2. Review and literature

The toxicity of arsenic has long been of concern. From the ancient times, its toxicological effects are known due to its environmental as well as industrial contamination. The consequences of the toxic effects of arsenic contaminated drinking water on a vast number of human pollutions have compelled the investigators to find out the different aspects and mechanism of its toxicity. It is helpful to design several experimental models and collect data with their proper documentation. The studies carried out by previous investigators could be helpful for programming proper experiment as well better understanding of the toxic nature of arsenic. More clear under stains on arsenic toxicity mechanism might be helpful for screening good therapeutic agents against arsenic toxicity.

2.1. Source of arsenic

Arsenic (As) is a ubiquitous element found in the atmosphere, soils and rocks, natural waters and organisms. It is mobilized in the atmosphere through a combination of natural processes such as weathering events, biological activities and volcanic eruptions as well as through a range of anthropogenic activities. Most environmental on arsenic toxicity issues are the result of mobilization of this element under natural situations. However, people have a crucial impact of arsenic exposure through mining activity, combustion of fossil fuels. The use of arsenical insecticides, herbicides and crop desiccants are increases arsenic exposure. The use of arsenic as an additive to farm animals-feeds, especially for poultry has a great impact directly on the primary consumer and then indirectly on the human beings and other animals. The usage of arsenical products along with pesticides and herbicides has decreased appreciably in the previous couple of decades. The adverse effects on the environment of using arsenical compounds, sustain for several years. Even its residual effects are also capable of increase toxicity rock during land slide and soil erosion. Arsenic found in rock

and/or sediment is immobile in nature; as a result in sediment into groundwater and that groundwater are subsequently used for drinking. Only trace amount of arsenic are found in groundwater. However, certain natural geochemical conditions and strategies can lead to excessive amount of arsenic in groundwater. Some journalists claiming that shallow/deep tube wells are in particular responsible for the growing on arsenic of attention in the drinking

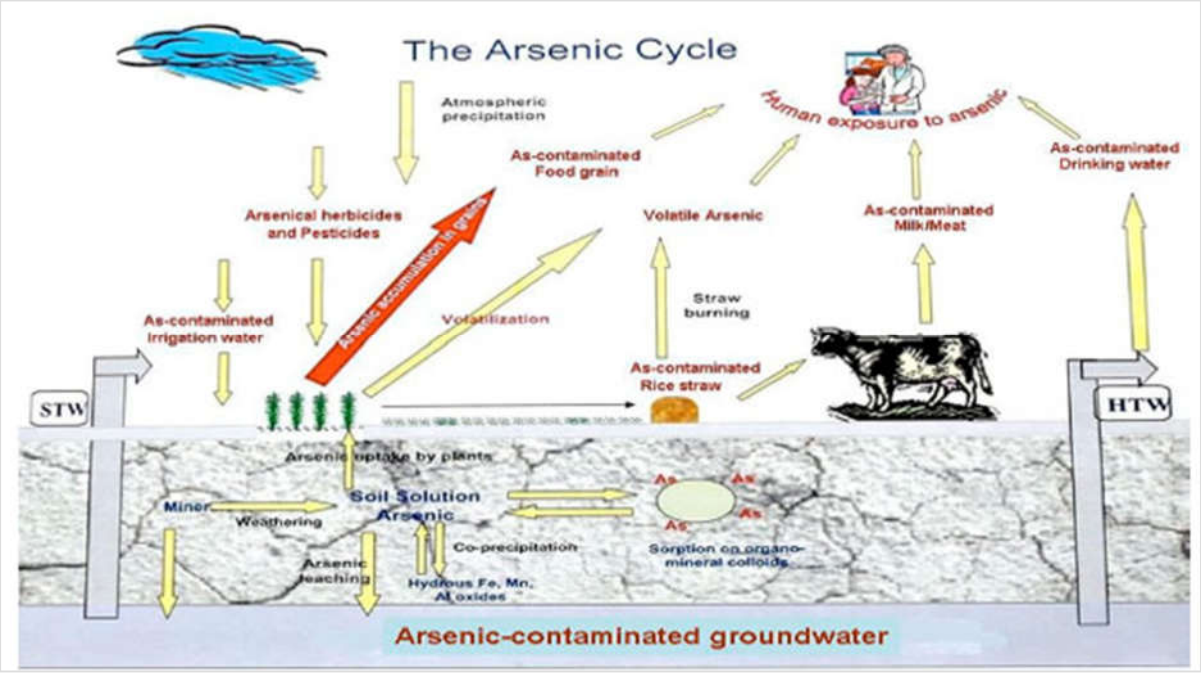


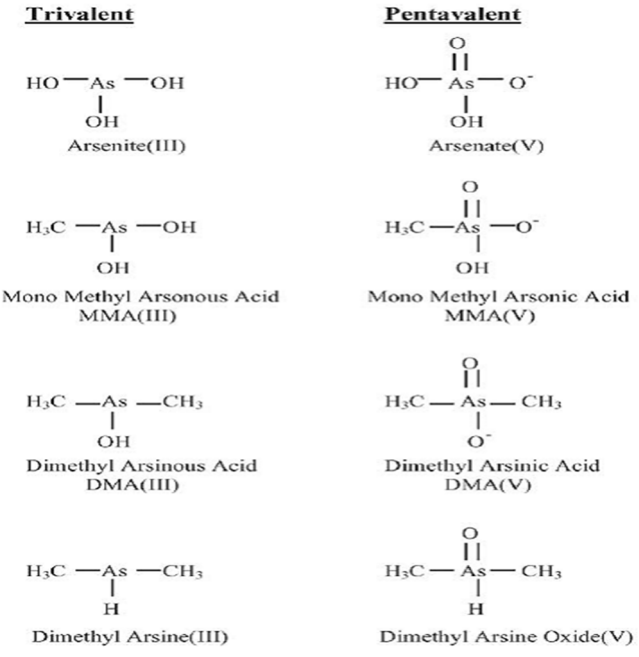
Fig 1: The arsenic cycle in soil – water-plant interfaces

water (Gul et al., 2015). A collection of studies on the extent of arsenic in foods and drinks consisting of juice, rice, milk, broth (red meat and chicken) have shown its presence (Wilson 2015). Volcanic eruption is one of the crucial natural resources of arsenic in the environment. It was reported that several volcanic eruption give raises the arsenic concentration in Europiun union (D'Ippoliti et al., 2015). Moreover, contamination from these resources on only increases the exposure of people to arsenic but also instantly it affects several physiological systems of their individuals.

Inorganic arsenic mainly exists in minerals and ores that contain copper or lead to it. When these ores are heated in smelters, most of the arsenic goes up the stack and enters the air as a fine dust. Eventually smelters may collect this dust and take out the arsenic as a compound called arsenic trioxide (As_2O_3). There are many possible routes of human exposure to arsenic from both natural and anthropogenic sources. Arsenic occurs as a constituent in more than 200 minerals and there ore. It primarily exists as arsenopyrite and as a constituent in several other sulfide minerals. The introduction of arsenic into drinking water can occur as a result of its natural geological presence in local bedrock. Which are generally found in Bangladesh, West Bengal (India), China, and other endemic areas (Garelick et al., 2008).

2.2.Different forms of arsenic species present in the Environment

Arsenic is widespread throughout the environment. The toxicology of Arsenic is a complex phenomenon. Although Uthus et al, considered arsenic as an essential element (Uthus, 1992), Arsenic is one of the top five toxic chemicals that are listed in the US Comprehensive Environment Response, Compensation, and Liability (CERCLA) Act of hazardous substances (Pfeifer et al., 2002, Rosen and liu., 2009). The toxicity of arsenic is associated to the different chemical forms and oxidation states in which it can be found. The oxidation states of Arsenic are - III, 0, + III and + V, among them + III and + V are regarded to be the most abundant in environmental resources. Inorganic oxoanions arsenite (As(III)) and arsenate (As(V)) are highly toxic than its organic species (e.g. monomethylarsonic acid MMA, dimethylarsinic acid DMA) that are



the result of different biological and metabolic activities (Singh et al., 2015). More complex molecules, such as arsenobetaine or arsenocholine, are considered to be nontoxic. Overall, it is proved that the oxidation state of As(III) is more toxic than As(V). At the cellular level, trivalent arsenic interacts with proteins and enzymes, causes oxidative stress and alters DNA by methylation reaction (Kitchin et al., 2008).

2.3.Arsenic as an environmental contaminants and pollutants

Leaching of arsenic compound from soils and rock containing high concentration of arsenic, into hot spring mineral water has been reported in Japan (Kuroda, 1941; Tsuzuki et al., 1966), New Zealand (Sabadell and Axtmann, 1975) and in United States (Brannock et al., 1948). A high level of arsenic has also been documented in drinking water in Chile (Borgono and Greiber, 1972), Silesia and Cordoba, Argentina (Hueper, 1966) and Taiwan (Tseng et al., 1968). The supply drinking water to several places of the United States also held back a considerable quantity of arsenic exposure (Pringle, 1971; Berg and Burbank, 1972; Feinglass, 1973). Some divisions of the United Kingdom are also arsenic contaminated (Thornton and Webb, 1970). According to WHO, the safe limit of arsenic in drinking water is 0.01 mg L^{-1} however, the maximum permissible limit for Bangladesh and India at 0.05 mg L^{-1} (WHO, 2007).

Arsenic level in sea water also has been investigated by many scientists. The concentration of arsenic in sea water ranges from 2-5 μg/l (Johnson, 1972; Johnson and Pilson, 1972). The pentavalent arsenate is the predominant valency state present in seawater (Johnson and Pilson, 1972). The methylated forms of arsenicals have also been reported (Foy et al, 1992) as a reason for chronic arsenic poisoning from well water in the mining area of several South East Asian Countries .Valentine et al., (1992) reported about the arsenic poisoning of a population exposed to contaminated drinking water at Nevada, USA, where

the arsenic level in drinking water was 0.1 mg/l and in California, this level was approximately 0.39 mg/l. Report of Chen et al., (1992) reveals that a huge expansion of the South Western coast of Taiwan was also affected due to arsenic contaminated drinking water. Contamination of arsenic from industrial wastes often creates problems for a large number of human populations and the environment (Mazumder et al., 1992). The affected individuals often manifest chronic arsenicosis. High concentration of arsenic in soil and foliage has also been reported by Mossop (1989) which indicates that humans and animals are living in an arsenic polluted atmosphere. Das et al., (1995) reported that approximately 30 million population of an area of 34,000 km^2 in West Bengal of India are affected as they drink arsenic contaminated water. A seven-year follow up study by Chiou et al., (1995) demonstrates the arsenic toxicity following its' environmental exposure in some places of Taiwan. In Bangladesh, arsenic concentration in ground water is above 0.05 mg/l, the maximum permissible limit laid down by World Health Organization (WHO, 2007), With the help of water arsenic cycled enormously in the environment. Ingestion of this arsenic added water, foodstuff, drugs; wines may affect people in a chronic manner (Aronson, 1994). In industrial area the workers are exposed to airborne arsenic from the industries of smelting and refining metals in their occupational hour, such as handling of arsenic-containing chemicals. Others industrial work life manufacturing of glass, semiconductors and various pharmaceutical products (USPHS, 1989). From earlier time some medicines are used as arsenical compounds which are used to treat some diseases like syphilis, asthma, rheumatism, cough, pruritus and itching, thereby people also affected via medicines also (Wong et al., 1998, Ko, 1999). Sea-foods contains very high amount of organo-arsenicals, which are considerably less toxic than inorganic arsenic (ATSDR, 1998). Drinking water is the most abundant route of exposure to arsenic. In south-East India, 206 tube wells (95% of total) in a

village were tested and result showed that 56.8% tube wells have arsenic concentration of 50 µg/l or above and 19.9% have more than 300 µg/l arsenic in it (Chakraborti et al., 2003; Acharyya et al., 1999). In Bangladesh, more than 80 million people are at a risk of arsenic containing drinking water. The arsenic levels in drinking water in this region were ranged from non-detectable to 4700 µg/l (British Geological Survey, 2001). Smith et al., (2000) reported, the arsenic level in drinking water was very high and it was 750 to 800 µg/l, in Chile, which caused several skin and lung disease. In Taiwan, the arsenic concentration in well water was also very high and it is 10- 1800 µg/l causing a peripheral vascular disease called Black foot disease, which occurs due to arsenicism (Tseng et al., 1995; WHO, 2003; Lamm et al., 2006). In Romania and Hungary, arsenic detected at a concentration of 2-176 µg/l (WHO, 2003). In Argentina, the groundwater arsenic concentration was ranged from 100 to 2000 and about 200,000 people use found to be affected by the contaminated water (British Geological Survey, 2001). In China, the concentration of arsenic in well water in contaminated areas was 50 - 2000 µg/l.

2.4.Arsenic accumulation in foods chain.

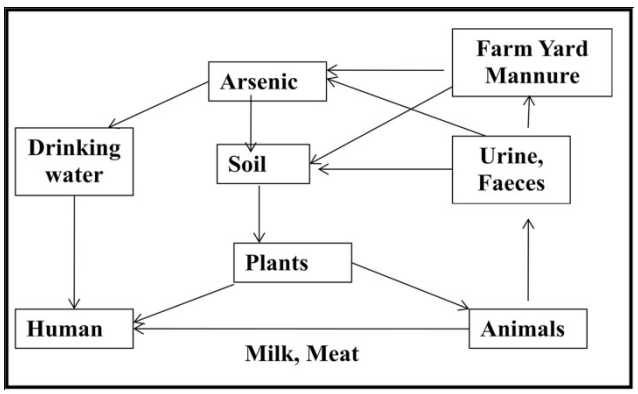


Fig. 2 Diagram of arsenic contamination in both human being and livestock (Mandal, 2017)

Arsenic can accumulate in some plants and plant materials. Schroeder and Balassa (1966), and Westoo and Rydalv (1972) have reported arsenic concentrations in several vegetables, grains, fruits, seafood, and meats. Warren et al., (1964, 1968) have reported that arsenic is poorly absorbed from soil by some plants but it can be extensively contaminated in the bark needles of Douglas fir grown in areas with high soil concentration of arsenic. Fruits and vegetables sprayed with arsenical compounds may also contaminate this element (Williams, 1972). Smith (1970) has reported that arsenic containing dust might be released from trees and woods treated with arsenical preservatives during the sawing process. Woolson (1972) reported that the effects of fertilizers on the uptake of arsenic related materials arsenic rich soil. Evidence suggests a strong influence of available soil phosphorus on arsenic accumulation in the soil. Physiochemical properties between arsenic and phosphorous results in their close association in their reactivity pattern. And this close relationship is noticed in not only geological perspective but also in different metabolic processes in the biological processes. Competing environments and ability to replacing each other are the important determination in arsenic toxicity in living system. Arsenic rich soil residue can cause considerable impact in relation to its uptake by the plants grown in this soil. Especially in rice, if arsenic concentration in very high then the subsequent entry of this arsenic into the environment through its consumption by animals and human will make high accumulation and bio magnification of this toxic metal in the living body. Among the harvests especially rice is more efficiently accumulate arsenite (As ^{III}). The paddy fields in the South and Southeast Asia have AsIII concentrations ≤ 20 μM (Zhao et al., 2010) in soil. Approximately, more than 3 billion people around the world consume rice as their primary meal. Recent study regarding rice has also been demonstrated that this is the major route of arsenic exposure to human (Banerjee et al., 2013) It is evident by the observation of a strong

association between rice consumption and urinary arsenic concentration in human (Cascio et al., 2011; Gilbert-Diamond et al., 2011). Not only human, but also cattle which consume agricultural end products like rice- wheat straw also accumulate high level of arsenic in their tissues and body fluids. Arsenic has been used in inorganic pesticides (e.g., calcium arsenate, lead arsenate, and copper arsenate) for many deeds. Applied to orchard crops such as apples and peaches, as well as to some other crops such as potatoes are very common to accumulate arsenic. Because arsenic leaching occurs very slowly in soils (Hood, 2006; Veneman et al., 1983), so the contamination in orchard soils by arsenate began in the late 1800s and still now it persists today (Schooley et al., 2008).

2.5.Arsenic toxicity on animal health

Arsenic is one of the major components and heavy metal that results poisoning in extensive plantation domestic animals, birds, humans and even in wild animals. Lawton et al. (1945) observed that arsenite accumulated mainly in the liver and kidney when it is administered to laboratory rodents. DuPont et al., (1941) studied in rabbits, the distribution of radioactive arsenic as sodium arsenate. They observed a rapid urinary excretion of arsenic and its accumulation in the liver, kidney and lung after application. Muscle, bone and skin had moderately low arsenic concentrations, but because of the large percentage of total body mass, they comprised the main storage sites and the accumulated amount become very high. Ducoff et al., (1948) examined the distribution and excretion pattern of arsenic in mice, dogs, rabbits and human after natural and laboratory exposure of these toxic metals. It was one of the most in depth and extensive studies regarding arsenic accumulation in living bodies. Rats were observed to cause a much slower arsenic excretion rate than humans or rabbits after 48 hours. Observations also reveal that rats had much higher concentration of in their arsenic blood concentration than that of the other species for up to 96 hours after injection.

Clinically, arsenic intoxication occurs as acute or per-acute intoxication initially. The chronic forms of the disease have been noticed, especially in cattle which are exposed to little concentration of arsenic but for a long time. Report reveals that severe poisoning might be occurring from the use of the trivalent inorganic or organic forms of arsenic. Katsura (1953) examined the tissue distribution of arsenic in dogs given oral doses of arsenious acid for 4 months. He noticed an initial rapid increase in kidney and liver levels of arsenic for the first 1-2 months, followed by a decline for the next 2 months. This alteration was due to a decreased rate of absorption of arsenic from their gastrointestinal tract. This might suggest that GI–tract and associated organs are very much sensitive to accumulate arsenic. And when this metalloid is consumed chronically, the rate of accumulation increases rapidly with respect to an acute exposure. Schreiber and Brouwer (1964) observed and reported that most pentavalent arsenics given by intravenous injection were rapidly and primarily excreted in the urine of rats which are in fasting condition. But the trivalent arsenicals were excreted at a slower rate and mainly via bile excretion. Byron et al., (1967) establish that both rats and dogs survived a 2-year feeding study with sodium acetate and sodium arsenite in the diet at concentrations up to 400 ppm. Expansion and inflammatory responses were noticed in the common bile duct in rats but not in dogs given both arsenate and arsenite. Fermer and Carpenter (1968) reported a higher incidence of exencephaly in golden hamster embryos of mothers given at 20 milligram/kg body weight of sodium arsenate (V) on 8th day of gestation. This is one of the important studies that suggest arsenic accumulation during maternal inheritance. Moderately long period during the gestation period is sufficient for the passage of arsenicals from mother body to her children. Hood and Bishop (1972) observed the manifestation of exencephaly and many other malformations in offspring of mice given intraperitoneal injections of arsenate (25 mg/kg) during gestation. Beaudoin (1974) reported

that arsenate at a dose of 30 mg/kg body weight caused teratogenesis in rats. The mutagenic and teratogenic effect of arsenic was known in several natural observations. On the other hand, the toxicity of organo-arsenicals was also studied earlier. Its toxicity varies greatly with the valence state of the incorporated arsenicals and chemical properties of the materials which influence its absorption, distribution and elimination. Amongst those, the pharmacokinetics of the feed additive was extensively examined (Overby and Fredrickson, 1965, Underwood, 1971). During this observation the rapid excretory nature of this arsenical compound was described. Keenan and OE (1973) demonstrated the toxicity of arsenicals in pig following high-level exposure. Ledet (1973) observed the effect of arsanilic acid as a reproducible neurological degeneration in pigs fed a diet. The renal and hepatic damages were also reported after the use of organo-arsenical herbicides (Dickinson, 1972). This paragraph explored some references. All these observation are very much important because these deal with a moderately high level of exposure for a long time in diverse group of animals. At that time different regulatory and ethical issues were not so specific. In present days, this type of experiment is hardly possible to make such elaboration in toxicity studies. With full support to the present days regulatory and ethical issues on animals experiments, we may conclude that these old experiments were the ideal stepping stone for present days advanced investigation. The modern investigation wouldn't have been possible without the finding of the previous day's experiments.

Arsenic exposure and human poisoning

Arsenic, a human carcinogen, potentially affects a large number of people worldwide via exposure through contaminated drinking water, industrial operations and the multiplication of power from coal. Watrous and McCaughey (1945) reported about the workers involved in the manufacture of arsphenamine. In this event, increased urinary excretion of arsenic was

observed in plant workers, having no toxic effects of arsenic on the haematopoietic system. Perry et al., (1948) studied workers of sodium arsenite manufacturing plant. They also observed elevated hair and urinary arsenic concentrations within industrial workers. An increased incidence of pigmented dermatoses and warts was also noted. Rathus (1963) reported urinary arsenic concentrations of 0.01 to 1 ppm in Australian banana growers and this is correlated with ambient air arsenic concentrations of 0 1-0.5 ppm during the spraying process. Report reveals that among forestry workers excretion of urinary arsenic increased as an effect of the rate of use organo-arsenical silvicides (Tarrant and Allard, 1972; Wagner and Weswig, 1974). Lisella et al., (1972) estimated the average daily human intake to be about 900 μg of arsenic in severely affected areas. Around 1900, arsenic contaminated beer resulted in 6,000 poisonings and out of which approximately 71 death cases were recorded (Kelynack, 1900; Satterlee, 1960). Most of the patients were afflicted with peripheral neuritis characterized by pain, muscular weakness, and paresthesias of the extremities, ataxia, anorexia, brown pigmentation, herpetic lesions, localized edema, and fatty degeneration of the heart. This finding was the most important, because for the first time this study extensively evaluated the adverse physiological effect in human. Conley (1958) reported about 410 deaths (from 1946 to 1955) in the United States due to the contamination from the arsenic pesticides. Hayes and Pirkle (1966) reported 54 arsenical-pesticide deaths in 1956 and 29 in 1961. In Malaysia, arsenical compounds were commonly used for suicides between 1963 and 1966 with a total of 308 cases or an average of about 62 per year (Amarsingham and Lee, 1969). Reports of Deeths and Breeden (1971) also reveal that 1,057 cases of poisoning occurred in children between 1962 and 1968. Powdered milk contaminated with As_2O_3 at concentrations of 25-28 ppm and an outbreak of arsenic toxicosis occurred in Japan in 1955-1956. A total of 12,083 cases were reported with 128 deaths in this toxicity incidence

in japan. Liver enlargement, anemia and reduction of white blood cell numbers were observed in the infants with the highest arsenic levels of the blood (Tokanehara et al., 1956). Nagai et al., (1956) observed melanosis, hyperpigmentation, white strain of the fingernails (Mee's lines) and abnormal electrocardiograms in some infants. The observations of Eiji (1955) suggest that livers contained the highest visceral arsenic concentrations in those infants who died due to arsenic intoxication and this was associated with fatty degeneration and necrosis of the liver parenchyma. Clinical follow up studies of Yamashita et al. (1972) indicated residual functional impairment in children who survived after this incident. An outbreak of arsenic toxicosis occurred in 1959 in Japan as the result of well-water contamination by a plant manufacturing arsenic trisulphide (As_2S_3). That well water contained from 1 to 3 ppm arsenic. Deep soil irrigation or the natural springs. Desquamation of skin, melanises and keratosis followed by anaemia, liver swelling, electrocardiographic anomalies, proteinuria and altered reflex actions were observed in the majority of these cases (Terada et al., 1960). The factors that influence arsine toxicity to humans include its concentration (Dernehl et al., 1944; Morse and Setterlind, 1950; Spolyar and Harger, 1950), proximity to the source of evolution, duration of exposure and inter individual variability in susceptibility (Morse and Setterlind, 1950; Derot et al., 1963). Arsine intoxication results in nausea, headache, and signs of shock, anaemia, decreased haemoglobin levels, haemoglobinuria and coppery skin pigmentation within an hour after exposure (Kipling and Fothergill, 1964). This gaseous form of arsenic is highly toxic. Because it is distributed to all the body parts via an exposure to lungs and easily mixing in blood. Oliguria and anuria commonly develop after 24 hours depending on the level of arsine exposure. In most of the cases renal failure is the suggested cause of death (Jenkins et al., 1965). Differential effects of arsine gas on other body organ systems have also been reported. Damages and tissue

degeneration are the fate of arsine gas exposure. High concentrations of arsenic have been noted in the livers, lungs, and kidneys of persons seriously poisoned by arsine. The kidneys and lungs have been observed to be more sensitive to arsine toxicity than liver (Hocken and Bradshaw, 1970). Liver is the main organ and assumed as the metabolic part of entry. The damage of liver makes this organ system in capable to several normal physiological processes. The inter-relationship of this organ to other important organ are severely impaired. After a chronic exposure to arsenic as a result the severely malfunction of the liver result towards a multi organ failure. This may cause the death of the individuals.

2.6.Effects of arsenic on various organs

Arsenicals have diverse effects on many organ systems. The differences in tissue specific accumulation of arsenical compounds and their complex interaction patterns with several metabolic pathways determine the nature of arsenic toxicity. Differentially capable cellular protective mechanisms are the main basis for of arsenic. Chronic arsenic exposure and poisoning cause elevated hepatic- density and also increase hepatic and splenic attenuation (Dick et al., 1990). Reports of Labadie et al., (1990) reveal that arsenic poisoning causes hepatic damage i.e. veno-occlusive disease and perisinusoidal fibrosis in humans. Degeneration of hepatocyte structure disintegration on central canal and the associated lobuler structure are the main cause of liver damages. This study also suggests that these types of hepatic damages are secondary to vascular endothelial injury and support the hypothesis that different patterns of vascular injury might proceed from a common mechanistic pathway. Inorganic arsenicals and a number of organic-arsenical compounds are particularly toxic to the liver and produce fatty infiltration with central necrosis and chirrosis. Reports are there (Chen et al., 1992) which reveal that chronic exposure to arsenic causes cancer of various organs showing a higher mortality rate in lung cancer. A significant number

of mortality also occurs in liver, bladder and kidney cancer cases. Arsenic poisoning often causes renal insufficiency, which is caused by tubule interstitial nephritis. These conditions are known to be associated with an elevated urinary arsenic excretion (Prasad and Rossi, 1995). Hirata et al., (1990) also showed the nephrotoxic potential of arsenic. The researchers pointed out a relationship between glutathione-dependent arsenic metabolism and manifestation of nephrotoxicity. This group of investigation suggested that the biotransformation via arsenic methylation is also impaired during arsenic-induced nephrotoxicity which ultimately causes the necrosis of the kidney tissue. The action of arsenic on the renal capillaries, tubules and glomeruli may cause severe renal damage at different layers of boumen's capsule and glomerular filtration bed. Initially the glomeruli are affected and proteinuria results in oliguria with proteinuria, and hematuria and casts frequently result from exposure to arsenic (Curtis and Klaassen, 1995). A study by Ademuyiwa et al.,(1996) was implemented to note whether the accumulation of Cu in the kidney of rats and guinea pigs observed following exposure to arsenite (As-III) was an effect of arsenite alone. Because it is reported that Cu and Fe accumulation is influenced by arsenic. Other metabolites of arsenic like arsenate (As-V), dimethylarsinic acid and monomethylarsonic acid are also capable to influence rectal deposition. From this study, these in restigaters concluded that neither the metabolic transformation of inorganic arsenic to its methylated products, nor its metabolites caused the observed Cu accumulation in renal tissues. In rectify it was the inorganic form of arsenic, either in the trivalent or pentavalent form was responsible for the deposition of different transition metals. Organic arsenical causes rapid onset of pain and severe vesication on contact with epithelial tissues. In vitro experiment demonstrated that the lewisite is toxic for the isolated perfused skin (King et al., 1992). Long term ingestion of low doses of inorganic arsenicals causes cutaneous

vasodilatation and a specific type complexion (Curtis and Klaassen, 1995). Prolonged exposure to arsenic, however, also causes arsenical skin lesions that are the late stages of manifestation of arsenic toxicity. Because after prolonged exposure arsenic first accumulation in different internal organ. And then it's downstream metabolic other organic forms are accumulated and deposited in skin tissue. Most of the three stages of arsenic-related clinical manifestations are observed amongst the arsenic-affected people. The common symptoms are conjunctivitis, melanosis, depigmentation, keratosis and hyperkeratosis the trunk and in different surface of arsenic toxicity areas and other extremities of the body. Eventually, these actions lead to atrophy and degenerative changes which ultimately cause gangrene and malignant neoplasm (Das et al., 1995; Valentine et al., 1992). Both short and long term exposure to arsenic can cause encephalopathy; however, the most common arsenic-induced neurological lesion is a peripheral neuropathy with a 'stacking glove' distribution of dysesthesia. The syndrome is similar to acute inflammatory demyelinating poly - radiculoneuropathy called Guillain Barre Syndrome (Dohofrio et al., 1987). Brouwer et al., (1992) also observed mental deterioration and several other anomalies in an arsenic-intoxicated patient who manifested severe paraparesis with areflexia and bilateral Babinski signs. All these work suggest that arsenic has also a strong influence on the neuronal cells and brain tissue. So, it may be hypothesized that arsenicals or its downstream metabolites may cross the blood brain barrier and deposited in brain tissue sufficiently to cause the biochemical changes. Bansal et al., (1991) reported about the symptoms of an arsenic-intoxicated patient who showed acute arsenic neuropathy with asymmetric bilateral phrenic nerve involvement. The dysfunction of phrenic nerve was confirmed by prolonged phrenic nerve conduction time. Studies by Curtis and Klaassen (1995) demonstrated that small doses of inorganic arsenicals, specially the trivalent compounds cause mild splanchnic hyperemia.

They further demonstrated that capillary transduction of plasma, resulting from larger doses many produces vesicles in the gastrointestinal mucosa. These, in turn rupture epithelial fragments and as a result plasma is discharged into the lumen of intestine, where it coagulates. Normal proliferation of the epithelium is suppressed in this situation which accentuates the damage of the local tissue. Occasionally the faces become bloody. Damage of upper gastrointestinal tract and stomatitis may also be present (Curtis and Klaassen, 1995). Acute arsenic toxicity causes immediate gastrointestinal symptoms like abdominal pain, nausea, vomiting and diarrhoea (Jollife et al., 1991). Small dose of inorganic arsenic induces mild vasodilatation of the GI tract and epithelial lining. This may lead to occult edema, when arsenic accumulation in subcutaneous areas particularly in facial region and this has been mistaken for a healthy weight gain (Tam et al., 1979). Larger doses evoke capillary dilatation, increased capillary beds, pronounced, particularly in the splanchnic area. Transduction of plasma may occur, and the decrease in the intravascular volume may be significant. Long term exposure of arsenic results in gangrene of the extremities, especially of the feet, and is often referred as a black foot disease. Myocardial damage and hypertension may also become evident after more prolonged exposure (Tam et al., 1979). Experiment (in-vitro) revealed that the inorganic arsenic specially arsenite and arsenate can inhibit lymphocyte proliferation and it was also found that chronic arsenic exposure can inhibit the proliferation of whole blood lymphocytes the inhibition of this stimulation of proliferation is directly related to the length of the toxic exposure (Gonsebatt et al., 1992). To find out the basis of the inhibitory effect of arsenic-induced lymphocyte proliferation, another experiment (Meng, 1993) showed that both trivalent and pentavalent arsenic at low doses cause stimulation of DNA synthesis. But at the high concentration both arsenicals inhibit DNA synthesis in lymphocyte. Does dependent biphasic effect is prominent in case of arsenic exposure. It was further found that

the trivalent arsenic is potent to manifest this dual role, i.e., as a co-mutagen at a very low concentration and inhibitor of mutagenesis at a high concentration (Meng, 1993). The work of Lindgren et al., (1984) revealed the distribution of arsenate and arsenite in pregnant mice and monkey. It was observed that 74As-arsenic appeared to pass the mouse placenta relatively free and approximately to the same extent. In early gestation, high activity was registered in the embryonic neuro-epithelium, which is correlated with central nervous system malformation in rodents. Arsenic exposure may enhance oxidative damage causing adverse health effects in pregnant woman (Tabacova et al., 1994). Ma et al., (1994) described effects of arsenic exposure on offspring development in pregnant mice. Their results showed that arsenic contents of the body and brain tissue increased and the structure of neural cells in cerebral cortex became abnormal after arsenic exposure. The neurobehavioural development of the offspring appeared also retarded. Arsenic toxicity in reproductive tissue and its transduction to placenta / offspring are evident. Neuro-degenaration by arsenic is the one of major anomalies in natural control on peripheral organs.

2.7.Pharmacokinetics of arsenicals

Arsenic, in biological systems, may exist in multiple oxidation states and can undergo electron transfer reactions. These arsenical compounds might be able to react with species of oxygen like molecular di-oxygen, superoxide, and--hydrogen peroxide. Further, these reactions may be modulated by endogenous reducing agents such as glutathione, ascorbate vit- E or micro nutrients. The metabolism of arsenic in humans involves a series of reactions that alternates reduction of pentavalent arsenic species to the trivalent state with oxidative methylation steps (Vahter and Concha 2001). Arsenate [As (V)] can react with glutathione to produce arsenite [As(III)] and oxidized glutathione. This particular reaction may be important in the methylation reactions of arsenic (Carter, 1995). In humans this process results in

distinct arsenic species, including As (III), As (V), monomethylarsonous acid [MMA(III)], monomethylarsonic acid [MMA (V)] and dimethlyarsinic acid [DMA(V)] all these compounds possess each with unique toxicological (Aposhian et al., 2004). The trivalent arsenic forms, which have a higher affinity for thiol groups (Vahter and Concha, 2001) are more cytotoxic and genotoxic than pentavalent forms. The binding of arsenic with GSH promotes the methylation of arsenic molecule. The two steps of methylation process have been observed i.e. monomethylation and dimethylation to produce monomethylarsonic acid and dimethylarsinic acid, respectively (Carter, 1995; Thompson 1993). Various organic derivatives are produced mainly by the methylation of arsenic, the importance of which varies among the species. Both the valence state and organic character influence the transfer of arsenicals through biological membranes and their further effects (Crecelius, 1977). At physiological pH, organic arsenicals also carry electric charges inducing differences in their absorption and elimination pattern. Biotransformation of arsenical compounds in human is the major way of elimination of arsenic via the urine (Buchet et al., 1981a,b, Crecelius, 1977; Lovell and Farmer, 1985; Mohrit et al., 1990; Vahter and Envall, 1983). In general, it may be stated that organic arsenicals are rapidly excreted than inorganic forms and pentavalent arsenicals are cleared faster than its trivalent form (Muehrcke and Piran, 1968).

2.8.Absorption, Distribution and excretion of arsenic

Inorganic arsenic is metabolized by most mammals, including humans. Metabolism of arsenic takes place via this reduction and methylation reactions with *S*-adenosylmethionine (SAM) as the group methyl donor (Marafante and Vahter, 1984; Vahter, 2002). Dimethylarsinic acid (DMA) is the main arsenic metabolite excreted in human urine, besides monomethylarsonic acid (MMA) and some remaining iAs, but there are major differences among individuals as well as between population groups (Vahter, 2002). Usually, the

proportions are 10–30% inorganic arsenic, 10–20% MMA, and 60–80% DMA (Vahter, 2002). This difference is attributed by the differential metabolic pattern and other physiological factors. The metabolism of arsenic implies both detoxification and activation. The reduced trivalent forms, in particular MMA (III), are more toxic than the pentavalent forms (Schwerdtle et al., 2003; Styblo et al., 2002; Wang et al., 2007). A high concentration of MMA in the urine indicates a low capacity of further methylation to DMA and, probably, elevated concentrations of the highly toxic MMA (III) in the cells. There is increasing evidence of positive associations between urinary MMA and the prevalence of As-related bladder cancer (Chen et al., 2003b; Pu et al., 2007; Steinmaus et al., 2006), skin cancer (Chen et al., 2003a; Hsueh et al., 1997; Yu et al., 2000), other skin effects (Ahsan et al., 2007; Del Razo et al., 1997) there are also other effect like structural chromosomal aberrations (Maki Paakkanen et al., 1998), cardiovascular effects (Tseng et al., 2005), and increased retention of ingested As (Vahter, 2002). Thus, it is essential to identify the mechanisms behind the wide inter individual variation in arsenic metabolism. Arsenic can be excreted through human urine in the form of arsenate, arsenite, monomethyl arsonic acid (MMAA) and dimethylarsinic acid (DMA) (Braman and Foreback et al., 1973; Crecelius et al., 1975). Most of the ingested dose of arsenite (As^{3+}) was excreted in the urine of a human subject as methylarsonic acid dimethylarsinic acid. Only 10% of the toxicant was excreted in the form of arsenite (Crecelius et al., 1975). In human and most of the animals studied, the major route of arsenic excretion is through the kidney with only marginal elimination through faeces (Vahter et al., 1981). Arsenobetaine (AsB), which together with tetramethyl arsonium (TMAs) represents the most important form of arsenic in food and these does not undergo biotransformation in human and is almost completely eliminated via the urine (Crecelius, 1977; Lovell and Farmer, 1985; Vahter and Envall, 1983). The form such as arsenobetaine

(AsB) is considered nontoxic (Yamauchi et al., 1986; Buchet and Lauwerys, 1985; Murer et al., 1992; Ochi et al., 1994). Schreiber and Brouwer (1964) have reported that most pentavalent arsenical given by intravenous injection were rapidly and primarily excreted in the urine of the fasted rats, while trivalent arsenicals were excreted at slower rates and mainly in the bile. They also observed that liver arsenic levels were higher in arsenite treated animals, while renal levels were higher in arsenate-treated animals.

2.9.Arsenic toxicology: Cellular and metabolic

The lack of an established animal model for arsenic-induced cancers has made studies that assess the possible mechanisms of cellular damage attributable to arsenic exposure important. Mutation assays using bacterial or mammalian cells have shown that As(III) is not a potent point mutagen (Rossman et al., 1980). More recently, it has been shown that low dose chronic exposure to As (III) in human osteosarcoma cells does cause the mutations at the HPRT gene locus (Mure et al., 2003). Hei et al., (1998) demonstrated that arsenic induces large deletion mutations in a human-hamster hybrid cell. This is consistent with work in mouse lymphoma cells, where large deletions were induced at the thymidine kinase (TK) locus (Moore et al., 1997). Genotoxic damage, including chromosomal abnormalities, sister chromatid exchange, micronuclei and unscheduled DNA synthesis, as well as DNA-protein crosslinks have been shown to occur in human cells exposed to arsenic (Dong and Luo, 1993; Gonsebatt et al., 1997; Ramirez et al., 2000). Arsenic has also been found to induce the neoplastic transformation of Syrian hamster embryo cells (Takahashi et al., 2002). Alterations of DNA repair enzymes have also been hypothesized to be a mode of action of arsenic in vivo and in vitro (Kitchin, 2001; Vogt and Rossman, 2001).

2.10. Therapeutic against arsenic toxicology

Some edible shell fishes are well-known to provide the economically and medicinally important nutraceuticals which are used in rheumatism, cardiac diseases, liver diseases, hypertension, asthma, rickets, hypocalcemia, nervousness and several other ailments. These are consumed by the indigenous people of the rural and urban areas of the different parts of the world (Mahata, 2002, Kim, 2012). After a long time of practices from the ancient times rural peoples have standardized the procedure and some formulation to develop some ethno pharmacological agents. There people are very much aware and experienced with the beneficial effects of these compounds. But they are unaware regarding the mechanism of activities of these compounds. From the ancient times and habit of the mythological practices the recipe of these substances have been used. Different species of these edible snails are biologically diverse in nature and belong to *Paratelphusa, Macrobrachium, Bellamya, Pila, Achatina, Lamellidens, Novaculina* and *Parreysia* (Arul-Prakash et al., 2011; Ma, 2015; Mahata, 2002; Kim, 2012). The foot flesh and the secretion extract of *Bellamya bengalensis* constitute potent anti-neoplastic/ anti-proliferative agent which is apoptogenic against human myeloid leukemia cells (Besra et al., 2013). Some other reports also explain the potential beneficial effects of these substances are attributed via the protection of cellular membranes and macromolecular compounds. The protection in the mitochondrial function and other organellar activities are also supportive to the protective effects of this compound. Several anti-degeneratives and anti-pathogenic activities are the added advantages of these compounds. Moreover, high nutritive values of these substances improve a healthy cellular and micronutrients also helps in the protection and regeneration, remodelling of the degenerated tissue substances. In brief, the anti-oxidative and anti-inflammatory pathways have been indicated as the major therapeutic potentials of above mentioned organism in some

of these cases. Though, the hepatoprotective activity of *Bellamya bengalensis* flesh extract has been shown in carbon tetrachloride-induced liver damages in rat, the underlying mechanism is still unclear (Gomes et al., 2011).

The habit of this mollusk is also, compelling that is these organisms mostly live in the muddy layer of water body, just upper surface of the soil. This soil is an important depository of several environmental, industrial- wastes, sewages, effluents, which are enriched with heavy metals, pesticides, herbicides, organic effluents, polyaromatic hydrocarbon etc. So, for a sustained exposure to with all these pollutants, these organisms become more stress or toxicity resistant.