Chapter 2

Review of Literature
When water is contaminated with As it cannot be seen, because As is invisible and does not affect the taste or smell of the water unless concentrations are extremely high. Exposure to As to general population can take place in several different ways, but consuming As-containing water and food (especially marine food) are the most common routes.

Unfortunately, there is no known cure for As poisoning and therefore providing As free drinking water is the only way to diminish the adverse health effects of As. Consequently, several methods are proposed to provide As-free water. These methods suggest either the treatment of As contaminated groundwater, or looking for the alternative options (e.g. surface water treatment, rain-water harvesting, etc). The use of alternative water sources, however, can only be possible after a major and costly technological shift and thus, the treatment of As contaminated water to the guideline values is the preferred option (Ahmed, 2003). As contamination in the affected districts of the Bengal Delta is potentially the greatest environmental calamity ever reported (Karim, 2000).

As contamination of drinking water is a major health concern, because As contaminated drinking water is linked to several types of cancers. It is important to note that the most effective way to overcome the adverse health effects of As is reduction in further exposure by providing safe drinking water. In view of this, the World Health Organization (WHO, 2004) has recommended a MCL for drinking waters of 10 ppb. MCL value is the concentration below which the presence of As is not considered to pose a significant health risk, even after a lifetime consumption of the water. Hence, when setting an MCL it is necessary to better understand and balance the health risks associated with drinking As bearing water against alternative sources of water, the cost and practicality of the treatment and the practical limitations of analytical methods (Waypa et al., 1997).
The removal of As from drinking water has attracted growing interest due to the negative health effects of drinking As contaminated water. A lot of research has been carried out with the specific aim of developing cost-effective As removal techniques. Several removal methods have been proposed and adsorption has emerged as one of the most practical method. However, these methods are not sufficient to provide safe drinking water to a large population around the world.

Treatment and Management

In recognition of the seriousness of the situation of As contamination especially in transition countries, where a large portion of population are at the risk of various health effects, early intervention and prevention can give relief to the affected population. In acute As toxicity, chelation treatment is a good remedial action to reduce the toxicity and elimination of toxic species, while in chronic toxicity chelation therapy is not effective and can produce severe side effects. Supplementation of vitamins and micronutrients in diet may enhance the recovery from initial levels of As toxicity (Singh et al., 2007; Zablotska et al., 2008).

a) Therapeutic Interventions

From the early 1950s, British Anti Lewisite (BAL or Dimercaprol) has been the drug of choice for the treatment of As poisoning in the United States (Klaassen, 1985). BAL is a lipophilic dithiol compound having a strong chelating affinity for As (Muckter et al., 1998). Although it is considered as one of the best treatment options for As poisoning, it has many serious disadvantages. Few recent studies suggest that it is responsible for redistribution of the metal into the brain from hard tissue deposits (Hoover and Aposhian, 1983). Moreover, being potentially toxic itself, it needs to be administered in small therapeutic doses.
(Aposhian et al., 1981).

All these disadvantages resulted in the development of analogs of BAL, i.e. meso 2, 3-dimercaptosuccinic acid (DMSA) and sodium 2, 3-dimercaptopropane 1-sulfonate (DMPS). These analogs are water soluble, orally active and less toxic than BAL. Recent reports show DMSA and DMPS to be better therapeutic agents against As poisoning due to their effectiveness in reducing mortality rate in laboratory animals as compared to BAL (Aposhian and Aposhian, 1990). These chelators are less toxic than BAL and consequently both DMSA and DMPS can be administered in much higher doses than BAL (Kreppel et al., 1990; Guha-Mazumder et al., 2001). Also, they can be administered in higher volumes because of their low toxicity (Kreppel et al., 1990). Analogues of BAL, DMSA and DMPS were successfully tried against chronic experimental As poisoning in animals (Flora et al., 1995). Recent advances in the treatment of As toxicity have shown that DMSA and DMPS are orally effective dithiol-chelating agents useful for treating As poisoning (Kreppel et al., 1993; Flora et al., 1995). DMSA and DMPS have been used successfully for the treatment of As, lead and mercury (Ding and Liang, 1991; Aposhian et al., 1992). Several studies demonstrated that both dithiols chelator DMPS and DMSA significantly increased the biliary excretion of As except BAL in perfused liver (Reichl et al., 1990a; 1992; 1994). Furthermore, Reichl et al. (1995) reported that combined oral administration of DMPS and colestyramine enhanced the fecal excretion of As. In post exposure treatment with DMSA and DMPS, DMPS proved more effective than DMSA in producing an effective reversal of altered immunological variables and reducing As concentration of vital organs. The result suggested that DMPS could be an effective chelating drug for reversing most of the gallium arsenide (GaAs) induced immunological alterations and reducing tissue As burden (Flora and Kumar, 1996).
Combine exposure of DMSA with captoril suppressed the As-induced oxidative stress (Kalia et al., 2007).

Active transport of DMPS into cell via an anion carrier system makes it available inside the cell to some extent but DMSA is unable to cross cell membrane and thus has the extracellular distribution only. In chronic poisoning where As has gained access into the cell, it becomes mandatory for chelating agent to cross cell membrane to chelate intracellular As and facilitate its extraction out of the body. The analogs of DMSA with lipophilic properties were synthesized and tested against chronic As poisoning in experimental animals. Kreppei et al., (1995) demonstrated superior efficacy of monoisoamyl DMSA (MiADMSA) and mono n-amyl DMSA (MnADMSA) in protecting mice from lethal effects As and reducing body As burden. Flora and the co-workers (2002; 2004) documented that MiADMSA is comparatively more effective then DMSA to prevent gallium arsenide induced pathological liver injury and tissue oxidative stress. On the basis of As chelation and restoration of biochemical variables, MiADMSA has the potential to counteract the chronic As poisoning in comparison to DMSA/DMPS (Flora et al., 2005; Mishra et al., 2008). MiADMSA has also shown a synergistic effect to ameliorate As-induced toxicity with iron (Modi and Flora, 2007) and quercetin (Mishra and Flora, 2008).

b) Nutritional Management

Nutrition can play an important role in As toxicity and good nutrition can modulate the delayed effects of As in drinking water. The individuals with well-nourished food are less susceptible to chronic As poisoning. In the reduction of As toxicity, nutritional substances like protein, carbohydrate, minerals and antioxidants play an important role (Gamble et al., 2005; Steinmaus et al., 2005;
Protein: With respect to the action mechanism of As; protein, iron and antioxidants play an important role in the prevention of As toxicity. Methylation of As acts as detoxification process while the diet rich in protein decreases the toxicity by improving the metabolism of As. Diet deficient in protein decreases the As methylation and less excretion of As resulting in enhancement of the toxicity (Vahter and Marafante, 1987). With reference to the methylation, S-adenosylmethionine (SAM) a prime physiological methyl group donor, play a key role in As induced toxicity/genotoxicity. Ramirez et al. (2007) reported that SAM reduced the mutagenic capability of As. As disrupts the enzyme systems by combining with the sulphahydryl groups which leads to toxicity. Another reason for the aggravation of toxicity with reference to the low protein diet is the reduction of the free thiol groups, which play an important role in the As metabolism (McKinney, 1992). Several other studies suggested that diet deficient of protein leads to the enhancement of the developmental toxicity and inhibition of cellular protection component (Maiti and Chatterjee, 2000; Lammon and Hood, 2004).

Carbohydrate: The exact mechanisms of As toxicity yet to known. It is proposed that inhibition of enzymes and production of free radicals are responsible for As toxicity (Chang et al., 2007). However, with regard to the energy production system, inhibition of carbohydrate and pyruvate metabolism and substitution of phosphorus from ATP may be the cause of As-induced toxicity (Mitchell et al., 1971; Gresser, 1981; Szinicz and Forth, 1988; Liebl et al., 1995). Glucose a carbohydrate and an instant source of energy play an important role in prevention of As toxicity (Reichl et al., 1991a; Liebl et al., 1995).
In reference to the carbohydrate metabolism (glucose/glycogen depletion), Reichl and their colleagues performed a series of experiments to confirm that As affects carbohydrate metabolism and administration of glucose improves the disease condition. In the first experiment, Reichl et al. (1988) reported that repeated As exposure can cause a marked depletion in carbohydrate content, mainly due to the depletion of glycogen. This study was also supported by the similar study of Szinicz and Forth (1988). In another experiment, As exposed animals showed significant depletion in glucose and glycogen content, while no depletion in glucose and glycogen content was found in glucose administered animals (Reichl et al., 1990b). Administration of glucose improved the survival and symptoms in mice after As exposure. Carbohydrate depletion is an important factor in As toxicity, and glucose supplementation should be considered as a treatment of As poisoning (Reichl et al., 1991a, 1991b). Pal and Chatterjee (2002) also documented that As poisoning induced carbohydrate depletion and hypoglycemia in vital organs. Dietary supplementation of methionine can counteracted the hypoglycemia with associated decreased glycolytic activity caused by As exposure (Pal and Chatterjee, 2004).

Vitamins: The increased concentration of free radicals in the body due to chronic As toxicity can result in carcinogenic and genotoxic effects. Antioxidant enzymes and vitamins play a vital role in the intervention of As caused toxicity. Vitamins and antioxidants are well known remedy against the oxidative stress. Besides radical scavenging activity, the antioxidants can also regulate the signal pathway and gene expression to intervent the cell death. Ascorbic acid is known to have a number of beneficial effects. It acts mainly as an antioxidant and its beneficial effects could also be attributed to its ability to complex metals. Vitamin C can also
regenerate the small-molecule antioxidant like as vitamin E (Chan, 1993). Vitamin E, on the other hand, is an important antioxidant that is suggested to play a physicochemical role in the stabilization of biomembrane by virtue of lipid–lipid interactions between vitamins and unsaturated fatty acids (Tappel, 1972). Several experimental studies proved that co-administration of vitamins like vitamin C and E with As, enhanced the modulating capacity by reducing reactive species and intervent the toxic effects of As (Ramanathan et al., 2002; 2003a; 2003b; 2005; Wei et al., 2005; Chang et al., 2007; Kadirvel et al., 2007). Besides the antioxidant properties of vitamin C and E, vitamin A also suppressed the oxidative stress induced by metals. In As-induced genotoxicity, co-administration of vitamin A can significantly reduce the genotoxic endpoints (Avani and Rao, 2007; 2009).

Iron: Iron functions mainly in the regulation of oxidative processes. It is a component of haem compounds that transports oxygen, cytochrome that functions in the electron transport chain and metalloprotein (McCormick, 1984; Baynes and Bothwell, 1990). Iron has a high affinity towards As. Iron binds with As and yields non-toxic iron-As complex and precipitates out from the living system. Therefore, iron is used in sorption/purification of water contaminated with As (Chen et al., 2007). Iron is a good chelator of As. The extent of accumulation of As in the liver and duodenum is more in the iron-deficient animals in comparison to iron-supplemented ones (Paul et al., 2002). Podder et al. (2000) demonstrated that supplementation of dietary iron alone also has the preventive effects against As toxicity by reducing the clastogenic effects. In the continuation, Podder (2004) had documented that supplementation of iron along with black tea ameliorate the As toxicity by reducing the incidence of chromosomal aberration.
Zinc: Zinc is one of the most important essential metals for human nutrition. Zinc plays a key role in genetic expression, cell division, and growth and is essential for the function of more than 200 enzymes (Salgueiro et al., 2000). The interaction between zinc and other metals or drugs in the development of mammals causes antagonistic action. When zinc was administered prior to As, there was a reduction in As concentration in several parts of adult mice contributing to a decrease in toxicity from the metal (Kreppel et al., 1994). The data from several experimental studies had provided some new and interesting evidence of beneficial role of zinc supplementation against acute As poisoning (Modi et al., 2005; 2006). The supplementation of zinc to As-treated animals reduced the As bioaccumulation in different vital organ of mice (Kamaluddin and Misbahuddin, 2006).

c) Alternative Therapies

For the amelioration/remediation of toxicological effects of environmental toxicant especially heavy metals, presently natural products from plants are extensively used by several researchers. Plants and their products without any chemical treatment have the active ingredients, which are effective against environmental toxicants without causing any harmful adverse health effects (Singh et al., 2008). Several studies found a positive correlation between the dietary supplementation of naturally occurring nutrients and the intervention of toxicity of environmental toxicant including heavy metals (Nandi et al., 1997; Gupta and Flora 2005a). Several naturally occurring dietary or non-dietary constituents, and parts of several species of edible plants having pharmacological activity, influence antioxidant enzymes and provide protection against free radical-induced damage (Scartezzini and Speroni, 2000; Gupta and Flora 2005b).
Garlic: Garlic (*Allium sativum*) is the second most widely used cultivated *Allium* which has long been recognized all over the world as a valuable spice for foods and a popular remedy for various ailments and physiological disorders. Garlic extract has strong therapeutic properties. Allicin (thio-2-propene-1-sulfonic acid S-allyl esters), alliin (S-allyl-L-cysteine sulfoxide) and cysteine are the principal constituents of aqueous garlic extract, in addition to other compounds with sulfur moieties (Asmus, 1983; Block, 1985). It is considered to be responsible for the inhibition of cholesterol synthesis (Yeh and Yeh, 1994), as well as diabetes (Sheela and August, 1992) and gastro-intestinal cancer (Mofty et al., 1994). Another important property of garlic is its radical scavenging ability (Reitz et al., 1995).

Mustard oil containing about 5.4% saturated fatty acids and 94.2% unsaturated fatty acids are an important source of unsaturated fats which are recognized as essential dietary elements and helpful to improve human health (Formo et al., 1979). According to Hayatsu et al. (1988) micelles of fatty acids may inhibit the mutagenic activity of food pyrolysate mutagens, polycyclic aromatic hydrocarbons and nitrosamines.

With regard of garlic, Das et al. (1993; 1996) reported that crude extract of garlic has the interventional efficiency against a well-known environmental genotoxigen. Choudhury and the colleagues performed a series of experiments using garlic alone and along with mustard oil to mitigate the clastogenic effects of As. Garlic alone and along with mustard oil significantly reduced the clastogenicity due to its active component (Roychoudhury et al., 1996; Choudhury et al., 1997a; 1997b). Chowdhury et al. (2008) reported that aqueous garlic extract has also the antioxidant activity and chelating efficacy despite its antigenotoxic properties. Continued administration of garlic extract can be potential protective regimen for
As mediated toxicity. Supplementation of mustard alone also reduced the As-induced oxidative stress at low dose and improves the antioxidant defence system (Khan et al., 2009).

*Embllica officinalis*: The extract of fruits of *Embllica officinalis* Gaertn of the family Euphorbiaceae or Emblic myrobalan, known as Indian gooseberry or Amla in Hindi, has been used extensively in Unani and Ayurvedic systems of medicine in India for the treatment of a number of diseases (Chopra et al., 1956). It is a rich source of vitamin C and has been shown to reduce the cytotoxic effects of several metals like zinc, lead, aluminium and nickel (Dhir et al., 1990; Agarwal et al., 1992).

The results reported that incidence of chromosome aberrations induced by As were significantly reduced by *E. officinalis* administration. It can be used as a natural dietary supplement to counteract the cytotoxic effects of As exposure through drinking water (Biswas et al., 1999).

*Moringa oleifera*: *Moringa oleifera* Lamarack (English: Horseradish-tree, Hindi: Saijan; Sanskrit: Shigru) belongs to the Moringaceae family. It is a multipurpose tree widely distributed in India and all over the world. Leaves of this plant are traditionally known for or reported to have various biological activities including hypocholesterolemic activities (Ghasi et al., 2000), regulation of thyroid hormone status (Tahiliani and Kar, 2000), anti-diabetic activity (Makonnen et al., 1997), anti-tumor activity (Murakami et al., 1998), cardiovascular action (Limaye et al., 1995), liver protective activity (Rao and Misra, 1998) and hematological, hepatic and renal functions (Mazumder et al., 1999).

*M. oleifera* significantly protected rats from the toxic effects of As in general,
and oxidative stress in particular besides, there was a moderate but significant depletion of As from blood and tissues. Gupta et al. (2005) reported that *M. oleifera* not only has a potent antioxidant activity but also has chelating property against As toxicity. The efficacy of seed powder of *M. oleifera* against As-induced oxidative stress in mice is also performed. The result showed the counteraction of oxidative stress by *M. oleifera* administration. It could be due to the antioxidant property and other important constituents in the seed powder of *M. oleifera* with As (Gupta et al., 2007).

*Aloe vera*: *Aloe vera* (*Aloe barbadensis*) is well-known in Hindi as Ghee kunwar or Gwarpattha and used in the traditional medicine of many cultures and said to be beneficial in the treatment of disorders such as arthritis, gout, dermatitis etc (Grindlay and Reynolds, 1986). The fresh gel, juice and formulated products have long been used for medical and cosmetic purposes and general health improvement (Chithra et al., 1998; Reynolds and Dweck, 1999). The antioxidant potential of *A. vera* has not been described in details. Yagi et al. (2002) recently reported antioxidant components in *A. vera*.

Simultaneous supplementation of *A. vera* prevented the appearance of signs of As induced oxidative stress in kidneys but had no effect on kidney As concentration at any of the three dose levels (Gupta and Flora, 2005a).

*Centella asiatica*: *Centella asiatica* mentioned as 'Madhya Rasayana' in Ayurvedic texts of the Indian system of medicine has been described for its intelligence promoting property (Chopra et al., 1956). *C. asiatica* is commonly known as Indian Pennywort in English, Brahmi in Hindi and Manduukaparni and Maanduuki in Ayurveda. Animal studies and clinical trials related to its effects on
the central nervous system (CNS) have shown promising results in improving memory and negative effects of fatigue and stress (Mukerji, 1953). *C. asiatica* is reported to possess anti-ulcer (Tan et al., 1997), cytotoxic (Sarma et al., 1995), antileprotic, antifeedant and wound healing properties (Srivastava et al., 1997). It has also been reported to protect against membrane peroxidation (Padma et al., 1998) and lipid peroxidation (Chandraprabha et al., 1996). *C. asiatica* contains asiaticoside, madecassic acid, thankunoside, thankunic acid, asiatic acid, brahmoside, brahminoside, brahmic acid, isobrahmic acid, centoic acid and centillic acid (Srivastava et al., 1997). Zainol et al. (2003) reported that *C. asiatica* had a high antioxidative activity, as good as that of α-tocopherol.

The supplementation of *C. asiatica* showed a significant protective value as a potent antioxidant activity against a few As sensitive biochemical variables in blood and hepatic oxidative stress (Gupta and Flora, 2006a). However, it had only limited or moderate ability to chelate As and kidney and brain oxidative injury. It has been suggested that supplementation of *C. asiatica* might prove beneficial in achieving optimum effects of chelation therapy. In another experiment, the aqueous extract of *C. asiatica* offered significant protection against As-induced oxidative stress by inhibiting lipid peroxidation and activating antioxidant defence enzymes. Besides, it has only limited or moderate ability to chelate As from liver and therefore, could be used as a supplementary agent during chelation therapy (Flora and Gupta, 2007).

*Mentha piperita*: *Mentha piperita* (Linn) (family Labiatae) commonly known as peppermint has shown antioxidant and antiperoxidative properties due to the presence of eugenol, caffeic acid, rosmarinic acid and α-tocopherol (Krishnaswamy and Raghuramulu, 1998; Al Seriti et al., 1999), antifungal (Aqil et
al., 2001), antibacterial (Lirio et al., 1998), antimutagenic (Vukovic and Simic, 1993), chemopreventive (Samman et al., 1998) and radioprotective activities (Samarth et al., 2001). These compounds have been shown to have antioxidant and antiperoxidant activities.

The result suggested that deleterious reactive oxygen species or lipid peroxides induced by As exposure may be alleviated by aqueous leaf extract of *M. piperita* which is reflected by a significant decline in LPO and a significant enhancement in LDH and GSH content in liver as compared to the As-treated group in Swiss albino mice. Several active components of *M. piperita* may provoke the activity of free radical scavenging enzyme systems and may protect against As-induced hepatic damages (Sharma et al., 2007).

**Andrographis paniculata:** The leaves and aerial parts of *Andrographis paniculata* (Burm. F.) Nees (Family: Acanthaceae) have been known as Kalamegha in Hindi and used in traditional systems of medicine for the treatment of hepatitis, bronchitis, colitis, cough, fever, mouth ulcers, sores, tuberculosis, bacillary dysentery, venomous snake bites, common cold, urinary tract infections, and acute diarrhoea (Panossian et al., 2002). Andrographolide, the active principle of this herb is implicated for its pharmacological activity. It is thus proposed that besides inhibiting lipid peroxidation by chain breaking, these could also scavenge other free radicals, mainly superoxides (Kamdem and Ho, 2002), thus exerting antioxidant potential on As genotoxicity. Though exact mechanism of action of *A. paniculata* extract is not known, results suggested that scavenging of free radicals and hydrogen transfer by andrographolide might play an important role in providing protection against As-induced oxidative and genotoxic damage (Avani and Rao, 2008).
**Hibiscus sabdariffa:** *Hibiscus sabdariffa* L. (family Malvaceae), commonly known in English as Roselle and Gudhal in Hindi, is widely grown in Central and West Africa and South East Asia. Extracts of plant are used in folk medicine against many complaints that include high blood pressure, liver diseases and fever (Wang et al., 2000; Ross, 2003). Citric and malic acids have been reported as the major organic acids in aqueous extracts of the flowers by Buogo and Picchinenna (1937) and Khafaga and Koch (1980) detected citric, hibiscus, malic and tartaric acids in the calyces of five strains of *H. sabdariffa*. In all strains, the concentration of acids increased during development of the calyces, but declined after they reached ripeness. The presence of ascorbic acid was reported in aqueous extracts by Buogo and Picchinenna (1937) and Reaubourg and Monceaux (1940). *H. sabdariffa* fruit has been used in medicine for its anti-inflammatory, antioxidant and anticholesterolemia properties (Tseng et al., 1997; Ali et al., 2005). Experimental studies have documented that *H. sabdariffa* extract inhibit cytotoxicity and genotoxicity of hepatocytes as well as inhibit xanthine oxidase activity (Tseng et al., 1997).

The protection afforded by the crude fruit extract of *H. sabdariffa* against sodium arsenite induced clastogenicity may be due to interaction between its complex components and sodium arsenite. Therefore, the crude aqueous extract of *H. sabdariffa* fruits could be used as a dietary supplement to prevent the clastogenic effects of As exposure through drinking water (Adetutu et al., 2004).

**Terminalia arjuna:** *Terminalia arjuna*, commonly known as Arjun in Hindi and holds a reputed position in both Ayurvedic and Unani Systems of medicine. The bark of *T. arjuna* is used since ancient times for the treatment of cardiac disorders (Ram et al., 1997; Gauthaman et al., 2001). *T. arjuna* is an important cardiotonic
herb and its bark has been used as a cardioprotective agent for treating hypertension and ischemic heart diseases (Karthikeyan et al., 2003). *T. arjuna* has also been shown to be beneficial for coronary artery disease, heart failure, and some cardio-protective activities (Bharani et al., 1995; Miriyala et al., 2001). Among the various constituents present in the bark of *T. arjuna* like arjunic acid, arjunolic acid, arjungenin, arjunglycosides, flavonoids, ellagic acid, gallic acid, phytosterols, calcium, magnesium, zinc and copper. Arjunolic acid has been shown to possess cardio-protective properties (Sumitra et al., 2001).

In addition to medicinal properties of arjunolic acid despite cardio-protective, arjunolic acid also has the beneficiary effects against chronic As toxicity. Supplementation of arjunolic acid depletes the oxidative stress and ameliorates the cytotoxicity induced by As exposure in hepatocytes (Manna et al., 2007a). Furthermore, continued administration of arjunolic acid protect the As-induced hepatic disorders (Manna et al., 2007b), oxidative myocardial injury (Manna et al., 2008a), testicular oxidative stress (Manna et al., 2008b), ameliorate the nephrotoxicity (Sinha et al., 2008a) and attenuates brain oxidative stress due to As exposure (Sinha et al., 2008b).

*Hippophae rhamnoides*: Seabuckthorn (*Hippophae rhamnoides* L., Elaeagnaceae) is thorny, nitrogen-fixing deciduous shrub, native to Europe and Asia (Rousi, 1971). Fruits of *H. rhamnoides* have been used extensively in traditional medicine systems and have many medicinal effects against flu, cardiovascular diseases, mucosal injuries and skin disorders (Beveridge et al., 1999; Eccleston et al., 2002). The protective efficacy has been suggested to be due to high contents of anti-oxidant substances present in the plant. It has been shown earlier that the fruits of seabuckthorn have potent antioxidant (Eccleston et
al., 2002; Negi et al., 2005), anti-ulcerative (Suleyman et al., 2001) and radioprotective properties (Goel et al., 2002). The berries of seabuckthorn possess significant amounts of ascorbic acid (100-700 mg/100 g), tocopherols (1-10 mg/100 mg) and carotenoides (3-15 mg/100 g) (Yao and Tigerstedt, 1992; Fu et al., 1993). Beside this, the fruit extract is a rich source of flavonoides (the main components are isorhamnetin and quercitin), carotenoides (including β-carotene, lycopene, zeaxanthin, etc.) and polyphenolic compounds, such as catechins and hydroxybenzoic acid (Rosch et al., 2003).

The fruit extract of *H. rhamnoides*, have a potent protective value against As induced oxidative stress, but does not show chelating activity (Gupta and Flora, 2005b). Furthermore, extract of *H. rhamnoides* significantly reduced the As-induced oxidative stress but again fail to remove As from vital organs (Gupta and Flora, 2006b).

**Tea (Camellia sinensis):** Tea is a popular beverage, derived from the tea plant. Green and black tea are derived from the same plant, after the leaves are fermented for different lengths of time. Both contain polyphenols and antioxidants. Green tea contains a lower proportion of caffeine then black tea and a higher concentration of polyphenols. The major polyphenols in green tea are catechins, including epigallocatechin gallate (EGEC), epicatechin gallate (ECG), epigallacatechine (EGC) and epicatechine (EC), of which EGEC has the higher antioxidant activity. In contrast, black tea contains tea flavour, thearubigens and higher concentration of caffeine (Koo and Noh, 2007). Animal studies as well as epidemiological studies reported the medicinal properties of tea against progression of atherosclerosis (Chyu et al., 2004), hyper-cholesterolemic (Vinson et al., 2004) and also has antioxidants and anticarcinogenic activities (Rees et al.,
Supplementation of tea extract has protects against As-induced clastogenicity reported by several experimental studies. Earlier, Sinha et al. (2003) reported that As-induced cytotoxicity was mitigated by the tea extract. The findings of experiment suggested that black tea was found to be as effective as green tea. Polyphenols as well as theaflavins play an important role in amelioration. Furthermore, extract of both green and black tea encounter the As-induced micronuclei formation in mammalian cells (Sinha et al., 2005a), attenuates the clastogenicity due to As exposure (Sinha et al., 2005b) and modulate the As-induced DNA damage in human lymphocytes (Sinha et al., 2007). Podder (2004) and Patra et al., (2005) also reported anticlastogenic properties of tea against As.

Functional Food-Jaggery: Ayurveda, the Indian traditional health care system (ayus = life, veda = knowledge, meaning science of life), is the oldest medical system in the world and is being revived in its complete form by scientific validation of Ayurvedic therapy. “Ayurveda” deals with the medicinal properties of the naturally occurring plants and plants products. These plants have inherent active ingredients, which are used for remediation of the diseases. International recognition of the functional food has suggested that the functional foods are the foods that provide health benefits beyond the basic nutrition to improve the physiological function of the body system (Arai et al., 2002). Jaggery is a natural sweetener made from sugarcane juice (Saccharum sinense) without the use of any chemicals/synthetic additives or preservatives. It is used in Ayurvedic medicines as well as a part of daily food. Jaggery, which contains protein, carbohydrate, vitamins and minerals, has a great nutritive and medicinal value (Table 1). Jaggery as functional food has specific nutrients and food components
that positively affect the target functions (especially biological response) in the body.

The previous experimental studies on jaggery reported that jaggery modified the coal-induced pathomorphological lesions in rats (Sahu et al., 1988a, 1988b). Beneficial ingredients of jaggery have shown dose-dependent and time-dependent alteration in asbestos induced fibrotic changes in mice (Sahu and Saxena, 1994) and improve the pulmonary defence system and lowering the incidence of occupational respiratory disease (Sahu and Paul, 1998). Administration of jaggery has also reduced the toxic effects of lead due to its active components especially vitamin C (Flora et al., 1988).

Table 1. General composition of Indian Jaggery

<table>
<thead>
<tr>
<th>Content</th>
<th>Value, range</th>
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<tbody>
<tr>
<td>Carbohydrate %</td>
<td>83.5-95.0</td>
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<tr>
<td>Sucrose</td>
<td>72.8-80.3</td>
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<tr>
<td>Reducing sugar</td>
<td>6.8-14.2</td>
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<tr>
<td>Minerals %</td>
<td>0.6-2.6</td>
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<tr>
<td>Calcium</td>
<td>0.2-0.36</td>
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<tr>
<td>Chloride</td>
<td>0.2-0.34</td>
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<tr>
<td>Phosphorus</td>
<td>0.03-0.22</td>
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<tr>
<td>Potassium</td>
<td>0.10-0.16</td>
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<tr>
<td>Sodium</td>
<td>0.006-0.025</td>
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<tr>
<td>Iron</td>
<td>0.005-0.020</td>
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<tr>
<td>Magnesium</td>
<td>0.008-0.105</td>
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<tr>
<td>Copper</td>
<td>0.007-0.010</td>
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<tr>
<td>Cobalt, Nickel and Molybdenum</td>
<td>0.001-0.008</td>
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<tr>
<td>Protein %</td>
<td>0.35-0.40</td>
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<td>Nonprotein nitrogen (mg/100g)</td>
<td>19.6-42.9</td>
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<tr>
<td>Protein nitrogen (mg/100g)</td>
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<tr>
<td>Vitamins, mg / 100g</td>
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<tr>
<td>Thiamine</td>
<td>0.018-0.030</td>
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<tr>
<td>Riboflavin</td>
<td>0.042-0.046</td>
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<tr>
<td>Nicotinic acid</td>
<td>3.92-4.50</td>
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<tr>
<td>Vitamin C</td>
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</tbody>
</table>
Carotene, mg / 100g  155.0-168.0
Phenolics, mg/100g  280.0-32.0
Fat, wax pectin and organic acid, %  0.10-0.60
Moisture, %  3.9-7.2

The above review of literature provides brief account of research work conducted so far on the toxic effects of As in animals and humans with especial emphasis on genotoxic and oxidative stress induced effect. In the above section of this thesis, review of literature related to work done on the prevention of As toxicity using natural compounds and herbal extract. Work related to prevention of As toxicity by such vitamin C, vitamin E and vitamin B has been also reviewed. Based on the review of literature it appears that there are many aspects on As toxicity which have yet to unravel. Similarly, there is no reliable, holistic and practical preventive measure for prevention of As toxicity in animals or humans. Therefore, there is a need to perform more research to identify the mechanism action of As toxicity at cellular and molecular level and identify new agents for prevention of As toxicity.

This study has been undertaken in order to identify newer action of As and to identify and test efficacy of newer preventive agents which are safe, cheap and simple to be adopt as food supplements.

Objectives:

Arsenic contamination in drinking water is among the most awesome environmental health challenge to our country as well as world over. With the clear understanding of the toxicological effects and mitigation strategies with physiological nutritive substance that may mediate the effect of exposure of
arsenic. It may be possible to reduce the toxic burden of arsenic. The present study is an attempt in that direction. The main objectives of the study presented in this dissertation were as follows:

➢ The effect of arsenic intoxication in mice.

➢ Possible mitigation effects of functional food - Jaggery in arsenic induced effects and in combination with other nutritive substance.