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REVIEW PAPER

A Toxicochemical Review of Gallium Arsenide

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ABSTRACT

Gallium arsenide (*GaAs*) is extensively used in defence as a semiconductor material, in radar and in electronic warfare. However, its toxicity is still not well understood. The chemistry of gallium arsenide in the body plays a key role in defining its toxicity. *GaAs* is found to be soluble in aqueous solution and forms unidentified gallium and arsenic species upon dissolution. *GaAs* causes toxicity to various organs including lung, testes, kidney, brain and immune system. The toxicity of *GaAs* can be attributed to the synergistic toxic effects associated with gallium and arsenic. Till date, there is no well defined treatment regime for *GaAs* induced toxicity. This review gives a recent account of work carried out in the toxicology of *GaAs* including chemistry involved in the mechanism of toxicity of *GaAs*, its toxicological effects on various organs and current therapy available.

Keywords: Gallium arsenide toxicity, organ damage, biochemical effects, preventive and therapeutic measure

1. INTRODUCTION

Gallium arsenide (*GaAs*) has a superior property as a photon emitter and is extensively used for light-emitting diodes and semiconductor lasers for the optical data storage and playback system and the high-speed optical communication system. *GaAs* also has a distinct advantage in electronic speeds compared with silicon and is increasingly used for the satellite communication system and the ultra fast supercomputer. The unique electromagnetic and photovoltaic properties of *GaAs* are now explored for its use as semiconductors. *GaAs* has certain advantages over other semiconductor materials[1,2].

Workers in semiconductor industries are prone to be exposed to this semiconductor material during various operations. Although numerous reports are available which have focused on monitoring arsenic levels in air samples, very few have assessed changes in workers health. It has been observed that industrial workers exposed to *GaAs* have significantly elevated urinary arsenic levels[3]. Gallium arsenide has been classified as an immunotoxicant and a group I carcinogen to humans even though no data on human cancer is available and the conclusions are principally based on few incidences of bronchioloalveolar neoplasms observed in female rats.[4] It may however be noted that gallium arsenide once reaches inside the body, dissociates into arsenic moiety which is a known human carcinogen. On the other hand, gallium moiety which is generally considered safe is reported to be responsible for pulmonary neoplasm observed in male rats[4,5]. In the past few decades, various studies have reported the toxicity of *GaAs.* A comprehensive account of the work carried out in the toxicology of *GaAs*[6] such as hematotoxicity[7,10], hepatotoxicity[11,13], pulmonary toxicity[14,16], renal toxicity[17,18], reproductive toxicity[19,21], immunotoxicity[22,25] and more recently toxicity in central nervous system[26]. Apart from this intratracheal and exposure of *GaAs* through inhalation produces pulmonary inflammation, mild fibrosis and pneumocyte[7,27]. *GaAs* is absorbed as aqueous soluble gallium and arsenic components, and these components, especially arsenic, enter the circulatory system[28,29]. After intratracheal or intraperitoneal exposure, the chemical causes a dose- and time-dependent systemic suppression of immune functions[30,31]. A study has shown that a single dose of 100 mg/kg of *GaAs* resulted in acute pulmonary inflammation and pneumocyte hyperplasia after 14 days[32]. Chronic exposure (2-year observation period) to lower doses (<1 mg/L) of *GaAs* produced systemic toxicity and definite pulmonary lesions[14]. In addition testicular toxicity was observed, and tumor reoccurrence increased significantly in mice when *GaAs* was injected intraperitoneally[33]. The same will be reviewed in detail in the later section.

The associated toxicity studies of this compound have attracted the attention of many toxicologists to explore its mechanism of toxicity. The toxicity mechanism of gallium and arsenic, principal moieties in *GaAs* compound have been studied widely as a cause of *GaAs* toxicity.

2. CHEMISTRY

Gallium arsenide is a crystalline solid that is resistant to reaction with air and water. Its formal oxidation state is between *Ga* (0) *As* (0) or *Ga* (+III) *As* (-III) and is called an intermetallic because it is only composed of metals. Strong acids, particularly oxidizing acids such as nitric acid, can dissolve crystals of *GaAs* to form gallium and arsenic oxides. *GaAs* can dissolve in water within few hours. *GaAs*, water and

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oxidizing acids form arsenious acids, $As(OH)_3$, a soluble form of *As* (III).

3. TOXICITY ASSOCIATED WITH *GaAs* EXPOSURE

GaAs causes toxicity to various organs including lung, testes, kidney, brain and immune system. The symptoms of toxicity are summarized in Fig 1.

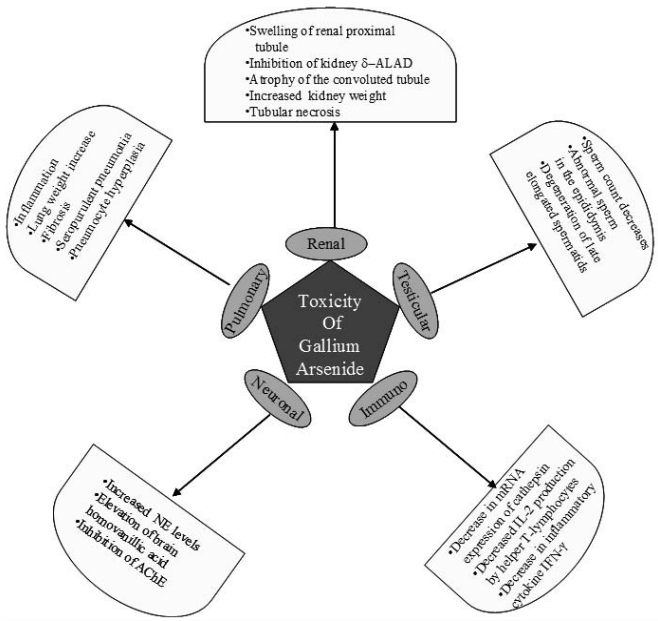

Figure 1. Symptoms of *GaAs* toxicity to various organs.

3.1 Hematopoietic Toxicity

The enzyme δ-aminolevulinic acid dehydratase (ALAD) in the haem pathway is most sensitive to *GaAs*[7]. Inhibition of this enzyme blocks the utilization of δ-aminolevulinic acid (ALA). Displacement of zinc from the enzymes may be a probable cause for inhibition of ALAD following dissolution of *GaAs in vivo*. Studies in experimental animals have also shown that a single exposure to *GaAs* produced a dose dependent inhibition of blood ALAD activity at various time intervals (1 day, 7 days and 15 days) following exposure[8]. Significant changes in blood zinc protoporphyrin and urinary ALA excretion were also found. Blood *As* contents increased significantly in a dose dependent manner. No detection of *Ga* was observed at a lower dose of 500 mg/kg in the blood; however at higher concentration *Ga* was detected which resulted in marked inhibition of blood ALAD indicating that the *Ga* probably is the true inhibitor of ALAD in *GaAs.* Authors' group reported that *GaAs* had a strong effect on heme synthesis but only a mild secondary effect on major physiological variables like blood pressure, respiration, heart rate etc[34]. Authors' report proved that ALAD inhibition following *GaAs* exposure is more related to blood gallium concentration than arsenic[35].

3.2 Lung Toxicity

The absorption of *GaAs* is higher when it is administered intratracheally as compared to oral. The absorption from the lung was about 30 times more than the *GI* tract as evident by increased urinary porphyrins coupled with blood arsenic levels[36]. After intratracheal administration of *GaAs* pulmonary inflammation was observed accompanied by histopathological changes. The increased dissolution of *GaAs* by lung fluids as compared to *GI* fluids suggested that an inflammatory process or macrophage activation contributed to the dissolution of the organic compound. It might be possible that the activated oxygen species released from the inflammatory response may have reacted with *GaAs* to oxidize the arsenic. A single dose of 10 mg/kg, 30 mg/kg, or 100 mg/kg of *GaAs* particles resulted in a dose-dependent increase in lung weight which was associated with inflammation and pneumocyte hyperplasia after 14 days[37]. Furthermore, they indicated that an intratracheal instillation of smaller sized *GaAs* particles (100 mg/kg) to rats induced more serious acute pulmonary lesions including a marked inflammatory response and mild pulmonary fibrosis[27]. Systemic arsenic toxicity occurred in their prior study[37] with larger *GaAs* particles. The study also reported increased blood arsenic levels but no gallium was detected. Another study reported that doses of 50 mg/kg, 100 mg/kg or 200 mg/kg *GaAs* particles instilled intratracheally to rats also caused lung inflammation. At 18 days following instillation of 100 mg/kg *GaAs* or 6 days following 50 mg/kg, 100 mg/kg and 200 mg/kg *GaAs,* marked body weight loss, lung weight increase, moderate seropurulent pneumonia and type II pneumocyte hyperplasia were evident[7]. *GaAs* inhalation caused an increased incidence of both the benign and malignant lung tumors in female F344 rats which had been exposed to 0.01 mg/m^3, 0.1 mg/m^3 or 1.0 mg/m^3 of *GaAs* particles for 2 yrs, but not in male rats. In both male and female B6C3F1 mice exposed to 0.1 mg/m^3, 0.5 mg/m^3 or 1.0 mg/m^3 of *GaAs* particles by inhalation for 2 yrs, there was no evidence of carcinogenicity in the lung[38]. Other reports provided incidence of nonneopastic pulmonary lesions including proteinosis, fibrosis, inflammation, alveolar epithelial hyperplasia, squamous cell metaplasia and histiocytosis[39].

3.3 Testicular Toxicity

Testicular toxicity was observed after *GaAs* was given intratracheally in rats and hamsters. A previous study has reported the testicular toxic effects of *GaAs* (7.7 mg/kg)[20,40]. *GaAs* produced a decrease in sperm count, an increase in abnormal sperm in the epididymis and degeneration of late elongated spermatids at the post-spermiation stages[21]. *GaAs* induced testicular damage, including testicular spermatid retention and epididymal sperm reduction.

3.4 Renal Toxicity

Renal toxicity was observed when CD rats exposed to *GaAs* developed mitochondrial swelling of renal proximal tubule cells and dose-dependent inhibition of δ–aminolevulinic acid dehydratase (ALAD) in blood, kidney and liver[7,18]. Repeated intratracheal instillations of *GaAs* in hamsters resulted in degenerative changes or atrophy of the convoluted tubule cells of the kidney. The exposure also resulted in increased relative kidney weight, tubular necrosis, and necrotic debris[17].

3.5 Hepatic Toxicity

Webb[36], *et a1*. reported impaired liver function due to the arsenic dissociated from *GaAs* as an increased urinary excretion of uroporphyrin following oral exposure to arsenic and also from animal experiments. Our group reported changes in some key biochemical variables in the liver of rats exposed to various doses of *GaAs* but the changes were mild[41].

3.6 Neuronal Toxicity

The administration of *GaAs* (200 mg/kg) resulted in a significant increase in norepinephrine (*NE*) levels while a significant elevation of brain homovanillic acid (*HVA*) was also observed. The inhibitory role of *GaAs* on plasma *AChE* indicated the probable systemic increase in ACh level which protects the animal from deleterious effects of increased levels of neurotransmitters during *GaAs* exposure[26].

3.7 Immunotoxicity

Some toxicity mechanisms are directly reported with *GaAs* e.g. immunotoxicity. The reports showed the direct mechanism of *GaAs* on immunomodulation; however, the moiety which is responsible for this modulation is not clear at this time. *GaAs* has both immune suppressor and immunoinducer nature. Cytokines level as well as cathepsins activity plays a central role in the mechanism of *GaAs* immunotoxicity.

GaAs causes decrease in mRNA expression of cathepsin activity especially cathepsin B, D and L[42,43]. The decrease in cathepsin activity correlates with decreased IL-2 production of helper T lymphocytes. In addition to this, the study also reported depleted expression of MHC II molecules on the cell surface which results in malfunctioning of antigen processing and presentation. Another immunosuppressive nature of *GaAs* can be mediated through binding of gallium. Gallium has affinity to bind with transferrin protein (Tf) which causes inhibition of the enzyme. Gallium moiety in *GaAs* has also been reported to decrease the secretion of inflammatory cytokines like IFN-γ, IL-6 etc.

Unlike systemic exposure, *GaAs* showed immuno-enhancement at the exposure site[44]. The study reported the role of cathepsin activity and cytokines level to understand the immunoenhancer activity of *GaAs*. The modulation in cytokine levels is also responsible for its immune-enhancement activity. The decreased expression of anti-inflammatory cytokines such as TGF-β family cytokines (TGF-β1, TGF-β2 and TGF-β3) and increased expression of proinflammatory cytokines like cytokines from IL-1 family, CCL2, CCL3, CCL5, CXCL1, IFN-γ, IL-6, etc. proves the enhancement of the immune system at exposure site is mediated through cytokines expression. This increased proinflammatory and inflammatory cytokines with decreased anti-inflammatory cytokines cause high inflammatory action at the exposure site.

4. PHYSICAL FACTORS AFFECTING TOXICITY OF GALLIUM ARSENIDE

After exposure, *GaAs* is reported to dissociate into its constitutive moieties and subsequently release *Ga* and As moiety. Since both moieties especially *As* is reported to cause toxic effects in the target tissue, the release of these moieties from *GaAs* is an important factor that affects the toxicity mechanism of *GaAs*. In other words, factor that affects the dissociation of *GaAs* into *Ga* and *As*, can also affect the toxicity of this compound.

4.1 Size

The size of *GaAs* particle is one of the important factors towards the toxicity of *GaAs*. Small particle size gets dissolved more rapidly and releases *Ga* and *As*[45] than the large crystal or wafer form. Reports have shown that the small inhalable particles of *GaAs* leads to an increase in the tissue arsenic as well as gallium burden with time[27,46]. Intratracheal instillation of *GaAs*, having a particle size with a mean count diameter of 8.30μ developed signs of systemic arsenic intoxication, pulmonary inflammation, and pneumocyte hyperplasia[27]. However, when particle size decreased to 1.63 μm they observed an increase in the *in-vivo* dissolution rate of *GaAs* which further increased the severity of pulmonary lesions. Another study demonstrated that 28 days following a single intratracheal injection of 30 mg to 300 mg gallium arsenide particles of 0.43 μ in Japanese white rabbits induced a diffuse pulmonary response[47]. Thus, results from the above studies strongly suggest the importance of particle size of *GaAs* in its metabolism and toxicity.

4.2 DISSOCIATION KINETICS

The dissociation of *GaAs* at the body's physiological environment is dependent on time which can be considered an important factor for its toxicity. High concentration of *GaAs* for small time causes higher excretion of *GaAs* through feces or urine. Peak adverse effects of *GaAs* reached at day 7 after exposure compared to observations at day 1 and 15[10]. Another recent study strongly suggested the same behaviour[48]. It is believed that *GaAs* dissociates slowly and release *Ga* and *As* moieties. Since the dissociation process is slow the toxic effects are not evident in the beginning, however at day 7, its metabolism is at optimum stage and maximum toxic effects can be observed.

4.3 Absorption Kinetics

The solubility of *GaAs* particles *in vivo* along with the tissue distribution and excretion patterns of *Ga* and *As* over time has been demonstrated, following administration of *GaAs* particles via different routes of exposure[27,36,37]. Oral single administration of Gallium arsenide (10 mg/kg, 100 mg/kg, or 1,000 mg/kg) to male Fischer rats or male Syrian hamsters was slightly soluble in the gastrointestinal tract and thus the absorption was minimal. *GaAs* mostly excreted through feces but poorly through urine. When *GaAs* was administered through oral route, *Ga* was detected in blood but not in the liver while arsenic showed significant increase in blood and hepatic tissues[49].

4.4 Medical Application

Besides its toxic effects, gallium compounds have a unique role in the field of medicine. Gallium interact with

cellular processes and proteins specifically it has a role in iron metabolism. Although, gallium has no known physiologic function in the human body, still it has widely been used as diagnostic and therapeutic agents in medicine especially in the areas of metabolic bone disease, cancer, and infectious disease. Clinically, radioactive gallium (^{67}Ga citrate) compounds has been used as tumor imaging agents. ^{67}Ga scanning has been used frequently in patients with Hodgkin's and non-Hodgkin's lymphomas to detect residual disease or disease that has relapsed following treatment with chemotherapy or radiotherapy[50,51]. Its short half life (68 min),^{68} *Ga* is used for the imaging of neuroendocrine tumors in patients[52]. Gallium nitrate is used as diagnostic and therapeutic agent in cancer and disorders of calcium and bone metabolism. Gallium nitrate has been shown to inhibit bone turnover and to decrease osteolysis in patients with multiple myeloma and in patients with bone metastases from a variety of different cancers[53,54].

In case of arsenic, its toxicity is well known while, medical application of arsenic trioxide has long been of biomedical interest. Arsenic trioxide under the trade name Trisenox (manufacturer: Cephalon) is a chemotherapeutic agent of idiopathic function used to treat leukemia that is unresponsive to 'first line' agents[55]. It is suspected that arsenic trioxide induces cancer cells to undergo apoptosis. The combination therapy of arsenic trioxide and all-trans retinoic acid (ATRA) has been approved by the US food and drug administration (FDA) for treatment of certain leukemias[56].

5. MECHANISM OF TOXICITY

Both arsenic as well as gallium is responsible for toxic effects of gallium arsenide. Although *Ga* gets rapidly excreted through urine and feces, its hematotoxic effects are well documented. Thus in the following section, we have briefly described the toxic effects of gallium and arsenic to understand the mechanism of *GaAs* toxicity (Fig 2).

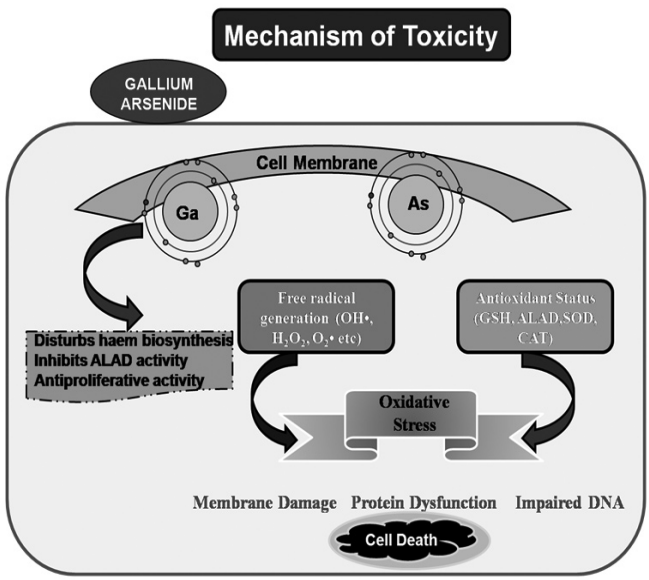

Figure 2. Mechanism of toxicity by Gallium Arsenide.

5.1 MECHANISM OF GALLIUM TOXICITY

5.1.1 Competition with Iron

Gallium primarily binds transferrin (Tf) protein, which is a blood plasma protein for iron ion delivery. Tf is a glycoprotein that binds iron very tightly but reversibly. Due to the similar charge and size ratio (Fe^{3+} = 0.64Å; Ga^{3+} = 0.62 Å) between gallium and iron, gallium directly binds to the free sites of plasma Tf, which subsequently facilitates the movement of gallium across cell membranes using the same receptor mediated mechanism as that for iron. After distribution of the gallium into the normal tissues, it disturbs normal cell iron incorporation and metabolism[57].

This formation of Tf-*Ga* complex is an important factor in the mechanism of gallium toxicity. This formed Tf-*Ga* complex can assist to understand following toxicities of gallium:

- The Tf-*Ga* induced disruption of normal haemoglobin production has been shown to be due to an inhibition of iron incorporated into the developing erythroid cells precurcors, which leads to anaemic condition[58,59].
- Formation of Tf-*Ga* complex results in decreased concentration of intracellular iron[60].
- Gallium from Tf-*Ga* complex further transfers and subsequently binds to another iron dependent enzyme lactoferrin[61]. In case of gallium toxicity, this protein actively binds with Ga^{3+} which results in inhibition of antimicrobial activity or weakness of the immune system.
- Another iron-binding protein to which gallium can bind is ferritin.

5.1.2 Effects on Haem Biosynthesis and Competition with Zinc

The mechanism of δ-aminolevulinic acid dehydratase (ALAD) inhibition following *GaAs* exposure has already been understood[7]. Significant inhibition in blood and tissue ALAD activity accompanied by excretion of urinary ALA is seen upon *GaAs* exposure. The study concluded that gallium is the primary inhibitor of ALAD activity and the competition between gallium and Zn^{2+} to occupy the active site of enzyme is the primary reason behind *GaAs* induced ALAD inhibition. The recovery of gallium inhibited the ALAD activity by Zn^{2+} administration has been observed in a separate study conducted which further points to the competitive inhibitory nature of gallium in ALAD inhibition[62]. The inhibition further results in accumulation of its substrate called ALA which is a very important factor of oxidative stress inducted in *GaAs* toxicity. Conversion of oxyhemoglobin to methemoglobin is mediated by ALA auto-oxidation, during which reactive oxygen species (ROS) are produced[63]. Thus accumulation of ALA is the indirect mechanism of ROS production in *GaAs* toxicity.

5.1.3 Oxidative Stress

Ga is not reported to cause oxidative stress. A recent report however suggests both gallium and arsenic induces oxidative stress via generation of ROS and RNS in brain parts and primary cortex culture, which subsequently leads

to neurodegeneration[26]. The possible mechanism behind *Ga* induced oxidative stress may be attributed to (i) binding of *Ga* with transferrin as well as ferritin which causes the release of iron and hence the production of ROS via Fenton reaction (ii) *Ga* induced inhibition of blood ALAD activity leads to the accumulation of its substrate ALA, which undergoes auto oxidation and produces ROS thus generating oxidative stress.

5.2 Mechanism of Arsenic Toxicity

Arsenic metabolizes into different metabolites (arsenate, arsenite, MMA, DMA). All these metabolites exhibit different toxicity profiles. Trivalent inorganic arsenicals readily react with sulfhydryl groups such as GSH and cysteine[64,65]. The activity of methylated arsenicals may alter cellular redox status and eventually lead to cytotoxicity.

5.2.1 Oxidative Stress Dependent Mechanism

Oxidative stress has been widely reported in literature as a consequence of arsenic toxicity[66,69]. Arsenic exposure causes both induction of ROS level and depletion in antioxidant levels. Many studies have confirmed the generation of free radicals during arsenic metabolism in cells. Arsenic mediated generation of ROS is a complex process which involves the generation of variety of ROS including superoxide ($O_2^{\bullet-}$), singlet oxygen ($^1O_2$), the peroxyl radical ($NOO^{\bullet}$), nitric oxide ($NO^{\bullet}$), hydrogen peroxide (H_2O_2), dimethylarsinic peroxyl radicals ([$(CH_3)_2AsOO^{\bullet}$]) and also the dimethylarsinic radical ([$(CH_3)_2As^{\bullet}$]). The metabolism of arsenic, which releases when GaAs dissociates is similar to the normal arsenic metabolism. This result again suggests the one of the possible mechanism of arsenic induced H_2O_2 generation. Under physiological conditions, the oxidation of *As*(III) to *As*(V) results in the formation of H_2O_2[70] which is a spontaneous reaction with estimated standard free energy change for H_2O_2 formation of –40.82 kcal/mol (–170.87 J/mol).

$$H_3AsO_3+H_2O+O_2 \rightarrow H_3AsO_4+H_2O_2((\Delta_rG^{\Theta}=-40.82 \text{ Kcal/mol})$$

Another indirect mechanism for ROS production is mediated through macrophages overproduction following acute exposure. Macrophages are well known source of ROS and reactive nitrogen species (RNS). In addition, many reports have observed the direct effects of exposure to arsenic[68] or *GaAs*[12,13] on ROS production. Like gallium, arsenic is also reported to release iron from ferritin, this released iron from ferritin causes ROS generation through Fenton reaction[71]. Literature studies have shown that the primary biochemical mechanism of arsenic toxicity is binding of the metal to cellular sulfhydryl groups resulting in inhibition of number of cellular enzyme system[72].

Arsenic induced ROS production and antioxidant enzyme inhibition thus results in oxidative stress.

5.2.2 Oxidative Stress Independent Mechanism

Various mechanisms of arsenic have been implicated some of these are not associated with oxidative stress. Apart from oxidative stress, arsenic associated toxicities and their mechanisms are due to DNA damage and cell proliferation.

Arsenic induced free radical generation may cause a number of DNA base alterations that can lead to carcinogenesis or mutagenesis. However, there are specific and general repair mechanisms that can repair DNA base modifications[73]. Arsenic is also reported to disturb DNA repair enzymes. This activity of arsenic is mainly independent of free radical generation. Human poly (ADP-ribose) polymerase (PARP) activity is also inhibited by arsenite that may have a role in DNA repair[74]. The enzyme contains two vicinal –SH groups, and due to high affinity for that group arsenite might bind to one or both groups and inhibit the enzyme activity. The theory that altered DNA repair is the cause of arsenic carcinogenesis is particularly attractive because trivalent arsenic species, such as arsenite, can bind strongly to dithiols as well as free sulfhydryl groups. Cellular proliferation induced by arsenic may be due to dysregulation of positive and negative proliferation regulators. Another important process of cell proliferation is DNA methylation. The alteration of DNA strand by increasing or decreasing its methylation process may have a role in the genotoxicity and development of cancer[75]. Both hypermethylation and hypomethylation have been observed as a consequence of arsenic exposure.

6. PROTECTIVE AND THERAPEUTIC MEASURES

There is no well defined treatment regime for *GaAs* induced toxicity as the toxicology and mechanism is not well defined. Reversal of *GaAs* induced suppression of the antibody response by a mixed disulfide metabolite of meso 2,3-dimercaptosuccinic acid has been reported in the literature[6]. The reversal of the suppression could not be attributed to the cleavage of L-cysteine from the 2:1 mixed disulfide metabolite, as the addition of equimolar concentrations of L-cysteine had no effect on *GaAs* induced suppression. The author pointed out to the conversion of DMSA to a transportable moiety to reach intracellular metal deposits. Figure 3 points out to various preventive and treatment strategies for *GaAs* induced toxicity.

6.1 Preventive Measures

6.1.1 Essential Metal Ions: Selenium and Zinc

The toxic elements interact with essential nutrients and interfere in the metabolic processes. The chemical similarity between arsenic and selenium, an essential micronutrient generally allows for antagonistic effects between these metals[76]. Selenium and arsenic each increase the biliary excretion of the other[70]. Selenium also decreases the teratogenic and thyroid toxicity of arsenic when both salts are injected simultaneously in hamsters and rat[77,78]. Administration of selenium in the diet resulted in significant recovery of blood ALAD activity upon *GaAs* exposure which is a protective mechanism against impairment of heme synthesis. Along with this favorable response on the biochemical and immunological variables were also observed. Concomitant administration of Se and *GaAs* significantly prevented the accumulation of arsenic, while the gallium concentration reduced moderately in the soft organs. The protective effect of selenium from arsenic/

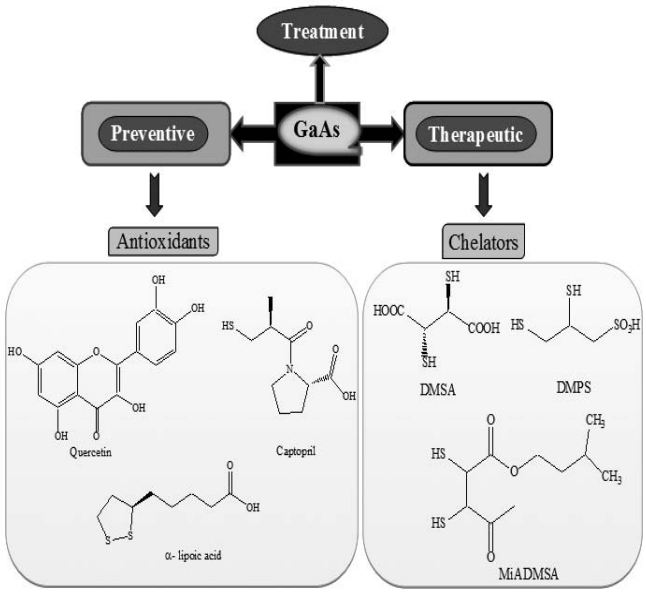

Figure 3. Treatment of *GaAs* induced toxicity.

gallium insult might be attributed to the formation of inactive selenium-arsenic/gallium complexes[9].

Administration of *Zn* together with *GaAs* was effective in reducing *GaAs* induced inhibition of ALAD activity, liver and kidney reduced glutathione (GSH) level and elevation of oxidized glutathione (GSSG) and thiobarbituric acid reactive substances (TBARS) levels. Zinc supplementation was also beneficial in reducing the elevated TBARS level which may be due to its antioxidant property and also the uptake of arsenic in the blood and liver in *GaAs* exposed rats[48].

6.1.2 Antioxidants: α–lipoic Acid, Quercetin, Captopril

α–lipoic acid, quercetin and captopril have common properties such as free radical scavenging activity, metal chelation activity, presence of thiol moiety in their structure and have been employed as an antioxidant for the treatment of *GaAs* toxicity[35]. Co-administration of α–lipoic acid with GaAs was most effective in reducing *GaAs* induced inhibition of δ–aminolevulinic acid dehydratase (ALAD) activity, liver, kidney and brain reduced glutathione (GSH) level and elevation of oxidized glutathione (GSSG) as compared to captopril and quercetin.

6.2 Therapeutic Measures

6.2.1 Chelating Agents: DMPS, DMSA, MiADMSA

Post-exposure treatment with the two thiols meso 2,3- dimercaptosuccinic acid (DMSA) and sodium 2,3-dimercaptopropane 1-sulfonate (DMPS) has been reported to be moderately effective in rats exposed sub-acutely to GaAs. Animals exposed to *GaAs* had a significantly higher gallium and arsenic level in blood and liver. Gallium level in the blood and liver remain uninfluenced by chelators but arsenic concentration reduced significantly by treatment with DMPS and DMSA which suggests the chelators could be an effective chelating agent for reversing most of the *GaAs* induced toxicity[79].

A comparative study of post treatment with chelating agents meso-2,3-dimercaptosuccinic acid (DMSA) and monoisoamyl meso-2,3-dimercaptosuccinic acid (MiADMSA) ,showed the latter to be better in the mobilization of arsenic and in the turnover of *GaAs* sensitive biochemical alterations[12]. The above difference is rising due to the structural difference in the compound with the more lipophilic moiety, MiADMSA, having the potential to chelate out arsenic from the intracellular sites also.

DMSA is an effective arsenic chelator[80] whereas oxalic acid has been reported to be an effective gallium chelator[81]. Another report suggests a greater effectiveness of the chelation treatment (i.e. removal of both gallium and arsenic from body organs) by the use of combined administration of the succimer (DMSA) with oxalic acid[13]. It was shown in the study that oxalic acid was able to remove gallium from the blood and tissues but had no role in the reversal of altered parameters.

A dose dependent study of chelating agent DMSA and two of its monoester derivative monomethyl DMSA and monoisoamyl DMSA has been carried out[24]. Recently, we reported comparative therapeutic efficacy of MiADMSA, MmDMSA and MchDMSA, individually and in combination against *GaAs* toxicity in male rats[82]. The study revealed comparatively more pronounced efficacy of MiADMSA than other monoesters in decreasing arsenic from the soft tissues and in the recovery of biochemical variables indicative of blood and tissue oxidative stress. The data also provided evidence that co-administration of MiADMSA with MchDMSA might be a better therapeutic strategy to treat *GaAs* intoxication than monotherapy with monoesters[83].

7. CONCLUSIONS

In the past few years, the awareness of the toxicity of *GaAs* has been increased. However, comparatively little is known about its toxicity mechanism. Since it is the compound of gallium and arsenic, it has toxicity properties of both of these metals. Dissolution into two constitutive moieties is the important step of its toxicity, which depends upon various factors like particle size, route of exposure, and duration of exposure. Gallium has been considered as a mild toxic as most of the part of this metal being excreted through urine and/or feces however it primarily causes hematotoxicity by directly competing with iron or zinc. On the other hand, arsenic exerts its toxicity directly via binding with a free thiol group of important metabolic enzymes or indirectly by producing oxidative stress. Some of immunotoxicity mechanisms have also been reported directly with *GaAs,* where it works as both immunosuppressant and immunoenhancer, depend upon the exposure site. In case of systemic exposure, it suppresses the body's immune system via inhibiting proinflammatory cytokines and depleting cathepsin activity, while in case of systemic exposure it acts vice versa.

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