*REVIEW*

# Arsenic-induced abnormalities in glucose metabolism: Biochemical basis and potential therapeutic and nutritional interventions

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## Abstract

Health hazards due to the consumption of heavy metals such as arsenic have become a worldwide problem. Metabolism of arsenic produces various intermediates which are more toxic and cause toxicity. Arsenic exposure results in impairment of glucose metabolism, insulin secretion in pancreatic β-cells, altered gene expressions and signal transduction, and affects insulin-stimulated glucose uptake in adipocytes or skeletal muscle cells. Arsenic toxicity causes abnormalities in glucose metabolism through an increase in oxidative stress. Arsenic interferes with the sulfhydryl groups and phosphate groups present in various enzymes involved in glucose metabolism including pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, and contributes to their impairment. Arsenic inhibits glucose transporters present in the cell membrane, alters expression of genes involved in glucose metabolism, transcription factors and inflammatory cytokines which stimulate oxidative stress. Some theories suggest that arsenic exposure under diabetic conditions inhibits hyperglycemia. However, the exact mechanism behind the behavior of arsenic as an antagonist or synergist on glucose homeostasis and insulin secretion is not yet fully understood. The present review delineates the relationship between arsenic and the biochemical basis of its relationship to glucose metabolism. This review also addresses potential therapeutic and nutritional interventions for attenuating arsenic toxicity. Several other potential nutritional supplements are highlighted in the review that could be used to combat arsenic toxicity.

Core tip: This review illustrated the interference caused by arsenic in enzymes, genes and transcription factors involved in glucose metabolism and possible nutritional aspects for attenuating arsenic toxicity.

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## INTRODUCTION

Arsenic is a toxic heavy metal and belongs to the 5th group in the periodic table. It is present in both inorganic and organic forms in different surroundings and its level is increased by anthropogenic contamination[1]. It is a ubiquitous element and is found in four oxidation states -3, 0, +3, and +5. It is an environmental contaminant of worldwide concern due to its high toxicity and presence

$$As^{V} \xrightarrow{(A)} As^{III} \xrightarrow{(B)} MMA^{V} \xrightarrow{(C)} MMA^{III} \xrightarrow{(D)} DMA^{V}$$
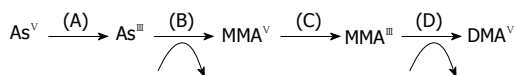
**Figure 1 Arsenic methylation pathway in the human body[25].** A: Arsenate reductase or purine nucleoside phosphorylase (PNP); B: Arsenite methyl transferase (As3MT); C: Glutathione S-transferase omega 1 or 2 (GSTO1, GSTO2); D: Arsenite methyl transferase (As3MT). SAHC: S-adenosylhomocysteine; SAM: S-adenosylmethionine; MMAV: Monomethylarsenic acid; MMAIII: Mono-methylarsonous acid; DMAV: Dimethylarsenic acid; DMAIII: Dimethylarsinous acid.

in groundwater aquifers. Arsenic contamination in water has been found in countries such as Canada, India, Bangladesh, United States, China, Taiwan, Mexico, Poland, Japan, Nepal[2] and Iran[3]. Inorganic arsenic is believed to be the major form of arsenic in water, soil and various foods[4] and is said to be a group I carcinogen based on clinical studies[5].

Flora reported that the major exposure route of inorganic arsenic (iAs) is by contaminated drinking water in India, Bangladesh, China and American countries. Argentina (200 ppb), Mexico (400 ppb), Taiwan (50-1980 ppb), and the Indo-Bangladesh region (800 ppb) are countries where arsenic concentration in drinking water is reported to be beyond WHO guidelines maximum permissible value (10 ppb)[6].

Epidemiological studies in various regions of the world with high levels of arsenic in groundwater have associated arsenic exposure with increased risks of different types of cancer (skin, liver, kidney and lung), arteriosclerosis and cardiovascular diseases, diabetes, hypertension and neurological diseases (Alzheimer and Parkinson)[7-13]. Arsenic stimulates alterations in oxidative stress, cell calcium signaling, impairment of cell mitochondrial function and affects cell cycle progression[14-17]. Some of these toxic effects at cellular and molecular levels ultimately lead to cancer[18]. Although arsenic induces adverse health effects, all exposed humans do not develop arsenic symptoms related to exposure, suggesting that genetic susceptibility is also an important aspect involved in the human response to arsenic exposure.

### *Metabolism of arsenic in the human body*

Metabolism of arsenic takes place in the liver where the first step is methylation. The presence of monomethylarsenic acid (MMA$^V$) and dimethylarsenic acid (DMA$^V$) indicates the methylation of arsenic in bile and urine. Monomethylarsenic acid is comparatively more toxic than dimethylarsenic acid[19]. It was previously suggested that arsenic metabolism was a detoxification procedure, but now it is reported that intermediates of arsenic metabolism generate more toxicity. Absorbed arsenic undergoes biomethylation to form MMA$^V$ and DMA$^V$ (urinary excretion products) and are more toxic than iAs[20]. Pentavalent arsenic (iAs$^V$) is quickly reduced to trivalent arsenic (iAs$^{III}$) and is then enzymatically methylated in humans and animals, which is then excreted *via* urine in the form of the dimethylated metabolite DMA$^{V[21-24]}$. Methylation of arsenic requires S-adenosylmethionine as the methyl donor

and glutathione sulfhydryl as a vital co-factor[25] (Figure 1).

Along with the major metabolite, DMA$^V$, dimethyl-monothioarsenic acid (DMMTA$^V$), a thiolated metabolite, is also found in urine as a minor metabolite[26-29]. In addition, DMMTA$^V$ and dimethyldithioarsenic acid (DMDTA$^V$) are found in organs *in vivo* and *in vitro*[30-32]. Moreover, iAs consumed by marine organisms is converted into arsenosugars and arsenobetaines and their thiolated metabolites are recognized as minor marine arsenic metabolites[33-36]. Arsenic is ingested as arsenate or arsenite, is altered into the dimethylated form for excretion, and inorganic arsenicals and their metabolite viz., DMA. Among these arsenic metabolites, DMDTA$^V$ and DMMTA$^V$ are the current arsenic metabolites observed in urine and organs in man and animals[26-29,31,32]. It has been suggested that DMMTA$^V$ is simply absorbed by organs/tissues and is more toxic in nature[37]. DMMTA$^V$ is absorbed efficiently by organs in a different way to that of DMDTA$^V$, although DMMTA$^V$ and DMDTA$^V$ are both thioarsenicals. In addition, the distribution and metabolism of DMMTA$^V$ are similar to DMA$^{III}$ in hamsters, while the distribution and metabolism of DMDTA$^V$ are similar to those of DMA$^{V[38]}$.

### *Oxidative stress*

Arsenic causes toxicity *via* oxidative stress by affecting the antioxidant enzymes[6,39]. It stimulates the production of reactive oxygen species (ROS) which results in the induction of adverse health effects[20,40]. The mitochondrion is the chief site of ROS generation in cells and enhanced ROS formation is due to the abnormal function of electron transfer through the respiratory chain in mitochondria which in turn results in the production of hydrogen peroxide ($H_2O_2$), superoxide anion ($O_2^-$) and hydroxyl radicals ($OH^{\cdot}$)[41]. Furthermore, in the electron transport chain, complexes I and III are the major leak sites for ROS formation, as some of the electrons passing through the mitochondrial respiratory chain leak out to molecular oxygen ($O_2$) to form superoxide radicals and then dismutate to $H_2O_2$. Increased ROS causes cellular and metabolic impairment through oxidative damage, which results in physiological abnormalities and deleterious chronic disorders. $H_2O_2$ is produced during the oxidation of As$^{(III)}$ to As$^{(V)}$ when intermediary arsine species are formed such as dimethylarsinic radicals [$(CH_3)2As^{\bullet}$] and dimethylarsinic peroxyl [$(CH_3)2AsOO^{\bullet}$] involving $O_2^{\bullet-}$[42]. Arsenic leads to an increase in consumption of oxygen by cells, which results in ROS production and hence an increase in oxidative stress[43]. Hepatic and renal heme oxygenase isoform-1 (HO-1) are also involved in the production of ROS by iAs which in turn results in extra free iron and biliverdin formation[44]. This free iron participates in the Fenton reaction resulting in the formation of hydroxyl free radical ($\bullet OH$) which attacks DNA[45].

ROS produced intracellularly at the time of physiological processes, regulate cell functions, for instance endocytic pathways, autophagy, gene expression, intracellu-
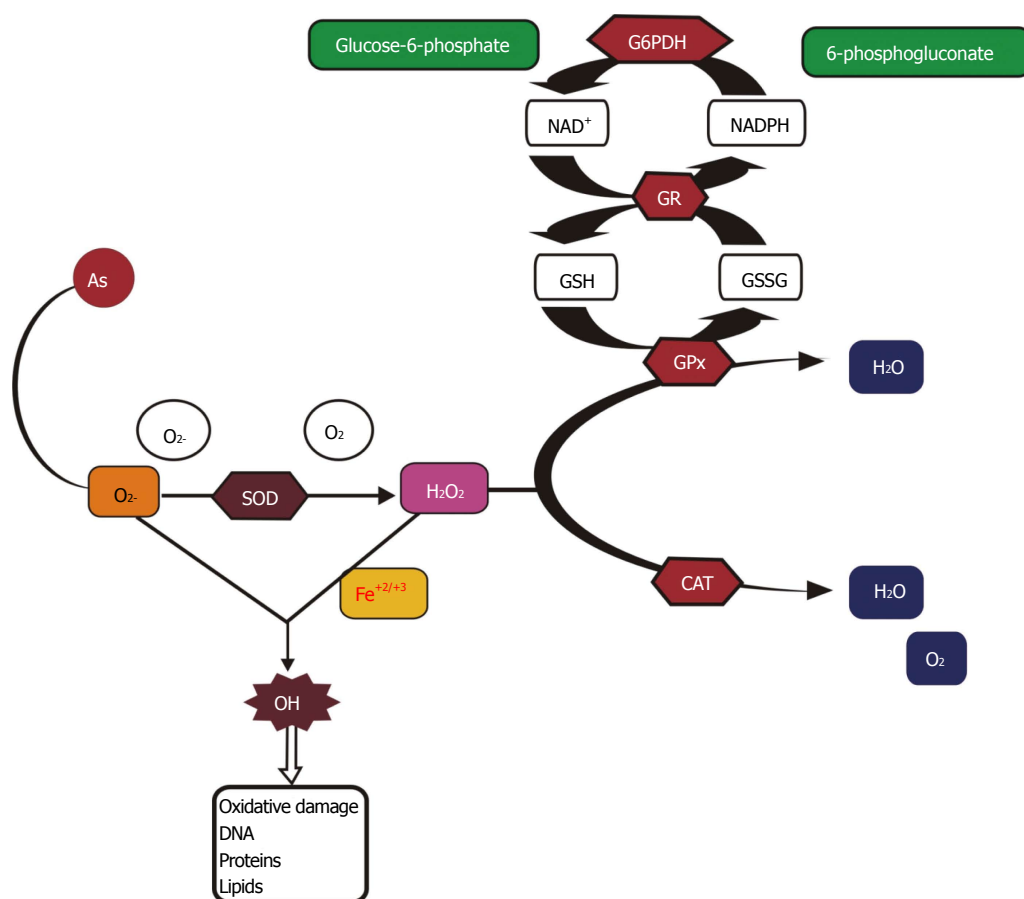
**Figure 2 Mechanism of arsenic toxicity: Arsenic enhances the production of superoxide anion radical which results in a higher oxidant level than antioxidant enzymes involved in the detoxification of superoxide anion radical *viz*., superoxide dismutase, catalase, glutathione reductase and glucose-6-phosphate dehydrogenase.** SOD: Superoxide dismutase; CAT: Catalase; GPx: Glutathione peroxidase; GR: Glutathione reductase; G-6-PDH: Glucose-6-phosphate dehydrogenase; NAD$^+$: Nicotinamide adenine dinucleotide; NADPH: Nicotinamide adenine dinucleotide phosphate reduced.

lar $Ca^{2+}$, glucose homeostasis, hypoxic and inflammatory responses[46-49]. ROS function as second messengers due to stimulation/suppression of numerous signaling features by the oxidation of sulfhydryl groups and by changing the intracellular redox status, therefore inducing cell signaling pathways, downstream gene expression and cell reproduction or death[13,20]. The signaling molecules affected include protein tyrosine kinases and phosphatases, protein serine/threonine kinases and phosphatases, small G proteins, lipid signaling, $Ca^{2+}$ signaling and transcription factors[50]. Biochemical reactions such as glycation results in the formation of advanced glycation end-products (AGEs) and protein oxidation causes alterations in cells which in turn results in the formation of disulfides between cysteine and methionine residues, cyclization of polyunsaturated fatty acid residues of phospholipids forming malondialdehyde (MDA), lipid peroxidation, 4-hydroxy-2-nonenal (HNE) and nucleic acid oxidation[7,8,51,52]. Free radicals produced during iAs metabolism are the source of oxidative stress[45]. Low concentrations of MMA$^{III}$ and DMA$^{III}$ are cytotoxic in human and rat skin, bladder, lung cells and human hepatocytes[53-56]. Cellular offense in response to methylated metabolites is involved in genotoxicity with strong proof of oxidative stress as a causal factor. Genotoxicity of MMA$^{III}$ and

DMA$^{III}$ can be reversed by ROS inhibitors[57]. Moreover, methylated metabolites mainly DMA$^{III}$ and trimethylarsenic oxide (TMAO), also play a role in arsenic-induced genotoxicity[58]. Cells having low methylation capabilities are more prone to cyotoxicity by arsenic specifying that other mechanisms are also employed in cytotoxicity induced by arsenic. An *in vitro* study on mammalian cell lines showed that there was no clear link between arsenic methylation capability by cells and resulting cytotoxicity induced by sodium arsenite[59]. The possible mechanism of arsenic toxicity is depicted in Figure 2.

### Arsenic and diabetes mellitus
Diabetes mellitus is one of the world's oldest known diseases. Type 2 diabetes mellitus (T2DM) is a widespread global metabolic disorder, distinguished by the unusual metabolism of carbohydrates and lipids, mainly resulting either from a fault in insulin secretion and/or insulin action, or adipocyte functioning[60]. In T2DM, the entire body glucose homeostasis is disrupted due to insulin resistance and impaired glucose uptake by peripheral tissues, consisting of skeletal muscle and adipose tissue. In these tissues, glucose homeostasis is regulated by a mechanism involving insulin-dependent stimulation of glucose uptake.
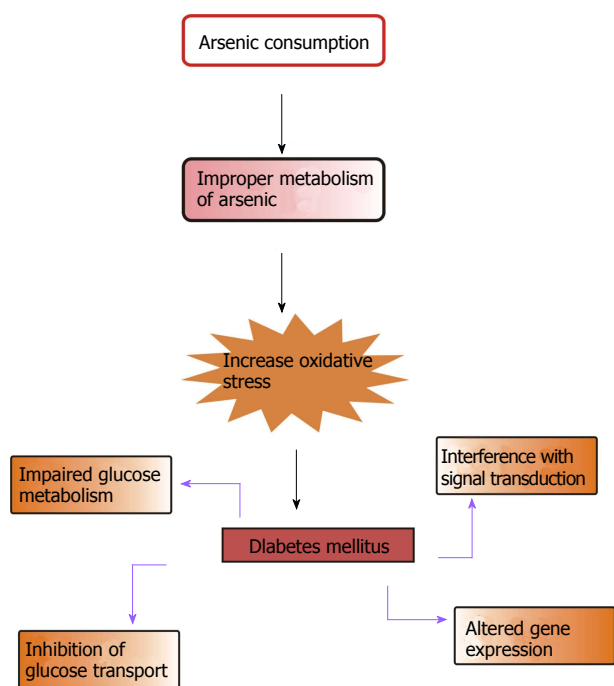
**Figure 3 Possible biochemical approaches by which arsenic induces diabetes.**

The worldwide incidence of diabetes among people aged 20-79 years was approximately 6.4% in 2010. This rate is supposed to rise to 70% in developing countries and 20% in developed countries from 2010 to 2030[61]. Globally, more than 0.39 million people die every year from diabetes which is due to increase in the next decade[62,63]. T2DM is more prevalent than type 1 diabetes mellitus. In India, the World Health Organization (WHO) reported that about 32 million people suffered from diabetes in 2000. According to the International Diabetes Federation (IDF), the total number of diabetic patients is nearly 40.9 million which is supposed to increase to 69.9 million in 2025[64]. Environmental and lifestyle factors are the main causes of this remarkable increase in T2DM prevalence[65,66].

Epidemiological studies suggest that T2DM is one of the most familiar non-cancerous metabolic disorders correlated with chronic exposure to iAs. Lai *et al*[67] in 1994 first established the link between diabetes and iAs. The correlation between arsenic toxicity and diabetes mellitus is a burning issue. Increased prevalence of T2DM is associated with the use of drinking water containing high levels of iAs and chronic occupational exposure to iAs[68-75]. This is more prevalent in people consuming contaminated water in Bangladesh and Taiwan and in those working in copper smelters and the art glass industry in Sweden[67,70-72,74-76]. According to the American Diabetes Association, diabetes due to arsenic toxicity or arsenic-induced diabetes may be classified under "the other specific types"[77]. In epidemiologic studies, arsenic exposed subjects showed symptoms of diabetes mellitus similar to T2DM[70]. As the symptoms were almost identical to those of T2DM, it is considered that the pathophysiol-

ogy of diabetes mellitus induced by arsenic is more likely to be similar to that of T2DM[6]. According to Wang *et al*[78], there is a relationship between increased risk of metabolic syndrome, one of the most important cardiovascular disease risk factors and exposure to iAs in the general population[78]. Figure 3 shows the possible way by which arsenic causes diabetes mellitus.

### Arsenate replaces the phosphate group

Arsenate ($As^V$) replaces the phosphate group in various biochemical reactions owing to their similar structure and properties[79]. Arsenate reacts *in vitro* with glucose and gluconate[80,81] to form glucose-6-arsenate and 6-arsenogluconate, respectively, which are corresponding similar to glucose-6-phosphate and 6-phosphogluconate. Arsenate also replaces the phosphate group in the sodium pump and anion exchange transport system of human erythrocytes[82]. Arsenate inhibits ATP formation during glycolysis by substituting arsenate for the phosphate anion in a process known as arsenolysis. In one of the steps of glycolysis, the phosphate group is enzymatically linked to D-glyceraldehyde-3-phosphate to form 1,3-diphospho-D-glycerate. In this reaction, phosphate is replaced by arsenate to form an unstable anhydride, 1-arsenato-3-phospho-D-glycerate, and hydrolyzes into arsenate and 3-phosphoglycerate. The instability of arsenic anhydride is due to the longer As-O bond length compared with the P-O bond length[79]. ATP is not generated during glycolysis in the presence of arsenate[83,84]. At the mitochondrial level, arsenolysis may occur during oxidative phosphorylation in the presence of succinate to form adenosine-5'-diphosphate (ADP) arsenate[81]. ADP-phosphate formed during oxidative phosphorylation is difficult to hydrolyze in comparison to ADP-arsenate. During the process of cellular respiration, arsenolysis diminished ATP production by substituting phosphate with arsenate in respiratory pathways. An *in vitro* study suggested that arsenate exposure caused a reduction in ATP in rabbit and human erythrocytes[85,86]. The activity of hexokinase is inhibited at higher concentrations of arsenate[87]. In contrast, the two pentavalent forms of methylated metabolites, monomethylarsonate and dimethylarsonate do not disturb the metabolism of phosphate or bind to sulfhydryl groups[88].

### Affinity for sulfhydryl group

Arsenic affinity for thiols, especially the vicinal thiols of enzymes, is an accepted mechanism for arsenic toxicity, thereby inhibits catalytic activity of an enzyme by binding to a thiol-containing active site[84]. Trivalent arsenicals easily react *in vitro* with molecules having a sulfhydryl group, for instance cysteine and reduced glutathione (GSH)[85]. The complex linking vicinal thiols and arsenic is generally strong. Three main pathways by which arsenic decreases cellular GSH level have been suggested: (1) In the reduction of arsenates to arsenites, GSH functions as an electron donor; (2) Arsenite has a strong affinity for GSH; and (3) Arsenic-induced free radicals oxidize GSH.

As a consequence of obstruction of the Kreb's cycle

and disruption of oxidative phosphorylation by arsenic, a reduction in cellular ATP followed by cell death occur. Due to the interaction of arsenic with thiol groups, methylated trivalent arsenicals such as MMA[III] inhibits GSH reductase and thioredoxin reductase[89,90]. Cellular redox conditions are modified by the activities of methylated arsenicals, which in turn results in cytotoxicity. GSH protects cells from cytotoxins and is also involved in the metabolism of arsenic, through the formation of GSH conjugates. Numerous proteins with regulatory functions such as nuclear factor kappa B (NFκB) and adiponectin (AP)-1 are susceptible to cellular redox conditions. These proteins are regulated by GSH by altering the redox state of particular sulfhydryl groups of target proteins including stress kinases, transcription factors and caspases[91].

### Arsenic impairs pathways of glucose catabolism

Insulin-independent diabetes is the common form of diabetes mellitus among people chronically exposed to iAs[71]. It has been suggested that at the cellular level, iAs or its metabolites disturb glucose metabolism and insulin signaling. Trivalent arsenicals are moderately effective inhibitors of numerous enzymes involved in glucose metabolism such as succinyl Co-A synthase, α-ketoglutarate dehydrogenase and pyruvate dehydrogenase (PDH)[92,93]. The PDH complex is the most studied enzyme and is considered most sensitive to inhibition by arsenite. During cell respiration, pyruvate is converted into acetyl-CoA in the presence of the pyruvate dehydrogenase enzyme complex (dihydrolipoyl transacetylase, dihydrolipoyl dehydrogenase, pyruvate decarboxylase, thiamine pyrophosphate, lipoic acid, CoASH, FAD, NAD$^+$). Arsenite inhibits PDH by binding to the lipoic acid moiety[94]. It has been reported that MMA[III] is a stronger inhibitor of PDH than arsenite[93]. The Kreb's cycle provides reducing power in the electron transport chain for ATP generation. Inhibition of PDH leads to decreased generation of ATP and energy resulting in cell damage and cell death.

In addition, an organic derivative of arsenite, phenylarsine oxide (PAO) inhibits basal or insulin stimulated glucose uptake by canine kidney cells, adipocytes and intact skeletal muscle[95-100]. Arsenic interferes with sulfhydryl-containing enzymes such as pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, competes with the phosphate binding sites on glycolytic enzymes, uncouples oxidative phosphorylation and impairs glucose metabolism[101,102]. Arsenic interferes with phosphate binding sites in ATP resulting in the formation of ADP-arsenate which inhibits metabolic pathways which require ATP. Glucose-6-phosphate is an essential mediator for glycolysis, glycogenesis, gluconeogenesis and glycogenolysis, and the pentose phosphate pathway (PPP). The PPP generates nicotinamide adenine dinucleotide phosphate (NADPH), an essential cofactor for glutathione reduction. Insufficient production of NADPH from the PPP further interrupts the cell's ability to deal with oxidative stress[103]. Glucose-6-phosphate dehydrogenase (G6PDH) activity in mice exposed to arsenic, was significantly re-

duced in a time-related manner[104]. G6PDH is an enzyme of the PPP, an alternate metabolic pathway for glucose. Reduced blood activity of G6PDH can lead to oxidative stress-induced diabetes and diminished nitric oxide generation[105,106]. Exposure to arsenic also results in an increase in glycosylated hemoglobin level which indicates high blood glucose level and was reported in Danish people working in the wood industry[73]. Thus, individuals exposed to iAs both from the environment and occupationally exposed are prone to diabetes mellitus.

### Modulation of insulin signal transduction pathways

Signal transduction pathways activated by insulin which result in glucose uptake have been widely studied. This consists of binding of the insulin molecule to the α-subunit of the insulin receptor followed by activation of the tyrosine kinase moiety leading to autophosphorylation of the β-subunit of the insulin receptor, and consequent phosphorylation of insulin receptor substrate 1 or 2, phosphorylation and activation of phosphatidylinositol 3-kinase, and phosphorylation of phosphatidylinositol-4,5-biphosphate at the cell membrane to phosphatidylinositol-3,4,5-triphosphate (PIP$_3$)[107-109]. PIP$_3$ promotes phosphorylation of protein kinase B (PKB/AKt) and protein kinase C (PKC) enzymes that is, PKC λ and PKC ζ[110,111]. The phosphorylation of PKB/AKT results in the transport of GLUT4 from the perinuclear space to the plasmalemma and the activation of glucose uptake[112,113].

iAs[III] and methylated arsenicals interfere with the main signal transduction pathways in human cells[114]. Arsenic exposed cells show inhibition of the expression or activation of PKB/AKT, which is an essential component of the insulin stimulated signal transduction pathway. Thus, insulin-dependent signal transduction at the PKB/AKT level is inhibited, which is responsible for hyperglycemia in humans exposed to iAs. An *in vitro* study showed that iAs[III] interrupts the expression and phosphorylation of PKB/AKT and inhibits insulin-stimulated glucose uptake and mobilization of GLUT4[115]. Arsenic is also involved in the modulation of the mitogen-activated protein kinases (MAPK) pathway and related growth factors[114,116]. The MAPK signaling pathway regulates stepwise phosphorylation of protein kinases and terminates the activation of transcription factors needed for cellular proliferation, differentiation or apoptosis.

### Arsenic specifically inhibits glucose transport

Sulfhydryl groups play an essential role in insulin-dependent and insulin-independent mediated glucose transport (GLUT). The thiol component forms a structural bond linking the A and B polypeptide chains of insulin, the α and β subunits of the insulin receptor and the exofacial sulfhydryl moiety present on glucose transporters at the plasma membrane[6]. PAO forms stable cyclic thio-arsenite complexes with vicinal or paired sulfhydryl groups of cellular proteins and inhibits glucose transport in adipocytes[95,117]. Moreover, PAO prevents insulin-stimulated glucose transport without affecting insulin binding to its

receptor[117]. PAO only affects insulin-dependent GLUT4 present in adipocytes and myocytes[118].

However, the effect of arsenite on glucose transport is dose-dependent. Studies have shown that arsenite stimulates glucose uptake at higher concentrations, while at low level, glucose uptake decreases[119]. Arsenite does not disturb regulation of GLUT4 gene expression, thus overall GLUT4 quantity does not alter. Walton *et al*[115] examined the dose-dependent decrease in insulin-stimulated glucose uptake in 3T3-L1 adipocytes treated with iAs and its metabolites.

### Effect on gene expression

There are many studies which support that diabetes is induced by arsenic *via* alteration in gene expression. When isolated rat pancreatic β-cells were exposed to 5 μmol/L arsenite for 72 h, mRNA expression and insulin secretion decreased[9]. An *in vitro* study showed that exposure to arsenite decreased the gene expression and activity of catalase, whereas the production of ROS increased[120]. Peroxisome proliferative-activated receptor-γ (PPAR-γ) (a transcription factor) controls the main gene expression for insulin sensitivity. When mouse adipocytes from the C3H 10T1/2 cell line were exposed to 6 μmol/L arsenite, alteration in the expression of PPAR-γ and AP-2 genes occurred which resulted in the inhibition of mRNA and reversal of adipocyte differentiation[121]. The transcription of cytokines, namely tumor necrosis factor-α (TNF-α) and interleukins (IL), required in insulin resistance, are regulated by NF-κB[122]. When human bronchial epithelial cell lines were exposed to 18 μmol/L arsenite for 12 h, NF-κB dependent genes were activated. In contrast, exposure to 12.5 μmol/L arsenic in TNF-α stimulated HeLa cells for 2 h resulted in inhibition of NF-κB activation and IκB degradation[123,124]. When human GM847 fibroblast cells were exposed to 0.1 and 5 μmol/L arsenite for 24 h, upregulation and expression of c-fos and c-jun genes and DNA binding activity of AP-1 takes place[125].

Arsenic upregulates inflammatory cytokines from mononuclear cells. When human peripheral mononuclear cells were exposed to very low arsenite levels, TNF-α production increased 2-fold[126]. Studies have shown that when blood arsenic level ranged from 0.128 to 0.62 μmol/L, the expression of IL-6 increased 3-fold[127]. Expression and phosphorylation of AKT were suppressed when 3T3-L1 adipocytes were exposed to trivalent arsenicals[115]. Activation of AKT by PDK-1 phosphorylation, is also inhibited by arsenite[128]. In adipocyte cells, exposure to arsenite at high levels reduced the expression and phosphorylation of AKT genes, while at low levels expression was stimulated[115,129]. In addition, the expression of phosphoenol pyruvate carboxykinase (PEPCK) increased in chick embryos after exposure to high dose arsenite, which may be due to the interaction of arsenic with glucocorticoid receptor complexes[130,131].

## EVIDENCE OF ALTERED ARSENIC METABOLISM IN DIABETES MELLITUS

T2DM is hypothetically related to variations in blood arsenic concentration and there is evidence to suggest that arsenic metabolism is modified in people with T2DM and these factors have precise roles in the pathogenesis and progression of this disorder[132]. Many *in vivo* and *in vitro* studies have shown that iAs induces diabetes, but some experiments contradict these reports. There are convincing reports that diabetes alters the pharmacodynamics and pharmacokinetics of drugs/xenobiotics in humans and animals[133,134]. Our previous studies showed that arsenic exposure causes the inhibition of hyperglycemia in diabetic rats and mice (Kulshrestha *et al*, Unpublished observation). Arsenic exposure in diabetic rat results in the promotion of insulin secretion and decrement of arsenic concentrations[135,136].

The causal correlation between arsenic exposure and diabetes mellitus is still debated. Various epidemiological studies performed in arsenic-contaminated regions proved the relationship between chronic arsenic exposure and diabetes mellitus, however, the exact mechanism is not known[137]. Various animal studies on the effects of exposure to arsenic on glucose metabolism and insulin secretion show inconsistent results due to variations in animal species, dose and time of exposure[128,137]. The studies carried out by Wang *et al*[138] in both humans and rats suggested that glucose metabolism is altered by arsenic.

## ARSENIC AND NUTRITIONAL STATUS

Hsueh *et al*[139,140] suggested that arsenic toxicity is associated with nutritional status in residents living in arsenic-contaminated areas such as Taiwan. As arsenic causes toxicity *via* oxidative stress, thereby decreasing antioxidant enzyme activity, it is possible that there is a link between arsenic-induced diabetes mellitus and antioxidant deficiency, and that the individual consuming less antioxidants has an increased risk of diabetes mellitus and cardiovascular disease[141]. Thus, good nutritional status with sufficient antioxidant intake reduces the chance of arsenic-induced diseases. As arsenic interferes with GSH, people with diabetes have a lower level of GSH[142]. It was found that selenium, which is required for GSH biosynthesis, is significantly lower in arsenic exposed subjects than in normal controls[143,144]. GSH is required for the correct action of insulin and increased uptake of glucose, and is obligatory for the excretion of arsenic[145]. Animal studies have shown that nutritional status modifies arsenic toxicity. A choline or methionine deficient diet (source of methyl donor group) results in a reduction in arsenic methylation, which leads to high retention of arsenic in the body and an increase in toxicity[146-148]. Therefore, by consuming methionine rich diets, arsenic toxicity can be alleviated.

Preventive and therapeutic measures are available against arsenic toxicity. The roles of chelating agents, antioxidants, natural/herbal remedies as protective/therapeutic agents against arsenic toxicity are discussed below.

### Chelating agents

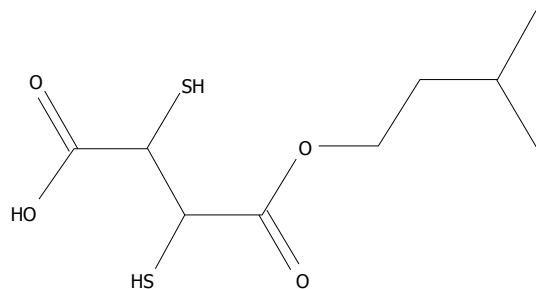The formation of a metal ion complex is known as che-

**Figure 4  Mono isoamyl 2,3 dimercaptosuccinic acid.**



**Figure 5  Mono methyl 2,3-dimercaptosuccinic acid.**

lation in which two or more separate coordinate bonds are formed between monodentate or polydentate ligands and metal ions. These ligands are referred to as chelators or chelating agents and are organic compounds able to link together metal ions to form a complex structure called chelates. In chelation therapy, chelating agents are used to detoxify toxic heavy metals such as arsenic, and convert them to a chemically inert form with greater water solubility, which increases their excretion by the kidney without further interaction within the body. Various chelating agents are used to treat arsenic toxicity[149]. The first chelating agent used was British Anti Lewisite (BAL) which was used during World War Ⅱ. This is a dithiol compound used as a therapeutic agent against heavy metal toxicity. Despite its capacity to treat metal toxicity, its use is limited due to a low therapeutic index[150]. Other metal chelators such as meso-2,3-dimercaptosuccinic acid (DMSA) and 2,3-dimercapto-1-propanesulphonic acid (DMPS) can be administered for a much longer time due to their very low toxicity[151]. DMSA decreases the arsenic burden in cells by inhibiting the constant formation of ROS[152]. Subsequently, numerous esters of DMSA have been produced to achieve more advantageous chelation. Flora *et al*[153] found that administration of dimethyl DMSA (DMDMSA), diethyl DMSA (DEDMSA), diisoamyl DMSA and diisopropyl DMSA (DiPDMSA) led to a decrease in arsenic content in blood and soft tissues, but was less effective in recovering biochemical alterations following sub-chronic arsenic exposure in rats[153]. Kreppel *et al*[154] observed that administration of the monoesters, mono isoamyl DMSA (MiADMSA), mono n-amyl DMSA (MnDMSA), mono n-butyl DMSA (MnB-DMSA) and mono i-butyl DMSA (MiBDMSA) were able to reduce the arsenic concentration in tissues, of which MiADMSA and MnADMSA were found to be most effective in mice[154]. Administration of MiADMSA (Figure 4) and mono methyl DMSA (MmDMSA) (Figure 5) resulted in a reduction in arsenic concentration in blood and soft tissues in experimental animals[155,156]. Despite the beneficial effects of chelating agents against arsenic toxicity, they have some drawbacks, such as non-specificity, low therapeutic index, failure to permeate the plasma membrane and metal redeployment, and induce side effects including headache, nausea, and vomiting, thus their use has been limited[157]. Although these chelating 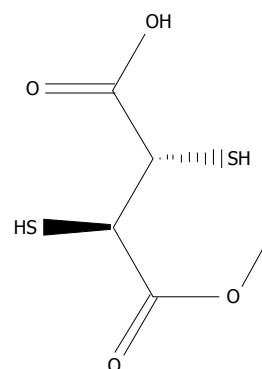agents enhance arsenic excretion, these agents have numerous drawbacks. Therefore, the identification of novel therapies without side-effects and complete medical recovery in terms of altered biochemical variables such as complete removal of metals are necessary.

### Antioxidants

Arsenic exposure results in the production of ROS, thus cellular antioxidants are reduced. To prevent the increased production of ROS and their deleterious effects, the body's antioxidant system which consists of superoxide dismutase (SOD), glutathione reductase (GR), catalase, glutathione peroxidase (GPx), and reduced glutathione (GSH) scavenge ROS. In addition to this endogenous system, antioxidant status is improved by the administration of exogenous antioxidants such as vitamin C and E, quercetin, N-acetylcysteine (NAC), and α-lipoic acid.

N-acetylcysteine (NAC), the thiol-based antioxidant, is an originator of L-cysteine and GSH and stimulates glutathione synthesis (Figure 6). It protects cellular components against oxidative stress[6,158]. It stimulates the production of GSH, hence retaining intracellular GSH level[159]. NAC plays an essential role in the chelation of toxic metals[160,161]. Co-administration of NAC and zinc alleviates arsenic-induced hepatic and renal toxicity[162]. Flora *et al*[163] developed a new treatment strategy consisting of combination therapy with DMSA and NAC, to achieve better results against arsenic toxicity in rats. NAC is effective against arsenic toxicity and recovered the level of hepatic malondialdehyde[164]. The protective effect of NAC against arsenic toxicity in animals has been suggested by Hemalatha *et al*[165] and Reddy *et al*[158].

Quercetin (3,3',4',5,7-pentahydroxyflavon) is a bioflavonoid found in fruits, vegetables, seeds and flowers (Figure 7). It has very strong antioxidant properties and prevents cell apoptosis caused by oxidative stress[166]. Quercetin scavenges superoxide radicals and protects against lipid peroxidation and chelates metal ions. An *in vitro* study showed that quercetin prevented cytotoxicity due to low-density lipoproteins[167]. Quercetin co-administration with a thiol chelator was found to be more efficient in reducing body arsenic burden[168].

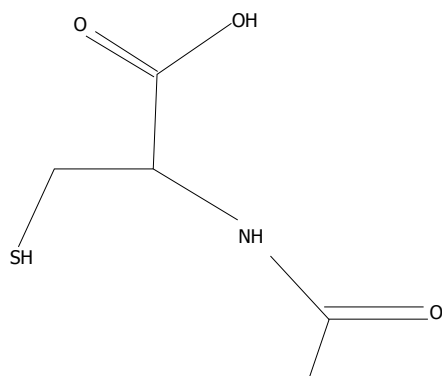α-lipoic acid (LA, 1,2-dithiolane-3-pentanoic acid) is a dithiol antioxidant produced from octanoic acid in the
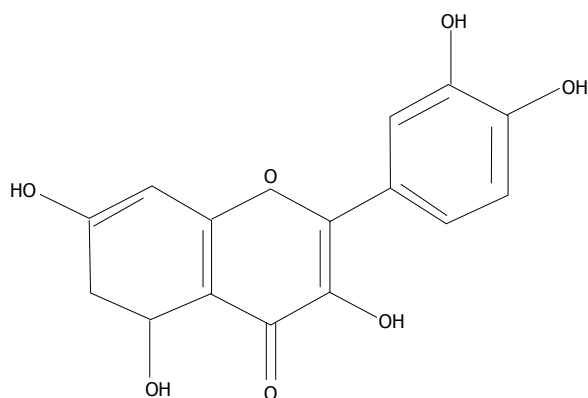
**Figure 6 N-acetylcysteine.**



**Figure 7 Quercetin.**



Lipoic acid (Oxidized form)

+2H    -2H

SH    SH    Dihydro lipoic acid (Reduced form)

**Figure 8 Reduction of lipoic acid.**

mitochondria. LA is an essential cofactor for α-ketoacid dehydrogenase in mitochondria. In addition to production, LA is also consumed in the diet from wheat germ, beer, yeast, and red meat[169]. After consumption, it is taken up into the circulatory system and traverses the blood-brain barrier, where it is reduced to dihydrolipoate[170]. LA and dihydrolipoic acid (DHLA) are able to scavenge free radicals and chelate metals (Figure 8). LA treatment reduces arsenic-induced oxidative damage *in vivo* due to its chelation and free radical scavenging properties[171,172].

A range of vitamins possess antioxidant properties against arsenic poisoning. The consumption of vitamins A, C and E plays a protective role against arsenic toxicity[173]. Vitamin C is hydrophilic and is an intracellular and extracellular antioxidant capable of scavenging ROS *in vivo* and *in vitro* by electron transfer to inhibit lipid peroxidation. It traps free radicals and protects biomembranes from oxidative damage. Vitamin C alleviates arsenic-induced oxidative stress in mouse liver[174]. Its advantageous effect is due to its capability to form a complex with arsenic[6].

Vitamin E is a lipid soluble vitamin and its active form is α-tocopherol. It is assembled in lipophilic sites of the cell membrane and protects the membrane against oxidative damage. It donates an electron to the peroxyl radical, which is produced during lipid peroxidation[175]. Vitamin E has the ability to scavenge free radicals, hence
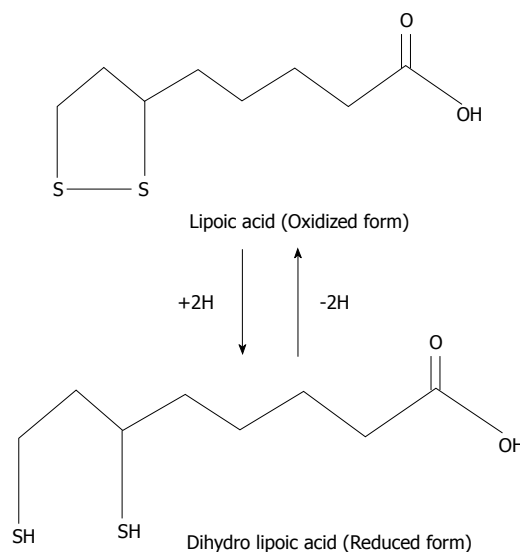
protects against arsenic toxicity. An *in vivo* study showed that vitamin E treatment is effective against hepatotoxicity, nephrotoxicity and regulates altered variables of the heme synthesis pathway[6].

Co-administration of vitamin C and E in combination with a chelator was found to be more effective than chelator alone in sub-chronically arsenic-exposed rats[39]. Administration of vitamin C and E reduced the rate of DNA fragmentation in arsenic exposed rats[176]. Some other vitamins such as A and B have also been reported to be effective against arsenic poisoning. Therapy with folic acid and vitamin $B_{12}$ alleviated oxidative damage induced by arsenic in cardiac tissue[177]. A cross-sectional study performed in Bangladesh, reported that the intake of B-vitamins and antioxidants may reduce the risk of arsenic-related skin lesions[178]. Other antioxidants such as taurine can be very useful in reducing oxidative stress induced by arsenic[179].

### Herbal/Natural remedies

For several years, herbal/natural remedies have been used all over the world as therapeutic and prophylactic agents. The synergistic action of a broad range of antioxidants from natural sources is better than the activity of a single or synthetic antioxidant[180]. The use of conventional remedies, obtained from plants has been very important in managing arsenic toxicity. Numerous plants/spices or their extracts possess antioxidant effects. The administration of various plant/spice extracts, such as *Spirulina*, Curcumin, *Moringa oleifera, Hippophae rhamnoides, Centella asiatica, Allium sativum, Mentha piperita,* and *Aloe vera barbadensis,* has shown preventive and therapeutic effects against arsenic exposure in animals[179,181].

With regard to natural and bio-available sources of antioxidants, we explored the beneficial effects of *Spirulina* in arsenic exposed diabetic rats. *Spirulina* administration was found to be associated with the alleviation of various metabolic disorders such as diabetes mellitus and

drug-metal-induced toxicities[181-183]. Our studies on arsenic toxicity showed that the administration of *Spirulina* suspension for one week resulted in a reduction in arsenic burden, restoration of blood glucose and insulin level in rats (Kulshrestha *et al*; Unpublished observations). *Spirulina* has significant antioxidant activity due to the presence of an enormous amount of phycobiliproteins, phycocyanin and allophycocyanin, phenolic compounds, γ-linoleic acid, minerals, tocopherols, β-carotenes, vitamin E & C and selenium[184,185]. *Spirulina* possesses free radical scavenging properties in addition to its biosorption effect against heavy metal toxicity[186-189]. Rahman *et al*[190] and Karkos *et al*[191] studied the efficacy of *Spirulina* in patients with chronic arsenicosis and found that *Spirulina* reversed the changes caused by arsenic[190,191].

Centella or Indian Pennywort, *Centella asiatica* (L.) Urban Syn. and *Hydrocotyle asiatica* L. belong to the family Apiaceae. *C. asiatica* is useful for restoring biochemical alterations in arsenic-induced toxicity. It depletes tissue arsenic concentrations, to some extent, in rats[192]. Sea buckthorn (*Hippophae rhamnoides* L.) Elaeagnaceae, is a nitrogen fixing shrub found in Europe and Asia. It is now cultivated in various parts of the world for nutritional and remedial purposes. The whole plant is an excellent source of various bioactive compounds such as carotenoids (α, β, δ-carotene, lycopene), vitamins (A, C, E, K, riboflavin, folic acid), organic acids (malic acid, oxalic acid), phytosterols (ergosterol, stigmasterol, lanosterol, amyrins), and a few vital amino acids[193-195]. *In vitro* and *in vivo* studies have shown the antioxidant and immunomodulatory properties of Sea buckthorn[196]. The antioxidant activities of *H. rhamnoides* extract is due to the presence of flavanoids and phenolic compounds which exhibit free radical scavenging properties[197]. Gupta and Flora evaluated the protective role of the aqueous extract of *H. rhamnoides* fruit against arsenic toxicity. However, this extract does not have the ability to chelate arsenic, and it is recommended that it should be administered along with an effective chelating agent to achieve the best possible outcome in chelation treatment[198].

Garlic, *Allium sativum* L. belongs to the family Alliaceae, and contains a high concentration of sulfur compounds. Some biologically active sulfur-containing lipophilic compounds are allicin (diallyl thiosulfinate or diallyl disulfide, DADS), S-allylycysteine (SAC), and diallylsulfide (DAS) and hydrophilic compounds include s-ethyl cysteine (SEC) and N-acetylcysteine (NAC), which are responsible for antioxidant activities due to the stimulation and modification of enzymes such as 3-hydroxy-3 methylglutaryl-CoA reductase, glutathione-s-transferase and catalase[199,200]. *In vitro* and *in vivo* studies demonstrated that administration of the aqueous extract of garlic resulted in the reduction of tissue arsenic burden and enhanced urinary arsenic excretion, which was due to the chelating properties of thiosulfur components such as allicin[165,201].

*Moringa oleifera* is another plant belonging to the Moringaceae family, which exhibits antioxidant and chelating properties. The seed powder of *M. oleifera* protected animals from arsenic-induced oxidative damage and reduced arsenic concentrations[202]. This protection may be due to the presence of ascorbic acid, and cysteine and methionine rich proteins in the seed powder[203,204]. Curcumin, a polyphenolic compound, is another herbal product which is a major constituent of *Curcuma longa* (Zingiberacea family). It possesses numerous pharmacological activities including antioxidant and anti-inflammatory. Curcumin protects the hepatic tissues from arsenic-induced imbalance in antioxidants and oxidants. It also reduces hepatic arsenic burden[205]. Curcumin prevents arsenic-induced neurotoxicity and hepatotoxicity during embryonic development[206,207]. Other herbal products including *Mentha piperita* leaf extract and *Aloe vera barbadensis* also showed protective effects against arsenic toxicity[208,209].

## CONCLUSION

Arsenic is omnipresent in the environment, however, drinking water, including both groundwater and surface water supplies, is regarded as a major route of human exposure to iAs in arsenic-contaminated regions. Arsenic ingestion through the food chain may affect physiological and biochemical processes in the body. Although human exposure to arsenic is known to induce adverse health effects, the level and time of exposure as well as genetic susceptibility are important factors in outcome. Arsenic exposure plays an etiological role in diabetes development. Low or moderate arsenic exposure plays a positive role, while a high level of arsenic is associated with the risk of developing type-2 diabetes. Studies associated with the biochemical mechanism(s) in relation to arsenic exposure and risk of developing diabetes are still contentious and need to be delineated further. Although various therapeutic and nutritional strategies are available to alleviate arsenic toxicity, more preventive and therapeutic measures against arsenic toxicity are required.

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