Review of Literature
Arsenic, found throughout the crust of the earth (Liu et al., 2012), is an environmental toxicant and a worldwide health hazard (Thorsen et al., 2012) that has caused one of the largest public health poisonings in the history of human civilization, affecting tens of millions of people worldwide especially in Bangladesh (Karim et al., 2010). Arsenic ranks first in "Top 25 Substances" on the 2007 priority list of hazardous substances (ATSDR, 2011). Among the general public, the word "Arsenic" has become almost synonymous with word poison (Shakhashiri, 2000). In the 8th Century A.D. an Arab alchemist named Jabir became the first to prepare arsenic trioxide, a white, tasteless, odourless powder. Arsenic became a favourite murder weapon of the middle ages and Renaissance. By the 19th Century, it had acquired the nickname "inheritance - powder" (Wikipedia, 2012a). Throughout history, Britancius, Pope Pius III, Pope Clemente XIV and Napoleon Bonaparte etc. were killed by arsenic poisoning (Graziano and Hamilton, 2008). The name of arsenic called in hindi “Sankhia”.

In the Victorian era 'arsenic' (colourless, crystalline, soluble 'white arsenic') was mixed with vinegar and chalk and eaten by women to improve the complexion of their faces. Arsenic was also rubbed into the faces and arms of women to 'improve their complexion'. The accidental use of arsenic in the adulteration of food stuffs led to the Bradford sweet poisoning in 1858, which resulted in approximately 20 deaths and 200 people taken ill with arsenic poisoning (Turner, 1999; Wikipedia, 2012a).

Arsenic is 33rd element and member of group Vth a of the periodic table, which combines readily with many elements. It exists in two oxidative states: trivalent arsenite [As(III)] and pentavalent arsenate [As(V)] (Wikipedia, 2012a). It exists in the metallic state in nature in three allotropic forms gray, yellow and black and in several ionic forms. Environmental arsenic exists
mainly as sulphide complexes e.g. realger (As$_2$S$_2$), orpiment (As$_2$S$_3$) and iron pyrites (FeAsS). It rapidly oxidizes to arsenic trioxide, which has a garlic odour. The non-metallic form is less reactive but dissolves when heated with strong oxidizing acids and alkalis (Kamrin, 1998).

2.1 Various oxidation stages of Arsenic

Arsenic is present in the environment in both organic and inorganic forms and can exist in many different chemical forms in combination with other elements. Some forms are inorganic, which do not contain carbon and others are organic, which always contain carbon. Inorganic arsenic can exist in four main chemical forms, known as valency or oxidation states (-3, 0, +3 and +5), depending upon environmental conditions. The dominant forms are arsenite (in most organoarsenic compounds) with a valency 3 and arsenate (the most stable inorganic arsenic oxycompounds), with a valency 5 (Greenfacts, 2004; Wikipedia, 2012a). Adverse health effects of arsenic are dependent on the chemical form and physical state of the specific arsenic compound. In general, organic arsenic is less acutely toxic than inorganic arsenic.

2.2 Various type of arsenic exposure media

I. Soil

Heavy metal pollutants including arsenic in soils can usually enter the human body and pose health risks through a soil-crop-human body pathway (indirect exposure) or soil-human body pathway (direct exposure) (Wang et al., 2011). Most arsenic (V) species are mainly present in the soil (Landrot et al., 2012). However, near smelting operations and around older orchards where arsenical pesticides were used, soil levels of 100 to 2,500 ppm arsenic have been found (WHO, 2001). Majority of arsenic released into the environment is inorganic and accumulates by binding to organic soil matter (Smedley and Kinniburgh, 2005). The natural content of arsenic found in soils varies between 0.01 mg/kg and a few hundred miligrams per kilogram.
(Monique and Fritz, 2003). Contour soil mapping confirmed that historical mine waste deposits without environmental control measures, are the main source of pollution soil by arsenic in the site (Gamiño-Gutiérrez et al., 2012).

Health hazard attributed to arsenic in contaminated soil and water in the vicinity of closed or abandoned metal mines may be high. Exposure to arsenic has affected the health of resident near closed metal mines (Cho et al., 2012). Compared with inhalation and dermal contact in direct soil exposure, soil ingestion is the largest contribution to potential health risks for children (Wang et al., 2011). The environmental concentration of total arsenic in top soils - in the 7-18ppm range is exponentially related to the prevalence and mortality of Alzheimer's disease and other dementias in European countries (Dani, 2010).

II. Water

Significant natural contamination of surface waters can arise when arsenic-rich geothermal fluids come into contact with surface waters (Garelick et al., 2008).

Millions of people are at risk of groundwater arsenic contamination, and there is no known remedy that can effectively remove the symptoms of prolonged arsenic poisoning (Nordstrom, 2002; Smedley and Kinniburgh, 2002; Khuda-Bukhsh et al., 2011; Jackson et al., 2012).

In Bangladesh, the problem is particularly widespread. Arsenic occurrences in 52 out of 64 districts of Bangladesh are estimated to be affecting 40 million people in an area of 118.012 km² (Karim, 2000).

Arsenic contamination of ground water in West Bengal (India) and neighbouring Bangladesh has affected millions of lives and has been called the “Largest mass poisoning in history” (Mead, 2005). Arsenicosis is a global
problem but the recent data reveals that Asian countries, India and Bangladesh in particular, are the worst sufferers. In India, the state of West Bengal bears the major brunt of the problem, with almost 12 districts presently in the grip of this deadly disease (Ghosh et al., 2008). Madhavan and Subramanian (2004) reported that surface water samples and ground water samples collected from Zawar (Pb and Zn sulphides) and Khetri, Rajasthan India (Cu sulphide mines) have been found to be arsenic contaminated.

Thousands of Cambodia populations are currently at high risks of both toxic and carcinogenic effects through drinking arsenic-rich groundwater (Phan et al., 2011).

Arsenicosis was reported in Nakhon Si Thammarat, Thailand in 1987, and the dissolved arsenic in the Chao Phraya River is suspected of containing high levels of naturally occurring arsenic (Wikipedia, 2012a). Considering the 10µg/L limit for As in drinking water established by international and several national agencies, the number of exposed people is estimated to be about 14 million (Bundschuh et al., 2012).

III. Air

Arsenic is the toxic element, which creates several problems in human being specially when inhaled through air. Arsenicals are emitted to the air by coal combustion and some coals are unusually high in arsenic because of geologic factors. This practice expels high levels of arsenic into indoor air, which become major source of exposure. Arsenic in the air coats and permeates food being dried producing high concentration in food (Liu et al., 2002a).

Atmospheric arsenic usually arises in particulate form from both natural sources, such as volcanic activity or forest fires & man made (anthropogenic) sources such as the burning of fossil fuel, automobile exhaust and tobacco smoke (OSHA, 2007). A wide variety of micro-organism have been found to
convert arsenic compounds into arsine or methylarsine gases. Arsine gas (AsH$_3$), the most toxic arsenic compound known, is formed when inorganic arsenic compounds are exposed to strong reducing conditions. Arsine is unstable in the presence of heat and can be readily oxidized by oxygen (O) or air, producing As$_2$O$_3$ and water as end products (National Occupational Health and Safety Commission, 1989; Oremland and Stolz, 2003).

Singh et al., (2011b) reported that the arsenic concentration in air varied from 1.44±0.25 to 5.58±0.55 ng/m$^3$ during analysis of data of seven diverse sites of Delhi (India).

The United States Environmental Protection Agency (USEPA) developed an inhalation unit risk factor of 4.3E-03 per µg/m$^3$ for arsenic in 1984 for excess lung cancer mortality based on epidemiological studies of workers at two smelters: the Asarco smelter in Tacoma, Washington and the Anaconda smelter in Montana (Erraguntla et al., 2012).

**IV. Food**

Organic and inorganic arsenic compounds may enter the plant food chain from agricultural products or from soil irrigated with arsenic contaminated water (Tamaki and Frankenberger, 1992).

Arsenic in food occurs as relatively nontoxic organic compounds (arsenobentaine and arsenocholine). These organic compounds cause raised arsenic levels in blood but are rapidly excreted unchanged in urine (Han et al., 1998). Arsenic intake is higher from solid foods than from liquids including drinking water (Thomas et al., 1999).

Arsenic is present in most food stuff in concentration of less than 1mg/kg. Marine fish may contain 5mg/kg wet weight. Due to arsenic concentration in algae and marine micro-organism, sea food is the highest
dietary source of arsenic (Tao and Bolger, 1999). Arsenic concentrations for fish and sea food average 4-5ppm (Bennett,1981), significantly higher than the concentration found in grains and cereals with average 0.02 ppm (Gartrell et al.,1986). The UK Food Standards Agency and its counterparts in other countries have warned consumers not to eat hijiki (Sargassum fusiforme; synonym Hizikia fusiformis), a Sargasso seaweed, because it contains large amounts of inorganic arsenic (Yokoi and Konomi, 2012).

The concentration of arsenic in the molluscs and crustaceans clearly revealed that these invertebrate accumulated arsenic to different degrees. The daily human intake of arsenic contained in food ranges from 0.5-1 mg, with the greatest concentration coming from fish and crustaceans (Graziano and Hamilton, 2008) in form of arsenobetaine (Zhang et al., 2012). Furthermore arsenic content in molluscs and crustaceans sample were below the Food and Agricultural Organisation (FAO) safe concentrations, thus there was no obvious health risk from the intake of the metals through marine molluscs and crustaceans consumption (Zhang et al., 2013).

Prior surveys have shown that rice is the primary source of arsenic exposure in a non sea food diet typically possessing higher inorganic arsenic level than seafood (Tao and Bolger, 1999). Rice-fortified foods had significantly higher total arsenic concentrations than non rice-based foods (Jackson et al., 2012). A very popular fish species including herring (Clupea harengus) containing organoarsenicals consumed mass scale in Europe. Current studies indicate that these arsenicals are metabolized to cancerous dimethylarsinic acid in humans (Lischka et al., 2013).

Infant milk formulas were low in total arsenic (2.2-12.6 ng/g (n=15). Non-dairy formulas were significantly higher in arsenic than dairy-based formulas. Arsenic in formula was almost exclusively inorganic and predominantly arsenic (V) (Jackson et al., 2012).
Organo-arsenical drugs are widely used in the production of broiler chickens in the United States due to this, meat contains arsenic. Arsenic has detected in all samples (44-4100 µg/kg) and speciation analyses revealed that inorganic forms of arsenic dominated, representing 37 - 83% of total arsenic (Nachman et al., 2012).

V. Anthropogenic Exposure

Anthropogenic arsenic is insidiously building up together with natural arsenic to a level unprecedented in the history of mankind. Anthropogenic sources of arsenic in the environment are the smelting of ores, the burning of coal (Wayne and Wendt, 2000), and the use of arsenic compounds in many products and production processes in the past. The release of arsenic from coal mine wastes into main waterways is an environmental cause for concern in the mining industry due to a myriad of subsequent ecotoxicological problems associated with the metalloid (Garelick et al., 2008; Dani, 2010; Pumure et al., 2011). Global industrial-age anthropogenic arsenic sources follow the order: Arsenic mining production > Arsenic generated from coal > Arsenic generated from petroleum. Arsenopyrite (FeAsS) is the principal ore of arsenic and gold in hard rock mines; it is formed by a coupled substitution of sulphur by arsenic in the structure of pyrite (FeS₂) - nicknamed "fool's gold".

Arsenic is also used as a feed additive for poultry and swine and in cattle and sheep dips to control lice and ticks. Nonetheless, lawsuits have been filed alleging environmental pollution and human health effects associated with arsenic containing additives in poultry feeds (Tyre, 2006). In addition, arsenic is used in alloys and in semiconductors and light-emitting diodes (Argonne National Laboratory, EVS, 2005). Portland cement (PC) is widely used in the building industry which contains arsenic and its release are at low levels (Tenório de Franca et al., 2010). Gallium arsenide (GaAs) is an important semiconductor material marketed in the shape of wafers and thus is
not hazardous to the end user. Exposure to GaAs particles may, however, occur during manufacture and processing (Bomhard et al., 2012)

The Texas Commission on Environmental Quality (TCEQ) has developed an inhalation unit risk factor for lung cancer mortality from exposures to arsenic and inorganic arsenic compounds based on a newer epidemiology study of Swedish workers (Erraguntla et al., 2012).

2.3 Utilization of Arsenic

(a) Therapeutic uses

Arsenic is a metalloid that is considered to be a paradox in terms of its role both as a carcinogen and as a therapeutic agent (Prajapati et al., 2011). During the 18th, 19th, 20th centuries, a number of arsenic compounds have been used as medicines. In 1909, the first synthetic chemotherapeutic agent (Salvarson) was released by Nobel Prize-Winning German pharmacologist Paul Ehrlich. Although inconvenient, Salvarson ("salvation by arsenic") was the first effective treatment of syphilis (Van den Enden, 1999) Tryparsamide ([4-[2-amino-2-oxethyl] - amino]-phenyl] arsonic acid) was used to treat African sleeping sickness (Carter and Fairlamb, 1993). Until recently, arsenic compounds were used in developing countries around the world as treatments for a variety of diseases. Fowler's solution in psoriasis (Roy and Saha, 2002). It is also used as Realgar (90% of \(\text{AS}_4\text{S}_4\)) has been used in traditional Chinese medicines for thousands of years (Lu et al., 2011). Ingredients of arsenic drugs were applied, either arsenic trioxide, arsenic disulfide, or arsenic containing Chinese herbal compositions including Qinghuang Powder and Realgar-Indigo naturalis formula, they all provided the distinct approaches for the management of malignant hematologic diseases, and good clinical efficacy was obtained with mild adverse reactions (Hu et al., 2010).

Arsenic trioxide has been used in a variety of ways over past 200 years, but most commonly in the treatment of cancer such as oral cancer
model (Tsai et al., 2010), acute promyelocytic leukemia (Breccia and Lo-Coco, 2012). Du et al., (2012) reported that arsenic trioxide is used as a drug for the treatment of breast cancers. The novel organoarsenical GSAO, 4-(N-(S-glutathionylacetyl) amino) phenyl-arsonous acid, has potential anti-angiogenic capability with application in cancer where tumour metastasis relies on neo-vascularisation (Elliott et al., 2012). $\text{As}_{2}\text{O}_3$ is considered to have anticancer activity via several biological actions, such as free radical production and inhibition of VEGF (Vascular endothelial growth factor) expression (Kim et al., 2012).

(b) **Use as Food additives :-**

Scheele's Green, a copper arsenate, have been approved for use in United States poultry feeds (Nachman et al., 2005). Chapman and Johnson (2002) estimated that from 1995 to 2000, roxarsone was used in 69.8 and 73.9% of broiler starter and broiler grower feeds in the United States. Roxarsone is approved for use in broilers and results in increased growth rates, improved feed utilization, and enhanced pigmentation. Because roxarsone has been shown to be an effective potential against intestinal parasites, particularly coccidiosis, the improved intestinal health is apparent reason for improved growth and feed utilization. In addition, recent field experience has revealed that roxarsone may be effective at suppressing *Salmonella* and possibly other enteric organisms that can cause food safety hands for consumers (Jones, 2007). The safe residual level for arsenic in poultry meat is 0.5 ppm in muscle tissue and 2 ppm in liver (USFDA, 1997).

(c) **Arsenic compounds as wood preservative**

Chromated copper arsenate (CCA) was widespread used as a chemical wood preservative with application in the construction of playground equipment, fences, jetties, and naval (Khumaeni et al., 2012). Environmental protection agency (EPA) had limited the use of CCA-treated wood on 2002,
due to probable implications on both human and environmental health (Matos et al., 2010).

The potential impact of municipal solid waste (MSW) landfill leachate quality on the loss of metals with arsenic from discarded treated wood during disposal is reported by Dubey et al. (2010) and Rasem Hasan et al. (2011).

(d) Miscellaneous uses
Arsenic is used to remove impurities so that clear glass is produced,
- To harden and increase the durability of plates and parts in lead acid batteries.
- To produce colour in fireworks, to act as alloy in the bronzing process.
- To act as an alloy with Gallium in integrated circuits and in laser materials to convert electricity directly into coherent light.
- Arsenicals have been used as herbicides, defoliants, fungicides, rodenticides and insectides (Calvert, 2004; Orme and Kegley, 2006).
- Recently new research has been done in locating tumors using arsenic-74 (a positron emitter) (Jennewein, 2008).
- Arsenic as copper acetoarsenite was a pigment in paints, the best known being “Paris-green” (ATSDR, 2011).
- A fungus Scopulariopsis breviculis present in damp wallpaper also metabolised the arsenic in Paris green to arsine (Wikipedia, 2012a).

Biological indicators of Arsenic toxicity:
Biological indicators of arsenic exposure are blood, urine, and hair although blood arsenic is only reliable within few days of acute exposure. In case of chronic exposure, urinary arsenic is the best indicator of current or recent exposure. Hair or fingernail concentration of arsenic may be useful in evaluating past exposure (Flora et al., 2007).
2.4 Metabolism and Toxicity of Arsenic

(a) Metabolism

The total human intake of arsenic is mainly caused by contaminated food and drinking water together usually account for 90% and above (Ontario Ministry of the Environment, 2001). In humans, 60-90% of ingested, soluble arsenic is quickly absorbed from gastrointestinal tract (OSHA, 2007).

Each of the forms of arsenic has different physiochemical properties and bioavailability. Tissue absorption and distribution of arsenicals depends on various type factors like blood perfusion, tissue volumes, diffusion coefficients, membrane characteristics, and tissue susceptibilities and affinities (Ratnaike, 2003).

The fate of ingested arsenic in the body (tissues) depends on following processes: (1) oxidation and reduction reactions between iAs(V) and iAs(III) in plasma (2) hepatic methylation reactions.

In mammals, there are two possible mechanisms that have been proposed for the metabolic pathway of inorganic arsenicals, oxidative methylation, and glutathione conjugation. Oxidative methylation, which was originally proposed in fungi, is based on findings that arsenite (iAs(III)) is sequentially converted to monomethylarsonic acid (MMA(V)) and dimethylarsinic acid (DMA(V)) in both humans and in laboratory animals such as mice and rats. However, recent studies in vitro observations have demonstrated that arsenic is only methylated in the presence of glutathione (GSH) or other thiol compounds (promotes arsenite methylation by stabilizing the redox state of the cell), which strongly suggests that arsenic is methylated in trivalent forms. The glutathione conjugation mechanism is supported by findings that have shown that most intracellular arsenicals are trivalent and excreted from cells as GSH conjugates. Since non-conjugated trivalent
arsenic compounds are highly reactive with thiol compounds and are easily converted to less toxic corresponding pentavalent arsenicals, the arsenic-glutathione conjugate stability may be the most important factor for determining the toxicity of arsenicals. In addition, "being a non-anionic form" also appears to be a determinant of the toxicity of oxo-arsenicals or thioarsenicals (Watanabe and Hirano, 2012) (Figure-1).

**Figure-1: Metabolic pathway of inorganic arsenicals (cited by Google)**

Abbreviations: SAM: S-adenosyl-methionine, SAHC: S-adenosyl-homocysteine, GSTO: Glutathione S-transferase-Omega, GSH-Glutathione.

Inorganic arsenic is methylated in the body by alternating reduction of pentavalent arsenic to trivalent and addition of a methyl group from S-adenosylmethionine. In a study suggested that glutathione complex mechanism of methylation plays an important role in arsenic biotransformation in mouse hepatocytes. The liver is the most important site of arsenic methylation, but most organs show arsenic methylating activity. The end metabolites are monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). These are less
reactive with tissue constituents than inorganic arsenic and readily excreted in urine (Percy and gailer, 2008).

Following absorption, the majority of inorganic arsenic is rapidly cleared from blood with a half life of 1 to 2 hour. Although some arsenic compounds are converted in testes, kidney and lung tissue, the liver is primary site of arsenic metabolism in mammals. In humans, most of arsenic exposure is absorbed metabolized and excreted within 48h (Cohen et al., 2006). Although arsenic is eliminated from the body primarily through kidneys, other less important routes of elimination include feces, sweat, skin desquamation and incorporation into hair and nails (WHO, 2001; ATSDR, 2011). Arsenic does not biomagnify in food chain (Hamilton, 2005).

(b) Toxicity:

Inorganic arsenic is a major concern for its toxicity. The chemical forms and oxidation states of arsenic are more important as regards to toxicity. Toxicity also depends on other factors such as physical state, gas, solution, or powder particle size, the rate of absorption into cells, the rate of elimination, the nature of chemical substituents in the toxic compound and, of course, the pre-existing state of the patient (ATSDR, 2011). Arsenic presents in two forms trivalent and pentavalent in environment but trivalent arsenic is considered more toxic than pentavalent (Yousef et al., 2008). Trivalent inorganic arsenic (As\textsuperscript{III}) –

- reacts with molecules containing sulfhydryl groups such as glutathione, δ aminolevulinic acid dehydrogenase etc. and form strong complex with vicinal thiols groups thereby inhibiting the activity of molecules.
- inhibits pyruvate dehydrogenase (PDH) activity, perhaps by binding to lipoic acid moiety.
- such as (MMA\textsuperscript{III}) methylated trivalent arsenicals are potent inhibitors of GSH reductase and thioredoxin reductase.
blocks the Krebs cycle and interrupt oxidative phosphorylation, resulting in a marked depletion of cellular ATP and depletion of the metabolizing cell (Chouhan and Flora, 2010).

Pentavalent inorganic arsenate (As\textsuperscript{V}) -

- undergoes reduction to form arsenite (As\textsuperscript{III}).
- mimics phosphate in \textit{in vivo} system thereby can replace phosphate in the sodium pump and the anion exchange transport system.
- can form esters with glucose and gluconate forming glucose-6-arsenate and 6-arsenogluconate respectively. These compounds resemble glucose-6-phosphate and 6-phosphogluconate thus inhibit activity of hexokinase.
- uncouples \textit{in vitro} oxidative phosphorylation termed as arsenolysis (Chouhan and Flora, 2010).

According to Environmental Health unit, acute toxicity of arsenic decreases in order, trivalent (+3) inorganic > pentavalent (+5) inorganic > organic arsenicals. Most organic derivatives have relatively low toxicity (Environmental Health, 2012).

\textbf{2.5 Health effects:}

Arsenic is transported by the blood to different organs in the body, mainly in the form of monomethylarsonic acid (MMA). It causes a variety of adverse health effects to human after acute and chronic exposures, such as respiratory, pulmonary, cardiovascular, immunologic, genotoxic, mutagenetic and carcinogenic effects (Mandal and Suzuki, 2002).

Arsenic poisoning has been manifested as abdominal pain, burning of mouth and throat, coma, diarrhea, nausea neuritis, skin lesion and vascular
collapse (Mahatab and Neelam, 2002) increased cardiovascular diseases (Navas-acien et al., 2005) and hepatic disorders (Sharma and Kumar, 2011).

Arsenic produced a range of behavioral impairments in male and female offspring. The most striking effects of arsenic are on the development of gait and other motor responses including acoustic startle, righting reflexes, and forelimb grip. These results suggest that developmental arsenic exposure can produce other behavioral impairments in children in addition to cognitive impairment (Markowski et al., 2012).

Acute exposure causes muscular weakness and cramping pain extremities, erythematous skin lesion and swelling of the eyelids, feet and hands. A progressive deterioration in the motor and sensory responses may also result finally leading to shock and death (Wasserman et al., 2006).

The effects of chronic arsenic poisoning (also called arsenicosis) are more complex. These include atherosclerosis, diabetes, hypertension, anemia, liver disorders, kidney damage, headache, confusion, peripheral neuropathy and a variety of skin lesion, notably hyperkeratosis or thickening of skin of both hypo and hyper-pigmentation (Meliker et al., 2007). Chronic toxicity also include weakness, GI hepatomegaly (jaundice > Cirrhosis), melanosis, arrhythmias, peripheral vascular disease (Black foot disease).

Chronic human exposure has also been linked to several systems in the human body: dermal (exfoliative dermatitis, keratosis, vitiligo, skin cancer), peripheral neuropathy, encephalopathy, bronchitis, pulmonary fibrosis, hepatosplenomegaly resembling, portal hypertension, peripheral vascular disease and BFD (Black foot disease), arteriosclerosis and cancers of lung, urinary bladder and other internal organs and diabetes. Experimental and epidemiological evidence support diabetes effect of high level arsenic exposure (Pimparkar and Bhave, 2010). The adverse effects of arsenic exposure also cause infant and adult disease mortality (Yunus et al., 2011).
Lung

Adverse health effects of arsenic (cited by Google)
**Arsenic as carcinogen:**

Inorganic arsenic a common environment contaminant and human carcinogen (IARC, 2004; NTP, 2007) has been associated with human liver cancer in childhood (Liu and Waalkes, 2008). Subchronic exposure to arsenic through drinking water alters the expression of cancer related genes in the liver of rats (Cui et al., 2004a). Chronic exposure to arsenic in drinking water has been linked with the development of various pathological conditions including cancer (Prajapati et al., 2011).

Arsenic induces benign and malignant tumors namely lung adenomas and carcinomas and bladder carcinomas (Suzuki et al., 2012). An elevated incidence of these types of ontological lesion is also observed among people living in geographical areas where arsenic is present at higher concentration in drinking water (Soffritti et al., 2006). The most notable risk factor strongly associated with bladder cancer is exposure to arsenic in drinking water at concentrations higher than 300 µg/L with occupational exposure (Letašiová et al., 2012). It is reported that variation in As3MT and MTHFR(arsenic methyltransferase and methylene-tetrahydrofolate reductase) is associated with bladder cancer among those exposed to relatively low concentrations of inorganic arsenic (Beebe-Dimmer et al., 2012).

Arsenic activity occurs in the cell metabolism by multiple forms as cell transformation is induced by low levels of arsenic (Desoize, 2003). Arsenite-induced rat lung epithelial cell (LEC) transformation, epithelial-mesenchymal transition, stimulation of the extracellular signal-regulated kinase signaling pathway, and enhancement of cell proliferation. The results clearly demonstrated that induction of p-ERK and cell proliferation by arsenite is mediated via oxidative stress (Li et al., 2011). Liu et al. (2007) reported that exposure of mouse fetus to inorganic arsenic significantly alters expression of various genes. The alteration could disrupt genetic programming at the very
early life stage, which could impact tumor formation much later in adulthood. Arsenic exposure promotes tumorigenesis by inducing changes in the expression of tumor-related genes by dysregulating DNA methylation at tumor-related gene loci (tumor-related genes, p16 (INK4a), RASSF1A, Ha-ras and ER-α as target genes) (Suzuki and Nohara, 2012). It is suggested that As(III) promote colorectal cancer tumorigenesis, at least partly, through ROS-mediated Wnt/β-catenin signaling pathway (Wang et al., 2012b). Prolonged arsenic exposure is a known cause of urothelial carcinoma (UC) and blackfoot disease (Liu et al., 2012).

Arsenic is a transplacental carcinogen in mice with the ability to target tissues of potential human relevance, such as the urinary bladder, lung and liver (Waalkes et al., 2007). Liver is a major target organ of arsenic carcinogenesis in transplacentally exposed animals models (mice) (Waalkes et al., 2004).

Inorganic arsenic increases the deoxyguanosine oxidation level, alters the cytosine methylation state, decreases the activities of glutathione reductase and glucose-6-phosphate dehydrogenase, decreases the protein expression of NAD(P)H quinone oxidoreductase-1 (NQO-1) and increases the protein expression of specific protein 1 (Sp1) in bladder tissues (Lin et al., 2012).

**Arsenic is potent endocrine disruptor**, altering hormone mediated cell signaling at extremely low concentration (Mead, 2005). It also alters gene regulation by the closely related glucocorticoid, mineralocorticoid, progesterone and androgensteroid receptors at concentration as low as 0.01 μM (Davey et al., 2007).

The current study provided evidence that subchronic inorganic arsenic exposure at 3 ppm from prenatal developmental stages to adult life resulted in damage to pancreatic β cells, affected insulin secretion and demonstrated
altered glucose homeostasis, thus supporting a causal association between inorganic arsenic exposure and diabetes (Dávila-Esqueda et al., 2011).

There was a significant dose response of arsenic exposure to risk of infant death, therefore women of **reproductive age** should urgently be prioritized for mitigation activities where drinking water is contaminated by arsenic (Tofail et al., 2009).

Arsenic induces dysfunction in relaxation of blood vessels (Lee et al., 2003) increased vascular permeability leading to vasodilation and vascular collapse (Mishra and Flora, 2008). A study suggested arsenic-induced oxidative stress in mouse where animals were chronically exposed to 25 ppm sodium arsenite in drinking water for 12 months. Arsenic exposure led to a significant depletion of blood δ-aminolevulinic acid dehydratase (ALAD) activity, glutathione (GSH), white blood cell (WBC) and red blood cell (RBC) count, significantly increasing the level of reactive oxygen species in RBCs (Mishra and Flora, 2008).

Zinc protoporphyrin, a sensitive indicator of iron deficiency and impairment of heme biosynthesis, showed a significant increase in arsenic exposure (Kannan et al., 2001; Nandi et al., 2005).

In patients with arsenic-induced Bowen's disease, there is a selective CD4 T-cell apoptosis through tumor necrosis factor-alpha pathway, decrease in macrophage differentiation and phagocytosis, reduced Langerhans cell numbers and dendrites, altered regulatory T-cell distribution and other immune alterations. The molecular bases of immune-suppression by arsenic in lymphocytes may include chromosomal and DNA abnormalities, decreased T-cell receptor activation, and the cellular status of oxidation and methylation (Lee et al., 2012).
The binding with sulfhydryl groups by arsenite compounds has the potential to influence a wide range of metabolic activities including cellular glucose uptake, gluconeogenesis, fatty acid oxidation and production of glutathione. However, binding of arsenic with sulfhydryl bonds is often reversible (Young, 2000).

Sodium arsenite induced cell death in the liver and brain of experimental rats (in vivo) showed by decreased GSH, SOD, CAT, induction of LPO, GPx and Cytochrome P-450 a significant increase in caspase-3 activity and caused DNA cleavage into DNA fragments manifested as DNA laddering a hallmark of apoptosis (Bashir et al., 2006).

Individual who are exposed to arsenic, showed decreased DNA repair (Angeline et al., 2003).

Shi et al. (2004) studied role of ROS and reactive nitrogen species (RNS) in arsenic induced DNA damage. Arsenic activity occurs in cell metabolism by multiple forms as cell transformation induced by low level of arsenic.

Arsenic elicits its toxic efforts through many mechanisms, including generation of reactive oxygen species (ROS). Nrf-2 is the primary transcription factor that controls expression of a main cellular antioxidant response, which is required for neutralizing ROS and thus defending cells from exogenous insults (Jiang et al., 2009).

Arsenic caused mitochondrial injury by increased oxidative stress and reciprocal regulation of Bcl-2, Bcl-xL/Bad, Bax, Bim in association with increased level of Apaf-1, activation of caspase 9/3, cleavage of PARP protein and ultimately led to apoptotic cell death (Das et al., 2010a).
2.6 Arsenic toxicity at biochemical level

Liver is the target organ of arsenic toxicity, the leakage of hepatic housekeeping enzymes, alanine transferase (ALT) and aspartate transferase (AST) are commonly used as an indirect biochemical index of hepatocellular damage (Klassen and Watkins, 1984). In study by Santra et al., (2000) BALB/C mice were given drinking water contaminated with arsenic (3.2 mg/L) *ad libitum*. After 12 months of arsenic feeding, serum aspartate aminotransferase and alanine aminotransferase activity increased significantly. After 6 months of arsenic feeding, hepatic glutathione and the enzymes glucose-6-phosphate dehydrogenase and glutathione peroxidase were significantly lower than those of control group. Hepatic catalase activity was significantly reduced at 9 months in the arsenic-fed group, while glutathione-S-transferase and glutathione reductase activities were also significantly reduced at 12 and 15 months. Plasma membrane Na\(^+\) / K\(^+\) ATPase activity was reduced while lipid peroxidation increased significantly.

Bashir et al. (2006) demonstrated the effect of acute arsenic administration in liver of Wistar rats. Sodium arsenite was administered orally at doses of 6.3 mg/kg, 10.5 mg/kg and 12.6 mg/kg of body weight on the basis of a lethal dose 50% (LD\(_{50}\)) for 24 hrs. Glutathione levels were decreased in liver at all doses. A significant lipid peroxidation and cytochrome-P 450 induction along with significant decrease in catalase and superoxide dismutase was observed. The activity of glutathione peroxidase was increased significantly. The study revealed that arsenic increased the activity of superoxide dismutase (SOD) and catalase (CAT) and the level of lipid peroxidation (LPO), protein carbonyl (PC) and nitric oxide (NO) at 1 hour, 1.5 hours and 2 hours of incubation (Rana et al., 2010).

Wang et al. (2006 b) conducted an experiment to investigate the effect of dietary arsenic levels on serum biochemistry of growing and finishing pigs.
Diets were supplemented with 0, 10, 20, 30 mg As/kg, as arsenic trioxide. Arsenic intake significantly increased (p < 0.05) serum glutamicpyruvic transaminase (SGPT) and alkaline phosphatase (ALP) activities. These enzymes being raised several fold after arsenic poisoning (Modi et al., 2006; Sharma et al., 2009).

A study revealed that an increase in lipid peroxidation, protein carbonyl and a decrease in the levels of glutathione and activity of superoxide dismutase, catalase and glutathione peroxidase with differential effects were observed in arsenic treated rats (Yadav et al., 2009).

Administration of sodium arsenite (100 mg/kg/day) for 28 days in Sprague Dawley female rats resulted in significant reduction of biochemical parameters such as delta-aminolevulinic acid dehydratase (ALAD), reduced glutathione (GSH), glutathione peroxidase (GPx), superoxide dismutase (SOD) and elevation of thiobarbituric acid reactive substances (TBARS) and the index of nitrite/nitrate (NOx) levels. The tissue arsenic burden was increased after arsenic exposure for a period of 28 days (Chandronitha et al., 2010). Increasing dose and duration of arsenic exposure in mice cause progressive increase of oxidative stress (depletion of hepatic GSH and antioxidant enzymes (GPx, SOD, CAT), increased LPO level) (Das et al., 2010b) and elevation of cytokines associated with increasing level of collagen in the liver (Das et al., 2005).

Hepatotoxicity is measured by the increased activities of serum hepatospecific enzymes namely aspartate transaminase, alanine transaminase, alkaline phosphatase, γ- glutamyl transferase, lactate dehydrogenase and total bilirubin along with increased elevation of lipid peroxidative markers, thiobarbituric acid reactive substances, lipid hydroperoxides, protein carbonyl content and conjugated dienes. The toxic effect of arsenic was also indicated
by significantly decreased activities of enzymatic antioxidants like superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase, glutathione reductase and glucose-6-phosphate dehydrogenase along with non-enzymatic antioxidant like reduced glutathione (Pari and Mohamed Jalaludeen, 2011).

Inhibitor studies and immunoblot analyses demonstrated that arsenic-induced apoptosis involved activation of caspase-3 and cleavage of poly (ADP-ribose) polymerase, a well-characterized caspase-3 substrate. The exposure to micro-molar concentration of arsenic induces ROS generation through the activation of NADPH oxidases, which in turn causes caspase-3 mediated HKM apoptosis (Datta et al., 2009). Arsenic causes fibrosis associated elevation of its gene expression in liver, plasma TGFs and release of cytochrome c in cytoplasm (Ghosh et al., 2010a).

Exposure to arsenic is associated with development of liver fibrosis and portal hypertension through ill defined mechanisms. Hepatic NADPH oxidase activity progressively increased in arsenic exposure with concomitant development of hepatic oxidative stress. Hepatic steatosis with occasional collection of mononuclear inflammatory cells and mild portal fibrosis were the predominant liver lesion observed after 9 months of arsenic exposure, while at 12 months, the changes included mild hepatic steatosis, inflammation, necrosis and significant fibrosis in periportal areas. The pathologic changes in the liver were associated with markers of hepatic stellate cells (HSCs) activation, matrix reorganization and fibrosis including α-smooth muscle actin, transforming growth factor-β1, PDGF-Rβ, pro-inflammatory cytokines and enhanced expression of tissue inhibitor of metalloproteinase-1 and pro(α) collagen type I. Moreover, pro-apoptotic protein Bax was dominantly expressed and Bcl-2 was down-regulated along with increased number of
TUNEL positive hepatocytes in liver of arsenic exposed mice (Ghatak et al., 2011).

Short-term arsenic exposure (3mg/kg body weight/day for 30 days) caused liver damage evidenced by activities of liver enzymes and necroinflammatory changes. These effects of arsenic were coupled with enhanced mitochondrial swelling, inhibition of cytochrome c oxidase, Ca$^{2+}$-ATPase, a decrease in mitochondrial calcium content, changes in indices of hepatic mitochondrial oxidative stress and iNOS expression. Arsenic also increased hepatic caspase-3 activity and DNA fragmentation (Majumdar et al., 2011).

The study revealed a novel exposure- and dose- response relationship between arsenic exposure metrics and serum hepatic enzyme activity. Elevated serum hepatic enzyme activities in the higher exposure gradients provided new insights into arsenic-induced liver toxicity that might be helpful for the early prognosis of arsenic-induced liver diseases (Islam et al., 2011).

Arsenic-altered gene expression included genes related to stress response, cellular metabolism, cell cycle regulation, telomere maintenance, cell-cell communication and signal transduction (Hernández et al., 2011).

The results are demonstrated a significant decrease in hepatic GSH levels, SOD and catalase activities and an increase in GST and TBARS levels after arsenic administration (Jain et al., 2011). Arsenic significantly increased serum alanine aminotransferase level. Sodium arsenite significantly enhanced lipid peroxidation, and prevented the increased glutathione depletion and nitric oxide elevation in the liver tissue.

It was reported that arsenic intoxication can give significant vulnerability against alterations in oxidative stress and apoptotic marker parameters and
downstream changes in mitochondria, namely pro-oxidative (NO, TBARS, \( \text{OH}^- \)) and anti-oxidative defense (SOD, CAT, GSH) markers, iNOS protein expression, mitochondrial swelling, cytochrome c oxidase and Ca\(^{2+}\)-ATPase activity, Ca\(^{2+}\) content, caspase-3 activity that helpful in liver injury (Majumdar et al., 2012).

Naranmandura et al., (2012) reported that rat liver mitochondrial swelling is strongly induced by exposure to the methylated forms of MMA(III) and DMA(III) in a dose-dependent manner in the absence of Ca\(^{2+}\), suggesting that the methylated forms may have potent effects on cellular mitochondria.

### 2.7 Phytoprotection

Recently, the use of herbal natural product has gained interest among the world population. Many of the herbs have been developed into herbal supplement which are claimed to assist in healthy lifestyle. (Ghasi et al., 2000).

Plants have formed the basis of sophisticated traditional medicine systems among which are Ayurvedic, Unani and Chinese. These systems of medicine have given rise to some important drugs still in use today (Guirel-Fakim, 2006). Plants ingredients used in traditional systems of healing have been the source of inspiration for several major pharmaceutical drugs.

The popularity of herbal medicines is connected with their ease access, therapeutic efficacy, relatively low cost and the assumption for absence of side toxic effects. The widespread public opinion is that being natural products, the herbal medicines are harmless, free from adverse effects and so even if the expected medical effect is not achieved, their consumption is not dangerous (Arpadjan et al., 2008).

A number of epidemiological studies have provided convincing evidence that a diet rich in plant-based foods is correlated with a reduction of the risk of developing several chronic diseases (Paur et al., 2008).
Public health authorities consider prevention and treatment with nutraceuticals a powerful instrument in maintaining and promoting health, longevity and life quality (Barros et al., 2009).

Nutritional compounds or dietary supplements are used for a number of different purposes, such as to provide nutrients, control weight loss and help fighting against a variety of illnesses. Some countries define dietary supplements as foods, while in others they are defined as drugs or natural health products (Arantes-Rodrigues et al., 2011).

Effects of single compounds, on the other hand, are not convincing (Halliwell, 2000) and suggests that several of the components of fruits and vegetables might cooperate (Blomhoff, 2005) to produce health benefits, and thus the benefit will not be evident by supplementation of one or a few compounds (Paur et al., 2008).

Throughout history the study of natural products has provided the impetus for great advances in drug development. For several years, a special attention was paid to the dietary regimen and more particularly to natural products (fruits, vegetables) for their capacities to reduce toxicity of various pollutants, and for their protective effects against oxidative stress and related disease including aging or cancer (Hfaiedh et al., 2008).

*Syzygium cumini* Linn. Skeels is a medium sized to large tree and it has been reported to possess several medicinal properties in the folklore system of medicine (Jagetia and Vantesha, 2005). The bark of the plant is astringent sweet, refrigerative, carminative, diuretic, digestive, antihelminthes, febrifuge, constipating, stomaching, and antibacterial. The fruit and seeds are used to treat diabetes, phryngitis, spleenopathy, urethrorrhea, and ringworm infection. The leaves are antibacterial and used to strengthen the teeth and gums (Warrier et al., 1995). The leaves have been extensively used to treat
diabetes constipation, leucorrhoea, stomachalgia, fever, gastopathy, strangury, dermopathy, and to inhibit blood discharges in the faeces (Warrier et al., 1995; Bhandary et al., 1995).

*Aegle marmelos correa* commonly known as beal is a spinous tree belonging family Rutaceae. Its edible fruits, leaf, root, bark, and seeds are valued in Ayurvedic medicine in (Sharma and Dash, 1998). The unripe fruit are bitter, acrid, sour, astringent, aids in digestion and stomach irritation, and are useful in treating diarrhea, desentery and stomachalgia (Shoba and Thomas, 2001). Beal also uses as cardiotonic for treatment of heart ailments in Ayurvedic medicine system (Haravey, 1968; Rastogi and Mehrotra, 1990).

Narigenin, is a predominant flavanone found in grapefruit *Citrus paradise*. Jagetia and Koti Reddy (2004) reported that it can elevates antioxidant status of cell.

*Moringa oleifera* Lam (Moringaceae) is a highly valued plant. Various parts of this plant such as leaves, roots, see, bark, fruits and flowers act as Cardiac and circulatory stimulants, possesses antitumor, antipyretic, anti-inflammatory, antiulcer, antioxidant and anti-diabetic activities (Anwar et al., 2007). *Chlorophytum borivilianum* root extract have free radical scavenging activity as well as lipid peroxidation inhibition (Kaur et al., 2010).

Fennel (*Foeniculum vulgare Mill.*) is a widespread perennial umbeliferous herb. Fennel is highly recommended for diabetes, bronchitis and chronic coughs, and for the treatment of kidney stones. The species is also considered to have diuretic, stomachic and galactagogue properties. Infusions of leaves, stems or seeds, root or seeds decoctions, liqueurs prepared with stems and inflorescences, baths, ointments and poultices are some of the therapeutic applications reported in Portuguese folk medicine (Singh et al., 2006). Fennel as source of crucial compounds in the neutralization of radical species
involved in the oxidative stress and responsible for several chronic diseases such as cancer, cardiovascular diseases and diabetes (Valko et al., 2007).

Sinha et al., (2003) revealed that black tea and green tea both are effective against arsenic toxicity. The protective effect is attributed to the epigallo catechingallete and theaflavin in Chinese hamaster.

Both green tea and black tea extracts have equal potential in modulating the arsenic induced genotoxicity in mammalian cells. This effect was perhaps induced by the constituent polyphenols present in green and black tea. In addition, the repair activity of the damaged cells was enhanced when treated with these tea extracts and their polyphenols (Sinha et al., 2005 & 2007a).

Silmyrin and quercetin are polyphenol antioxidant flavonoid widely found in vegetable source (Volate et al., 2005). Bongiovanni et al., (2007) reported that oxidative stress induced by arsenic, inhibited by silmyrin and quercetin.

Ghosh et al., (2010b) reported that fruit extract of Termanalia arjuna reduces cadmium induced oxidative stress. Puerarin, a natural flavonoid, could protect the rat liver against lead induced injury by reducing reactive oxygen species (ROS) production and renewing the activities of antioxidatant enzymes (Liu et al.,2012a).

Gupta and Flora (2005a) reported that simultaneous supplement of Aloe vera protect against arsenic induced oxidative stress in liver, kidney and blood in rat.

Hippophae rhamnoides is used as an herbal remedy for gastric ulcers, burns and some skin and allergic disease. It significantly protects against arsenic induced oxidative stress and shows therapeutic efficacy in mice
(Gupta and Flora, 2005b). Flora and Gupta (2007) reported beneficial effect of *Centella asiatica* against arsenic induced oxidative stress in rat.

Since the time of Ayurveda numerous therapeutic activities have been assigned to tumeric, derived from the plant *Curcuma longa* for a wide variety of disease and condition, including those of the skin, pulmonary and gastrointestinal systems, aches, wounds, sprains and liver disorders (Aggarwal *et al.*, 2007).

Garlic (*Allium sativa*) is well known folk remedy, its aqueous extract have beneficial role against arsenic toxicity pertaining to its ability to eliminate arsenic from blood and soft tissue and in reversal of arsenic induced oxidative stress in affected tissues (Flora *et al.*, 2009).

Pre treatment with arjunolic acid, a triterpenoid saponin isolated from the bark of *Terminalia arjuna* could prevent the arsenic induced hepatic oxidative stress, and injury to the histological structure of the liver in mice. Arjunolic acid could maintain its antioxidant system. This may be due to its intrinsic antioxidant property (Manna *et al.*, 2007).

Banerjee *et al.* (2009) reported that ascorbic acid combats arsenic induced hepatic oxidative stress in mice.

In a study, ameliorating effect of *curcumin* suggests that *curcumin* protect arsenic induced oxidative damage (Lipid peroxidation) in different organs (El-Demerdash *et al.*, 2009) and biochemical alteration in serum of rats (Yousef *et al.*, 2008).

Saxena *et al.* (2009) revealed that *curcumin* from *Curcuma longa* have protective effect against arsenic induced oxidative renal injuries. Argentinian medicinal plants, *Lantana grisebachi*, *Eupatorium buniifolium*, *Mandevilla*
*pentlandiana* and *Sebastiania commersoniana* prevent the formation of aqueous and lipid hydroperoxide so it is potentially beneficial against arsenic induced renal injury in human (Soria *et al.*, 2008).

Sharma *et al.* (2009) reported antioxidant property of *Emblica officinalis* against arsenic toxicity in mice.

Akinmoladun *et al.* (2007) exhibited phytochemical constituent and antioxidant activity of extract from the leaves of *Ocimum gratissimum*. The post arsenic administration of *Ocimum sanctum* has significant role in protecting animals from arsenic induced oxidative stress and in the depletion of arsenic concentration in rat (Sharmilla *et al.*, 2009).

Pea (*Pisum sativum*) are both good sources of dietary plant proteins. As a possible mechanism it could be stated that either pea or wheat or both have a recovery role on arsenic trioxide mediated toxicity by inducing an antioxidant effect against the oxidative stress (Mukherjee and Mukhopadhyay, 2009).

Das *et al.* (2010b) reported that administration of aqueous extract of *Corchorus olitorius* leaves prior to arsenic intoxication has significant role in protecting rats from arsenic induced hepatic and renal injury.

Administration of aqueous extract of *Corchorus olitorius* leaves prior to arsenic intoxication has significant role in protecting rats from arsenic induced brain oxidative stress (Das *et al.*, 2010c) and myocardial injury (Das *et al.*, 2010d).

It has been established that *Jaggery* (sugarcane juice) the natural functional food has the efficiency to encounter the genotoxic effects in mice, induced by arsenic (Singh *et al.*, 2010).
Continued dietary administration of black tea infusion showed protection against the chromosome damaging effect of sodium arsenite at a significance level, protection may be attributed to the antioxidant and scavenging properties of tea (Patra et al., 2005). The tea polyphenols by virtue of their antioxidant potential may be used as an effective agent to reduce the arsenic (III) induced oxidative stress in Swiss albino mice. Elevated levels of lipid peroxides and protein carbonyl by arsenic (III) were effectively reduced with green as well as black tea. They also exhibited protective action against the arsenic (III) induced depletion of antioxidants like catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST) and glutathione (GSH) in mice liver tissue (Sinha et al., 2010).

Supplementation of dietary phosphate can ameliorate arsenic induced hepatic oxidative stress in rat (Majumdar et al., 2011).

In a study strong evidence for the hepato-protective and antioxidative efficiencies of Moringa oleifera seed extract against oxidative stress induced by arsenic (Chattopadhyay et al., 2011) was reported. Roy and Roy (2011) reported the ameliorative potential of Psidium guajava leaf extract on arsenic induced biochemical alterations in Wistar rats such as glucose serum urea and serum creatinine, total protein, calcium and phosphorus.

The study by Tandon et al. (2012) revealed that treatment with AEPG (aqueous extract of Psidium guajava) 100 mg/kg body weight) significantly restored activities of oxidative stress markers like LPO levels, GSH levels, SOD, and CAT activities but having the limited protective activity of the herbal extract was observed on tissues (erythrocyte, liver, kidney and brain) architecture. Prophylactic co-administration of AEPG could provide specific protection from oxidative injury and to some extent on tissue damage.
Bhattacharya and Haldar (2012a) elucidated that *Trichosanthes dioica* root (TDA) DA (5 and 10mg/kg) was administered orally to rats for 20 consecutive days before oral administration of sodium arsenite (10mg/kg) for 8 days. Then the body weights, organ weights, haematological profiles, serum biochemical profile; hepatic and renal antioxidative parameters viz. lipid peroxidation, reduced and oxidized glutathione, glutathione-S-transferase, glutathione peroxidase, glutathione reductase, superoxide dismutase, catalase and DNA fragmentation were evaluated. Pretreatment with TDA markedly and significantly normalized body weights, organ weights, haematological profiles, serum biochemical profile and significantly modulated all the hepatic and renal biochemical parameters and reduced DNA fragmentation in arsenic intoxicated rats.

Pachauri and Flora (2013) reported that Nicotine plays a role to reduce the adverse effect of arsenic at some extent.

In recent years, numerous studies describing the therapeutic properties of extracts from different parts of various medicinal plants have developed. Indeed the use of such extracts as complementary and alternative medicine has lately increased and also served as an interesting source of drug candidates for the pharmaceutical industrial research (Newman and Cragg, 2007).

Trends on applying nutritional antioxidants in diseases related to oxidative stress have gained immense interest in recent years. Plant products are known to exert their protective effects by scavenging free radicals and modulating antioxidant defense system. In order to combat against arsenic induced organ-toxicity, scientists are looking forward in search of suitable protective agents. Although very few reports are available on such agents (Mallick et al., 2003).
Chlorophytum Borilianum (RUBL No. 19902)
“Fight Arsenic poisoning with the help of Herbal product.”

**Chlorophytum borivilianum**

**Common name:** Safed musli, Biskandri (Hindi);

Shweta musli (Sanskrit).

belongs to the family liliaceae and is probably christened so because of the white milky texture of its tubers after peeling.

*Chlorophytum borivilianum* (*C.borivilianum*), is a perennial flowering plants, native to the tropical and subtropical regions of Africa and Asia (Kaushik, 2005). It is found in the oldest mountain ranges on the continent, the Aravalis from where it spread to the near-by areas of the sub-continent, presently known as the states of Gujarat, Rajasthan, Madhya Pradesh and the Central Deccan Plateau (Thakur and Dixit, 2006). They grow to 10-60 cm tall, with a rosette of long, slender leaves 15-75 cm long and 0.5-2 cm broad, growing from a thick, fleshy rhizome. The flowers are small, usually white, produced on sparse panicles up to 120 cm long; in some species the panicle also bears plantlets, which take root on touching the ground. *C. borivilianum* is a traditional rare Indian medicinal herb which has many therapeutic applications in Ayurvedic, Unani, Homeopathic and Allopathic system of medicine (Thakur *et al*., 2009). Its tubers are used in Ayurvedic medicine.

**Chemical constituents**

It is a rich source of over 25 alkaloids, vitamins, proteins, carbohydrates, steroids, saponins, potassium, calcium, magnesium, phenol, resins, mucilage, and polysaccharides and also contains high quantity of simple sugars, mainly sucrose, glucose, fructose, galactose, mannose and xylose (Thakur *et al*., 2009). Major phytochemical component reported from roots of *C. borivilianum* include fructans and fructooligosaccharides (FOS), acetylated mannans, phenolics compounds and protein (Kaushik, 2005; Narasimhan *et al*., 2006;
Acharya et al., 2009). Its root contains steroidal and triterpenoidal saponins, sapogenins and fructans which act as therapeutic agents and play vital role in many therapeutic applications (Thakur et al., 2009). Among all the species of Chlorophytum present in India, C. borivilianum produces highest yield of roots along with the highest saponins content (Bordia et al., 1995). It contains about 30% alkaloids, Natural steroid saponin (10-20%), polysaccharides (40 to 45%), carbohydrates and proteins (5 to 7%) (Tandon et al., 1992; Deore and Khadabadi, 2008).

**Medicinal properties**

Roots are widely used for various therapeutic applications in the Ayurvedic and Unani systems of medicine. The root is used for treating sprue, piles, blood disorder, diabetes, arthritis, dysmenorrhea and as an aphrodisiac, rejuvenator and valuable nerve and general tonic for strength and vigor. The fried root powder is chewed to promote healing of ulcers of the mouth and throat (Kirtikar et al., 1935; Nadkarni, 1954; Chopra et al., 1956; CSIR, 1948-1992; Yoganarasimhan, 1996; Mei et al., 2002; Kaushik, 2005). Its roots used for rheumatism and joint pains, increase lactation in feeding mothers, as antimicrobial, anti-inflammatory, antitumor agent, also used in diarrhea, dysentery, gonorrhea, leucorrhea etc. It has spermatogenic property and is found useful in curing impotency, now it is considered as an alternative 'Viagra' (Thakur et al., 2009).

Roots of the plant are used both in Ayurveda and Unani system to treat oligospermia (The Wealth of India 1996).

The saponins and alkaloids present in the plant are the source of its alleged aphrodisiac properties (Wikipedia, 2012b).