paragraphs.

Chelation of Arsenic

Several metal binding substances function by chelation. A substance which binds metals is called a ligand. When a metal is gripped in a ligand between any two of the elements i.e. N, O, or S, a chelate ring is formed. This process is known as chelation. The term was coined by Morgan and Drew [46] and is derived from the Greek word *khele* meaning crab's claw.

The first experimental use of a chelator against metal poisoning was made by Kety and Letonoff [41] to treat lead poisoning with sodium citrate. However, traditional chelating agents include calcium disodium ethylamine diamine tetra acetic acid (CaNa2EDTA), British Anti Lewisite (BAL), and meso-2,3-dimercapto succinic acid (DMSA). Recently mono and diesters of DMSA have been developed and tried against experimental heavy metal poisoning. Other chelating agents with established clinical use include D-penicillamine and desferrioxamine [48].

The therapeutic efficacy of chelation depends upon metal chelator and organism related factors e.g. ionic diameter, ring size and deformability, hardness/softness of electron donors and acceptors, route of administration, bioavailability, metabolism, intra/extra cellular compartmentalization and excretion. Hydrophilic chelating agents promote renal excretion of the metal while lipophilic chelators may deplete intracellular stores and may redistribute toxic metals. In long term therapy, side effects of the administered chelating agent may be limiting. The metal selectivity of chelator is important because of the risk of depletion of stores of essential metals.

Chelation therapy to prevent metal toxicity perhaps started 70 years ago with the development of British Anti Lewisite (BAL) or dimercaprol in Britain [49]. Later on DMPS (unithiol) and DMSA (succimer) were developed in Soviet Union and China in late 1950s. These three agents have been extensively used to treat arsenic and mercury intoxication [50,51]. BAL possesses marked side effects and low safety ratio, however, DMPS and DMSA are non toxic. A comparative study on their efficacy in the liver and kidney of mice treated with arsenic by Tripathi and Flora [52] confirmed that DMSA was more effective than DMPS. Muckter et al., [53] suggested that BAL should be replaced with 2,3-Dimercaptopropane-Sulphonate Sodium (DMPS) and meso-2,3-Dimercaptosuccinic Acid (DMSA) due to their low toxicity. However, in case of severe poisoning by organic arsenicals, BAL remains to be a preferred antidote for arsenic. Another chelate-Monoisoamyl Dimercaptosuccinic Acid (MiADMSA) has also been found to elicit significant protection against arsenic induced oxidative stress and apoptotic cell death in human keritinocytes [54]. A concept of using chelation therapy with essential elements like calcium and zinc has also been suggested. Kadeyala et al., [55] reported that MiADMSA combined with calcium and zinc could be more effective in reducing arsenic toxicity. Recently Anderson and Aaseth [56] reviewed the shortcomings of chelation therapy. Chelation procedures should alleviate and not aggravate the clinical status of poisoned patients.

There are a few reports where combination therapy has been used against arseniasis. Co-administration of DMSA and MiADMSA at a concentration of 0.15mM/kg was found effective in reducing arsenic load from blood and soft tissues and also in reducing oxidative stress. DNA damage caused by As was also repaired [57]. Subsequent study showed that combination of DMSA with long chain carbon analogues like MiADMSA and monocyclohexyl DMSA (MchDMSA) significantly reduced arsenic burdeon and reversed altered biochemical variables indicative of oxidative stress and apoptosis [58]. Thus further attempts to use suitable combination(s) of chelating agents and essential element may be made to prevent arsenic toxicity.

Arsenic is known to cause reproductive toxicity also. Available literature shows that it could be prevented by DMSA and DMPS [59]. Flora and Mehta [60] has reported that MiADMSA protects against arsenic induced developmental toxicity in stem cell derived embryoid bodies.

Studies on the protective role of nanoparticles of chelating agents against arseniasis are also being undertaken in a few laboratories. Yadav et.al., [61] showed better efficacy of nano-MiADMSA (50nm) than bulk MiADMSA in reducing oxidative stress and efficient removal of arsenic from blood and tissues of sodium arsenite treated Swiss albino mice. Histopathological observations and urinary

level of 8-OHdG also proved better therapeutic efficacy of nano-MiADMSA than bulk MiADMSA. Another report on the application of nanotechnology in the prevention of arsenic poisoning was published by Ghosh et al., [62] who nanoencapsulated quercetin and DMSA and tested against chronic arsenic toxicity in a rat model. Their combined treatment displayed a synergistic effect. It decreased arsenic burdeon, normalized mitochondrial function and reduced the formation of reactive oxygen species in liver. It was a novel approach of therapeutic intervention combining hydrophilic and hydrophobic drugs into a single delivery system. Earlier, Mishra and Flora [58] have also shown that combined administration of quercetin with MiADMSA decreased arsenic concentration in blood and soft tissues. Similar study was made with taurine and MiADMSA in rats treated with sodium arsenite for 24 hours. Co-administration of a higher dose of taurine (100mg/kg) and MiADMSA improved antioxidant status of liver and kidney and reduced arsenic burdeon compared to their individual treatment [63].

Protection by Antioxidants

It has been established now that arsenic toxicity is manifested through oxidative stress. Therefore, antioxidants have been at the forefront of chemotherapeutic intervention against arseniasis. Nonenzymatic antioxidants function as free radical scavengers and include ascorbic acid (vitamin C), alpha tocopherol (vitamin E), B-carotene, N-acetyl cysteine, alpha lipoic acid and selenium.

Ascorbic acid: L-ascorbic acid ($C_6H_8O_6$) is the trivial name of vitamin C that has been accepted by IUPAC-IUB commission on biological nomenclature [64]. The systemic chemical designation is 2-oxo-L threo-hexono-1,4 lactone-2,3-enediol. Vitamin C refers to compounds exhibiting full or partial biological activity of L-ascorbic acid. These include esters of ascorbic acid such as ascorbyl palmitate, 6-deoxy-L-ascorbic acid and primary oxidized form of ascorbic acid, dehydroascorbic acid.

The concept that arsenical toxicity could be modified by nutrients was initially proposed in early 1930's by Mayer and Sulzberger [65] who suggested that adequate concentration of ascorbic acid in the diet prevented or reduced arsenic induced occurrence of anaphylaxix. Subsequently, a number of researchers confirmed this hypothesis on ascorbic acid-arsenic interaction [66-69].

Several workers like Tanaka [70]; Tabacova et al., [71]; Mc Call and Frei [72]; and Odunuga et al., [73] reported on free radical scavenging role of L-ascorbate as a major mechanism of protection against arsenic poisoning. Vitamin C in combination with methionine also reduced toxicity of arsenic [74,75]. [76] concluded in their studies in rat that L-ascorbate plays a pivotal role in maintaining normal ovarian activities and brain monoamines in arsenic treated rats. Anti myeloma effect of ascorbic acid has also been observed by Bahlis et al., [77]. Improvement in microsomal function by ascorbic acid in arsenic treated rat has also been observed [78]. It was also concluded that ascorbate overcomes drug resistance in myeloma and significantly increases the anti myeloma effects of arsenic trioxide in animal models.

A number of studies especially made in last decade attribute the protective effects of ascorbic acid to its antioxidative property. It was suggested that ascorbic acid forms first line of antioxidant defence [80,81]. Nandi and coworkers (2005) also observed that ascorbic acid reduces tissue burdeon of arsenic and reverses oxidative stress in rats. Studies made in our laboratory also suggested that it reduces oxidative stress [84]; improves mitochondrial function [83]; and reverses disturbances in the structure and function of liver and kidney of arsenic treated rats [84] Not only liver and kidney, protective effects of ascorbic acid have been observed in testis [86] and neural function of rats [87]. Combined treatments with vitamin E and vitamin C have also displayed protection against arseniasis in rats [88,89].

These properties make ascorbic acid a suitable antidote for arsenic poisoning even in human subjects.

Vitamin E (a-tocopherol): Vitamin E is a family of lipophilic antioxidants, termed tocopherols that contain a chromanol nucleus and isoprenoid side chain [90]. Individual tocopherols differ by the position and number of methyl substituents on the aromatic ring. Of these, the principal tocopherols found in human and animal diets are y-tocopherol and a-tocopherol. a-tocopherol from natural sources (R.R.R. a-tocopherol is the most potent form of vitamin E. Peroxyl radicals analogously oxidize a-tocopherol to the tocopheroxyl radical, an unusually stable phenoxyl radical that does not propagate the radical chain [91]. Recognizing these kinetics, several studies have been made using a-tocopherol as antidote for several xenobiotics.

A population based study was conducted in Bangladesh using vitamin E and selenium to protect against nonmelanoma skin cancer caused by arsenic amongst 7000 adults [12]. Vitamin E together with vitamin C and zinc was found to ameliorate hematological effects of arsenic in rats during pregnancy and lactation [92]. Plasma a-tocopherol might modify the risk of inorganic arsenic related urothelial carcinoma [93]. A few reports indicated the protective effects of vitamin C and E against arsenic induced teratogenicity [89]. Effects of vitamin E together with other nutrients like selenium have also been found protective against co-carcinogenicity induced by arsenite and solar UVR [94].

An excellent review by Liebler [95] on the role of metabolism in the antioxidant function of vitamin E concluded that a-tocopherol is the principal chain breaking antioxidant in biological membranes. It prevents toxicant/carcinogen induced oxidative damage by trapping reactive oxygen radicals.

β- carotene: Very few workers have studied the amelioration of arsenic poisoning by B carotene. It is a lipophilic antioxidant. Its protection against many xenobiotics has been attributed to its role in the prevention of oxidative DNA damage. It can induce GSH synthesis. An association between as induced skin cancer and B -carotene was first reported by Hsuch [96] in arseniasis affected villages of Taiwan. Skin cancer patients had significantly lower serum levels of B-carotene than matched healthy controls. The same group of workers recorded a reverse dose-response relationship with arsenic related Ischemic Heart Disease (ISHD) [97]. Another study from west Bengal (India) by Chung et al., [93] showed that arsenic toxicity could be influenced by micronutrients in particular, selenium, methionine and B-carotene. In a recent study made by Das et al., [98], B -carotene displayed ameliorative effect against arsenic induced toxicity in Swiss albino mice. They also attributed this effect to its antioxidative and antigenotoxic properties. In future, attempts can be made to introduce

a combination therapy using B- carotene and chelating agents.

N-acetyl cysteine: N-Acetyl Cysteine (NAC), a synthetic aminothiol, possesses antioxidative and cytoprotective properties. L-cysteine is a precursor to the biological antioxidant glutathione. Hence, in principle, administration of NAC replinishes glutathione stores. Patrick [99] suggested mitigating role of NAC against arsenic and cadmium toxicity. *In vitro* and *in vivo* models have shown that NAC modulated cellular thiols for protection against reactive oxygen species [100]. In a recent study, da Silva [101] observed that co-administration of NAC and As_2O_3 in male mouse prevented the harmful effects of arsenic on male genital system. However, no protective effects were observed in the urinary bladder of rats treated with dimethylarsinic acid [102]. Reddy and coworkers [103] showed that treatment of arsenic exposed mice with NAC increased the weight of reproductive organs, reduced arsenic induced oxidative stress and impaired steroidogenesis indicating the beneficial role of NAC.

Pre-treatment of NAC to arsenic treated mice abrogated apoptosis in liver, as determined through TUNEL test, caspase assay and histology [104]. It was hypothesized that since these processes are GSH dependent, supplementation of NAC would display beneficial effects. Pal et al., [105] suggested that NAC prevented As induced hypoglycemia and glycogenetic effects. As induced changes in glucose-6-phosphatase activity in liver and kidney both were counteracted.

Another approach adopted by a few workers was to use NAC with another suitable therapeutic agent. Combined therapy of NAC and DMSA was tried against oxidative stress and hepatic dysfunction induced by sodium arsenite in male rats. Combined therapy was found to be superior than monotherapy in recovery of glutathione and structural changes [106]. Another group used NAC and zinc to combat As induced oxidative stress in male rats [107]. Concommitant administration of Zinc and NAC showed protection against delta amino levulinic acid dehydratase, oxidative stress and catalase activity in the liver of male rats. Combined therapy using NAC and suitable nutrient(s) or chelating agent(s) may be a good alternative to treat arsenicosis in humans.

Reduced glitathione(GSH): Arsenic and GSH relationship is as old as the discovery of this tripeptide (glutamyl cysteinyl glycine) by Hopkins and coworkers in 1922 [108]. There is a serene phrase coined by Kosower and Kosower [109],"*Lest I forget thee glutathione*". This statement has now been replaced by "*inevitable glutathione*" by Rana et al., [110]. Cysteinyl moiety of GSH binds with trivalent arsenicals and thus offers protection against their toxicity. Investigations during 1920s and 1930s on GSH-As interactions laid the groundwork for development of an antidote for lewisite (chlorovinyl dichloroarsine). BAL (2,3-dimercaptopropanol) was the product of this early development at national drug design [111].

Molecular mechanisms involved in As-GSH interaction are associated with reduction reactions that convert pentavalent arsenic to trivalent arsenic [112,113]. Trivalent arsenic is complexed by GSH, hence GSH dependent reduction and complexation are inextricably linked in cells. These complexes have been detected in diverse biological systems [114,115]. These complexes inhibit Glutathione Reductase (GR) [116]. Regeneration of GSH from GSSG due to inhibition of GR may affect the intracellular GSH: GSSG ratio. The resulting shift in cellular redox status may contribute to its toxicity/ carcinogenesis.

There are a few reports that suggest that dietary GSH can modulate arsenic toxicity. Protective effects of GSH on sodium arsenite induced ovarian and uterine disorders in Wistar rats were observed by Chattopadhyay and Ghosh, [117]. Other compounds like resveratrol protect against As_2O_3 toxicity via cellular antioxidative pathway i.e. maintaining GSH homeostasis and suppressing apoptosis [118].

The formation of As-GSH complexes may also facilitate the efflux of arsenicals from cells. New findings suggest that glutathione-S-transferases especially glutathone transferase P_1 ($GSTP_1$) catalyzes the formation of As-GSH complexes which are preferred substrates for ATP binding cassette membrane transporters which mediate efflux from cells [119]. Nevertheless, there are no data concerning the kinetics of formation of As-GSH complexes in $GSTP_1$ catalyzed reactions [120]. However, this information favours the use of GSH as an antidote for arsenicosis.

Curcumin: Curcumin (CUR) is the active ingredient derived from the rhizome of turmeric, *Curcuma longa.* CUR is a good antioxidant but with limited clinical applications due to its hydrophilic nature and limited bioavailability. It is a naturally occurring polyphenolic compound with wide range of therapeutic and pharmacological properties. Garcia-Nino and Pedraza Chaveri [121] showed that curcumin reduces hepatotoxicity induced by several elements viz: arsenic, cadmium, chromium, copper, lead and mercury. Metal conjugation and free radical scavenging activities of CUR make it a safe antidote. Dutta et al., [122] showed that metal conjugates of CUR derivatives enhance its antioxidative activities. It has been observed that CUR counteracted DNA damage caused by arsenic. It decreased lipid peroxidation and increased the activities of Phase-II enzymes viz: catalase, superoxide dismutase and glutathione peroxidase in arsenic treated human lymphocytes [123]. These authors suggested that CUR can be an economic model for the mitigation of arsenic toxicity amongst rural population of West Bengal (India). Several reports support this proposition. Neurotoxicity of arsenic could be attentuated by CUR in rat [124]. They observed that strong antioxidant potential of CUR reduced genotoxicity of arsenic in Swiss albino mice. This activity was attributed to an increase in antioxidant enzymes viz: catalase, superoxide dismutase, glutathione peroxidase, glutathione transferase and glutathione itself [127]. *In vitro* studies on human peripheral lymphocytes have also confirmed that CUR mitigates genotoxic potential of arsenic and fluoride [126]. CUR treatment administered to arsenic exposed human population of West Bengal (India) enhanced DNA repair monitored through 8-OHdG. This study made on protein expression and genetic profile suggested protective effects of CUR both at protein and genetic levels [127].

Mechanism of chemoprevention expressed by CUR against arsenic toxicity was recently studied by Gao et al., [128]. They observed that it activates nuclear factor 2 (Nrf_2) and phase-II enzymes in the liver of mice. Further, it promoted arsenic methylation. Two Nrf_2 Downstream Genes NADP(H) Quinine Oxidoreductase I (NQO_1) and heme oxygenase-I (HO-I) were also upregulated after CUR treatment. Nrf_2 activation by CUR appears to be a valuable

factor in chemoprevention of arsenic toxicity.

CUR could protect arsenic induced cholinergic deficits by modulating the expression of pro and anti apoptotic proteins in the brain of rats. It improved mitochondrial structure and function as well [129].

Recent observations show that Tetrahydrocurcumin (THC) a metabolite of CUR was found to possess greater antioxidant activity than CUR. Treatment of THC to arsenic treated rats reversed its hepato-toxicity. This effect was attributed to the presence of identical to B-diketone of 3rd and 5th substitution in hepatic moiety [130]. Recently, a group of workers from India used nanocurcumin to ameliorate arsenic toxicity in rat. It prevented genotoxicity, hepatotoxicity and reduced arsenic induced oxidative stress in brain and kidney of rats [131-134]. It could express immunomodulatory effects better than free curcumin [132-134]. CUR definitely offers advantages over other antioxidants.

Selenium: Selenium (Se) was discovered in 1817 by Swedish chemist Berzelius, who named it after the moon goddess, *selene*, in Greek language. Today, almost 200 years later, selenium is well established as an essential trace element of fundamental importance to human health. Se is primarily known for its antioxidative properties [135]. Keshan disease is a potentially fatal form of cardiomyopathy prevalent in children and endemic in parts of China with extremely low levels of Se in soil. Condition can be prevented completely by Se supplementation [136].

The incorporation of Se as selenocysteine in 25 proteins by a highly elaborate cotranslation mechanism has defined the human "*selenoproteome*", in which the precise function of about half of the proteins is still unknown. Many of the proteins have functions ranging from antioxidants or oxidoreductases including Glutathione Peroxidases (GPxs) and Thioredoxin Reductases (TrxR). The enzyme glutathione peroxidase contains Se in the form of selenocysteine and catalyzes the oxidation of glutathione and reduction of organic hydroperoxides or H_2O_2 thereby protecting membrane lipids and other macromolecules from oxidative damage. Whereas, several studies demonstrate antioxidative properties of Se, there is no evidence in literature that Se exterts chemopreventive effects via such a mechanism [137,138]. However, inorganic Se salts i.e. selenite or dietary selenoamino acids lead to reductive metabolic pathway forming hydrogen sulfide (H_2Se). H_2Se then acts as Se donor to the Se containing amino acids found in various selenoproteins or it may lead to the formation of methylselenide anion [139]. Nevertheless, transcription factor modulation by Se may be relevant to chemopreventive mechanism [140].

Despite versatile nature of Se, Se-As interactions have been poorly described. Biswas et al., [141] in their experiment on Swiss albino mice demonstrated that organoselenium protects against As+UVR induced carcinogenesis through the formation of a compound seleno-bis (S-glutathionyl) arsinium rather than its antioxidative effect. Contrarily, Messarah et al., [142] in their observations made in sodium selenite and sodium arsenite treated male rats suggested that Se co-administration protected liver against As intoxication probably owing to its antioxidant properties. Recent report from Dash et al., [143] suggest that chronic arsenicosis in cattle could be mitigated by Zn and Se. Recently Krohn et al., [144] have shown that high Se lentils from Canadian prairies protect against As triggered atherosclerosis in mice.

Thus, there is ample experimental evidence to suggest that Se treatment can protect against arsenicosis.

Hormones as Antidotes

Melatonin: Melatonin (N-acetyl-methoxytryptamine), a main product of pineal gland functions as a time giver (zeitgeber) in the regulation of circadian rhythms [145]. It synchronizes the reproductive cycle with appropriate season of the year in photoperiodic species [146]. In non-photoperiodic species such as humans, the actions of melatonin are restricted to other functions of circadian clock i.e. consolidation of sleep and core body temperature [147]. Since 1993, melatonin has been recognized as a free radical scavenger [148-150]. Its widespread sub cellular distribution enables it to interact with toxic molecules, thereby reducing oxidative damage to molecules in both aqueous and lipid environment of the cell. Melatonin acts as an indirect antioxidant through activation of major antioxidant enzymes including superoxide dismutase, catalase and glutathione peroxidase [151-154].

A few investigators have studied the protective effect of melatonin on arsenic toxicity. Pal and Chatterjee [155] showed that melatonin treatment reverses the inhibition of antioxidant enzyme caused by arsenic. Anti-genotoxic potential of melatonin in arsenic affected human population was established by Pant and Rao [156]. Melatonin could ameliorate testicular injury mediated by arsenic [157]. A recent report from Teng et al., [158] showed that melatonin protects against arsenic induced neurotoxicity. All these effects have been attributed to general antioxidant properties of melatonin.

Thyroid hormones: Much is not known on thyroid-arsenic interaction. Reciprocal interaction between thyroid activity and arsenic toxicity was studied in our laboratory. It was reported by Allen and Rana [159] that thyroxine treatment diminished oxidative stress caused by arsenic trioxide in the liver and kidney of rat. Hyperthyroidic conditions restricted the accumulation of arsenic in liver and kidney. However, histopathological observations indicated severe lesions in the kidney of arsenic and thyroxine treated rats [160]. Further studies are needed to establish arsenic -thyroid-parathyroid interaction.

Conclusion

Arsenicosis or arseniasis are the common terms used to designate arsenic poisoning. They represent disease endpoints viz: specific skin manifestations like pigmentation and keratosis, respiratory diseases, liver and kidney disorders, haematological effects, neuropathy, diabetes and cancer. Despite that mortality is high in severe cases, effective management of arsenicosis remains elusive. Is there any "magic bullet" to treat arsenicosis? Perhaps the answer is no. During recent years, therapeutic intervention using a variety of molecules i.e. chelating agents, antioxidants, nutrients and hormones has been studied in a number of laboratories. A novel approach was made using a combination of these agents. Efficacy of nanoparticles viz: nano MiADMSA has also been investigated. It is interesting to know that tetra-hydrocurcumin a metabolite of curcumin expressed greater antioxidant activity than curcumin. While curcumin promotes arsenic methylation, As-GSH complex facilitates the efflux of arsenicals from

target cells. Protective effects of melatonin are attributed to its strong antioxidative and chelation properties. Perhaps a careful combination therpay may prove better than monotherapy. The studies reported so far have been mainly made in experimental animals and controlled conditions. Cohorts made in human population are insignificant. Suitable clinical trials using these therapeutic agents along with blind placebo controls, if made in future may lead to the discovery of magic bullet for arsenicosis.

Acknowledgement

The author is thankful to his colleagues- Dr Tanu Allen, Dr Sohini Singh, Dr Neetu Singh and Dr Seema Sharma for their valuable inputs and suggestions.

Conflict of Interest

The author declares no conflict of interest.

Acknowledgements

The financial support from Indian Science Congress Association (Kolkata) is gratefully acknowledged.

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