REVIEW

Inhibition of Oxidative Stress and Enhancement of Cellular Activity by Mushroom Lectins in Arsenic Induced Carcinogenesis

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Abstract

Chronic arsenicosis is a major environmental health hazard throughout the world, including India. Animals and human beings are affected due to drinking of arsenic contaminated ground water, due to natural mineral deposits, arsenical pesticides or improperly disposed arsenical chemicals. Arsenic causes cancer with production of free radicals and reactive oxygen species (ROS) that are neutralized by an elaborate antioxidant defense system consisting of enzymes and numerous non-enzymatic antioxidants. Dietary antioxidant supplements are useful to counteract the carcinogenesis effects of arsenic. Oyster mushroom lectins can be regarded as ingredients of popular foods with biopharmaceutical properties. A variety of compounds have been isolated from mushrooms, which include polysaccharides and polysaccharopeptides with immune-enhancing effects. Lectins are beneficial in reducing arsenic toxicity due to anticarcinogenetic roles and may have therapeutic application in people suffering from chronic exposure to arsenic from natural sources, a global problem that is especially relevant to millions of people on the Indian subcontinent.

Keywords: Arsenic - carcinogenesis - cytotoxicity - oxidative stress - mushroom lectin - amelioration

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Introduction

Arsenic (As is a native metallic element found in low concentration in virtually every component of the environment. Endemic areas of overt arsenic poisoning are present in several countries in Asia and other parts of the World through consumption of contaminated water, exposure to contaminated air, soil or industrial contact (NRC, 1999; IARC, 2004; Pal et al., 2007; Bera et al., 2011). Arsenic contamination of drinking water is a big problem with increased severity in India and Bangladesh (Nevens et al., 1990; Guha Mazumder, 2008). Arsenic (As). is found in many types of food. The highest levels are detected in seafood, meats, and grains. A typical U.S. dietary level of arsenic in these foods varies widely from 0.02 ppm in grains and cereals to 0.14 ppm in meat, fish, and poultry, but there is a wide range of values. High concentrations of As also occur in rice, mushrooms, poultry crops such as carrots, onions and potatoes (modified stem). In the early twentieth century fatal cases of As poisoning from food and beverages like wine, beer and cider have been reported from France, England, Japan and US. Arsenic concentration as high as 5600-71600 µg/L in soya sauce was reported from Japan (Guha, 2008). Compared to other countries, rice samples from India and Bangladesh have the higher percentage of inorganic As (80%), against 42 % in rice samples from the USA. This indicates that the percentage of inorganic As in rice is not a constant factor geographically and it probably depends on cultivar and growth conditions. A positive correlation was found between As levels in rice and groundwater (Roychowdhury et al., 2002). Bae et al. (2002) found that cooked rice had approximately twice the levels of As in raw rice probably due to parboiling and/or boiling rice in As contaminated water. On the other hand, Duxbury et al. (2003) showed that after processing (parboiling and milling) of rice grown in low and high As-contaminated areas, the As concentrations were reduced by ~20 percent. The level of arsenic in ground water used for drinking in West Bengal and Bangladesh is well above WHO recommended permissible limit of 10μg/L (WHO, 1993; Rahman et al., 2008).

The toxicity is manifested with skin lesions like spotted melanosis, hyperkeratosis, leucomelanosis, raindrop de-pigmentation, gangrenous extremities, hepatomegaly, spleenomegaly, cognitive impairments, cancers of different organs in human (Rahman et al., 2001; Guha Mazumder, 2008), abdominal pain, staggering gait, extreme weakness, trembling, salivation, vomiting (in dogs, cats, pigs, and perhaps even cattle),

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diarrhea, fast, feeble pulse, prostration, rumen atony, normal to subnormal temperature, collapse, and death (cattle). Animals may live for several days, exhibiting depression, anorexia, and watery diarrhoea, increased urination at first followed by anuria, dehydration, thirst, and partial paralysis of the rear limbs, trembling, stupor, cold extremities, subnormal temperature, and death. The watery diarrhea may contain shreds of intestinal mucosa and blood (Selby and Dorn, 1989; Rana et al., 2008).

Among several mechanisms, oxidative stress due to accelerated production of free radicals has also been implicated for arsenic-caused tissue injury in liver, kidney, brain and other tissues (NagChowdhury et al., 1999; Das et al., 2010). The literatures suggest that arsenic toxicity involves oxidative damage (Izquierdo-Vega et al., 2006; Hansen et al., 2006). Liver and kidneys are the target organs for toxic effects of arsenic as evidenced by clinical manifestations and biochemical alterations (Santra et al., 2000; Nandi et al., 2006). This bioactivation of arsenic generates reactive oxygen species (ROS). such as hydrogen peroxide, superoxide, hydroxyl and peroxyl ions (Garcia-Chavez et al., 2006). These radicals ultimately cause damage of the major cellular components like amino acids, carbohydrates, lipid proteins and nucleic acids (Nandi et al., 2006; Kadirvel et al., 2007; Modi et al., 2007).

Several studies have demonstrated that liver is the primary arsenic metabolizing organ (Hughes et al., 2003) where metabolic conversion of arsenic into methylated products (mono, di and trimethylated arsenic) occurs. The possible mechanisms of arsenic toxicosis include induction of micronuclei, alterations in gene expression, induction of oxidative stress, alteration in enzyme activities, change in carbohydrate metabolism, inhibition of DNA repair, perturbation of DNA methylation, alteration of signal transduction pathways, altered cell cycle control, aberrant differentiation, and altered apoptosis (Kitchin, 2001; Manna et al., 2007; Bagnyukova et al., 2007). Arsenic generates reactive oxygen species (ROS) during redox cycling and metabolic activation processes (Liu et al., 2001; Garcia-Shavez et al., 2006; Bashir et al., 2006). Sodium arsenite ($NaAsO_2$) reduces the activities of antioxidant enzymes, superoxide desmutase, catalase, glutathione S-transferase, glutathione reductase and glutathione peroxidase as well as depletes the level of reduced glutathione and total thiols. In addition, arsenic trioxide also increased the activities of serum marker enzyme, alanine transaminase and alkaline phosphatase, enhanced DNA fragmentation, protein carbonyl content, lipid peroxidation end-products and the level of oxidized glutathione (Kadirvel et al., 2007). It causes a series of biochemical events that lead to a variety of morphological changes, including blebbing, changes in the cell membrane such as loss of membrane asymmetry and attachment, cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation (El-Demerdash et al., 2009).

The ability of superoxide desmutase (SOD) to protect tissues against any particular insult (ischemia, inflammation, hypoxia, etc.) depends on several parameters such as its rate of plasma clearance, ability to equilibrate between extracellular fluid compartments, and the ability to closely approach negatively charged cell surfaces. The mitochondrial enzyme manganese superoxide desmutase ($MnSO_2$) involved in ROS detoxification catalyses the desmutation of superoxide radical (O_2-) into hydrogen peroxide (H_2O_2) and oxygen (O_2). (Drane et al., 2001). Superoxide desmutase 2 (SOD_2) gene, is one of the major cellular defenses against oxidative stress. Manganese superoxide desmutase 2 (SOD_2) is a critical mitochondrial antioxidant defense against superoxide produced by respiration (Oberley and Oberley, 1997; Qian et al., 2003).

Oxidative stress due to enhanced production of free radicals has been incriminated as one of the several mechanisms involved in arsenic-induced toxic effect in different organs. Gene expression following arsenic exposure can be used to identify specific biomarkers of arsenic exposure and to indicate potential mechanism of arsenic toxicityarsenic chronic methylated arsenical exposure increased the expression of the genes encoding mannose 6-phosphate receptor (MRP_1), MRP_2, MRP_3, SOD_2 and multidrug resistance (MDR). The depletion of cellular GSH and the inhibition of Mrps and p-gp functions increased cellular arsenic uptake and reduced arsenic tolerance in cultured cells (Kojima et al., 2006). Arsenic has shown to induce expression of IL-1, IL-6 and IL-7 receptors as well as iNOS in rat liver epithelial cells (Chen et al., 2004) and down regulates the expression of IL2 receptors (Yu, 1994).

In order to prevent/treat arsenic toxicosis several metal chelating agents have been tried and reported in the past which include British Anti-Lewisite, 2,3-dimercaptosuccinic acid (DMSA), 2,3-dimetcapto propane sulfate (DMPS). (WHO, 2001; Aposhian and Aposhian, 2006). Endogenous antioxidants, including vitamins, trace minerals, antioxidant enzymes, tripeptides and reductants, may quench reactive oxygen species (ROS) or suppress lipid peroxidation. Antioxidants have long been known to reduce the free radical-mediated oxidative stress. The supplementation of vitamins was significantly effective in restoring inhibition of blood delta-aminolevulinic acid dehydratase (ALAD). oxidative stress in liver, kidneys, and brain as reflected by reduced levels of thiobarbituric acid reactive substance and oxidized or reduced glutathione levels. Ascorbic acid has recently been demonstrated to enhance the apoptotic effect of arsenic trioxide (As2O3). (Ramanathan et al., 2002). Ascorbic acid (an antioxidant), an essential nutrient for the biosynthesis of collagen, L-carnitine and the conversion of dopamine to norepinephrine. Ascorbic acid causes decrease in the level of lipid peroxidation (LPO and enhanced levels of total sulfhydryls, reduced glutathione, the activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and glucose-6-phosphate dehydrogenase to near normal. Rats have been extensively used as an animal model to study arsenic toxicity and to evaluate the efficacy of antioxidants through different routes in ameliorating oxidative stress due to arsenic exposure (Flora, 1999; Nagchowdhury et al., 1999; Ramos et al., 1995; Ramanathan et al., 2002; Flora et al., 2008).

Several studies found a positive correlation between the

dietary supplementation of naturally occurring nutrients and the intervention of the toxicity of environmental toxicant including the heavy metals (Gupta and Flora, 2005). Different types of antioxidants viz. vitamin E, ascorbic acid etc. are being used to neutralize radical-mediated oxidative stress. Ascorbic acid has regulatory effect in the restoration of altered biochemical variables and its preventive role in acute and chronic arsenicosis has been well demonstrated (Kannan and Flora, 2004; Rana et al., 2011). Natural medicinal products originating from fungi and herbs have been used as feed additives for farm animals in China for centuries, and due to their antimicrobial, immuno-enhancing and stress reducing bioactivities (Wang et al., 2002). The recent research deals with the mitigation strategies of chronic arsenicosis through natural dietary antioxidant. To mitigate arsenic toxicity, naturally occurring Aloe vera and Moringa oleifera were administered against arsenic induced oxidative stress and the ameliorative effects were observed (Gupta and Flora, 2005; Gupta et al., 2007). Mushroom is one of the important ingredients of Indian traditional folk medicines. It is believed to consist of important dietary and medicinal properties, which are used against number of ailments and diseases (Wang et al., 1998 ;Wasser and Weis, 1999). Mushrooms are nutritionally functional food and a source of physiologically beneficial and non-toxic medicines (Jose and Jannerdhanan, 2000). Medicinal mushrooms have been reported to have antibacterial, antiviral, antitumor, hypotensive, hepatoprotective, anticholesterolic effects (Wang et al., 1995; Jose and Jannerdhanan, 2000; Ho et al., 2004; Zheng et al., 2007). Pleurotus florida is a mushroom belonging to species of the basidiomycetes class of fungi (Jose and Jannerdhanan, 2000). It is able to interfere with tumor initiation through a variety of mechanisms, such as enhancing the host's antioxidant capacity in upregulating phase I and phase II enzymes involved in the metabolic transformation and detoxification of mutagenic compounds (Wang et al., 1996b). A variety of compounds with important pharmacological properties have been isolated from mushroom, which include polysaccharides, polysaccharopeptides, polysaccharide protein with immuno-enhancing and anticancer properties (Wang et al., 1996a; Wang et al., 1998, Wang, 2002; Ho et al., 2004; Zheng et al., 2007). Due to antioxidant and immunomodulatory properties of mushroom lectin, it is gaining popularity in medical research (Dalloul et al., 2006). Mushroom lectins have different subunits, molecular masses, amino acid compositions, sugar specificities and biological activities (Ho et al., 2004). and its metabolites are useful as adaptogens and immunostimulants and they are now considered to be one of the most useful antitumor agents for clinical uses (Jose and Janardhanan, 2000).

Lectins are proteins/glycoproteins that have been found in various organisms (Wang et al., 1996a). They have been isolated from a diversity of plants, animals, and microorganisms. They play many important roles in their growth processes. Most plant lectins are storage proteins, which acquire a potential role in defense when the plant or the seed is confronted by insects and fungi (Wang et al., 1998; Ho et al., 2004). Some legume lectins mediate the symbiotic association between leguminous plants and nitrogen-fixing bacteria (Zheng et al., 2007). Lectins are sugar-binding proteins which are highly specific for their sugar moieties (Gange et al., 2004). β-Galactoside specific animal lectins regulate differentiation and organ formation (Wang et al., 2002). It accumulate a variety of secondary metabolites, including phenolic compounds, polypeptides, terpenes, variegatic acid, diboviquinone steroids and lectins (Gange et al., 2004). It has been reported that the antioxidant activity of plant materials are well correlated lectin content (Dalloul et al., 2006). They typically play a role in biological recognition phenomena involving cells and proteins. The interaction of mushroom lectin with arsenic have not been studied yet. Arsenic, a well-documented environmental toxicant is widely distributed in nature and it is released into the environment through industrial processes and agricultural usages. Contamination of arsenic in drinking water is a major health problem throughout the world. Human exposure to arsenic in drinking water has been associated with cancers (lung, bladder and skin). and other chronic diseases. Endemic areas of overt arsenic poisoning exist in several countries in Asia and other parts of the World and its incidences have been reported through consumption of well water, exposure with contaminated air, soil or industrial contact. Although arsenic poisoning is a global problem it is a grave concern for Asian countries like India and Bangladesh. Considering the gravity of the problem abundant flow of literature and reports are available. In this review efforts have been made to collect pertinent references from the available literature.

Sources of arsenic

Arsenic is of great environmental concern due to extensive contamination of ground water in the Bengal delta basin, thereby causing carcinogenicity to millions of people as well as animals. Inorganic arsenic is a common constituent of the earth's crust and is widely distributed in the soil and water (Morton and Dunnette, 1994; NRC, 1999). Soil contamination by arsenic contaminated water being used for irrigation may prove detrimental to plant through its uptake to the toxic level (Das et al, 1996; Jin et al., 2004).

Arsenic contamination of ground water has been reported from Malda, Murshidabad, Nadia, North and South 24 Parganas, Bardhaman, Hoogly, Howrah and Kolkata. Seventy-nine blocks of nine district of West Bengal were affected with the arsenic problem and it was suspected that 6 million people are exposed to arsenic contaminated water (>50μg/lit). (WHO, 2003; IARC, 2004; Pal et al., 2007). The arsenic crisis in Bangladesh is one of the worst cases of environmental toxicity. Fifty out of 65 districts involving nearly 85% of the total area of Bangladesh have arsenic in ground water. It is suspected that about 25 milaalion people are exposed to arsenic contaminated ground water (Chakraborti et al., 2003).

Besides, the Terai region of Nepal has been found to have arsenic contamination in ground water. Five million people are suspected to be exposed to arsenic

contaminated water. Localized distribution of arsenic of varying magnitude has been reported from Myanmar. It is suspected that about 5 million people are exposed to arsenic (WHO, 1993; WHO, 2003). Arsenic contamination in drinking water has been documented in China, Inner Mongolia, Thailand, Vietnam and Japan. Contamination of ground water by arsenic was also reported from other countries including Lao Peoples Demoratic Republic, and Cambodia (IARC, 2004). The main source of exposure to arsenic in South America has been the natural contamination of drinking water because of geological formations associated with volcanoes. The countries, mostly affected are Chile, Bolivia, Peru and Argentina, especially in the Andean region (Queirolo et al., 2000). Natural contamination of drinking water has also been reported in the Lagunera region of Central northen Mexico where approximately 400,000 people are exposed (Izquierdo-Vega et al., 2006).

Occurrence of arsenicosis

Out of a population of 7683 surveyed, 4216 people in West Bengal consumed water containing arsenic below and above 0.05 mg/L, respectively with hyperpigmentation keratosis, weakness, anaemia, burning sensation of eyes, solid swelling of legs, liver fibrosis, chronic lung disease, gangrene of toes, neuropathy, and skin cancer and other clinical manifestations. Except abdominal pain, the prevalence of all other clinical manifestations tested (e.g., pigmentation, keratosis, hepatomegaly, weakness, nausea, lung disease and neuropathy). were found to be significantly higher in arsenic exposed people (water arsenic>0.05 mg/L) compared to control population (water As level<0.05 mg/L) (Guha Mazumder, 2003). Arsenic levels were above 50 μg/ L in 2000 villages, 178 police stations of 50 affected districts in Bangladesh and 2600 villages, 74 police stations/blocks of 9 affected districts in West Bengal. Analysis of 34,000 and 101,934 hand tube-well water samples from Bangladesh and West Bengal respectively by Flow Injection Hydride generator Atomic Absorption Spectrophotometry (FI-HG-AAS). of which 56% and 52%, respectively, contained arsenic above 10 μg /L and 37% and 25% arsenic above 50 μg /L. 18,000 persons in Bangladesh and 86,000 persons in West Bengal were clinically examined in arsenic-affected districts. Of them, 3695 (20.6% including 6.11% children). in Bangladesh and 8500 (9.8% including 1.7% children). in West Bengal had arsenical dermatological features. (Rahman et al., 2001).

In addition, out of 93 animals suffering from arsenic toxicity in National Cancer Institute (Veterinary Medical Data Program, VMDP). 64-69% were dogs, 18 (l9%). cattle, 5 (5%) cats, 4 (4%) pigs, and 2 (2%). were horses (Selby et al., 1989). Besides, among 42 heifers 29 died from arsenic poisoning in South America, after an arsenical soil and the grass sample contained 2262 ppm as dry weight (Morgan et al., 1984). In those areas, over a 44 day period, 4 of 5 affected calves in a 170 herd of beef cattle died after exhibiting clinical signs of lethargy, ataxia, anorexia, and diarrhoea. Histopathological examination of tissues and toxicological analysis of a suspicious powder discovered in the pasture confirmed arsenic trioxide toxicosis (Faires, 2004).

It was previously published that the concentration of arsenic in the blood (19μg/kg) is at least two orders of magnitude higher than the level of blood in unexposed area in Northen Scotland (Feldmann et al., 2000). In experimental cases, the concentration of arsenic in blood of acute and subacute arsenic toxicity in goat ranges from 0.13 ± 0.01 to 4.95 ± 0.03 mg% and 0.12 ± 0.02 to 1.32 ± 0.27 mg% respectively (Biswas et al., 2000). In Spain the concentration of toxic element in blood of calves (male and female between 6 and 10 months old). and cows (2-16 years old). were 3.23 and 2.92 μg /L respectively in Spain (Lopez-Alsono et al., 2000). Arsenic is stored mainly in liver, kidney and spleen and most of it is excreted in urine (if salt is not readily absorbed) and much of it is eliminated in the faeces (Selby et al., 1989). It was earlier reported that the concentration of arsenic in urine of cattle was 3.53 mg/l after ingestion of 2.75-mg/kg-sodium arsenate for five days (Lakso and Peoples, 1975). The kidneys are a primary route of excretion with approximately 36% of the initial dose cleared by 2 hr post injection. Only about one-fifth of absorbed arsenic is promptly excreted through urine and faeces. The remaining four fifths is stored widely in the body. A single dose may require 10 days for complete elimination (Buck et al. 1976). Urine samples contained 0.15-16.4 mg/kg in an outbreak of arsenical poisoning in cattle in Mexico (Rosiles, 1977). The concentration of arsenic in urine of experimentally produced acute and sub-acute arsenic toxicity in goat ranges from 0.17 ± 0.01 to 3.05 ± 0.03 mg% and 0.13 ± 0.01 to 0.82 ± 0.02 mg% respectively (Biswas et al., 2000). In addition, it was also reported the level of arsenic in urine is 2667μg/kg of arsenic affected sheep that is higher than control sheep in Northern Scotland (Feldmann et al., 2000).

The ingestion of bovine milk is one of the most important pathways of exposure to chemicals and the accumulation of persistent organic chemicals in tissues in the agricultural food chain. The groundwater and milk samples from 30 small, medium and large dairy farms in Cordoba, Argentina, were analyzed to determine the levels of arsenic during August 2002 and April 2003. It was shown that arsenic concentrations in all water samples were over the suggested level for cattle intoxication and ranged from 0.23-2.54 mg/litre. They also reported that the milk of dairy cows from 5 farms, which used phreatic groundwater and deep wells had arsenic concentrations of 2.8-10.5 and 0.5 ng/g, respectively (Perez-Canara and Fernandez-Cirelli, 2005). High levels of arsenic (117 μg/l). were found in the cow's milk in France (Perez-Canara and Fernandez-Cirelli, 2004). Milk from healthy cows contained 0.0005-0.81ppm of As in U.K where contaminated grazing pastures contained 0.07-1.5 ppm As (Sahli, 1982). Besides, the total arsenic concentrations from cow's milk ranged from 0.9 to 27.4 ng/g at Francisco I, Maderond Matamoras countries (Rosas et al., 1999).

The arsenic contents in hair samples of in nine industrial contaminated sites of Hyderabad were 0.9 mg/kg, 0.8 mg/kg, 0.9mg/kg, 0.5mg/kg, 0.7mg/kg, 0.06mg/kg, 0.5mg/kg, 0.8mg/kg, and 0.4 mg/kg respectively.

(Chandra et al., 2003). An estimation of arsenic content in hair samples and the value went as much as 5-10 mg/kg while animals not exposed to arsenic (normal). should contain less than 0.5mg/kg (Radostits et al., 2000).

Mitranescu et al. (2003). reported that the highest values of arsenic were observed in young and dark-coloured bulls and it enters into the animal body through water and fodder and accumulate in the skin and bones. The liver is the best organ for assay and levels of over 10-15 mg/kg wet matter of arsenic trioxide in the kidney or liver. The concentration of arsenic, copper, and zinc in the liver, kidney, muscle, and blood of calves from across Galicia in Spain related them to the metal concentration in the soil from the areas in which the animals were reared and for each element, liver (but not usually kidney, muscle, or blood). concentration was significantly elevated in animals from areas with higher soil concentration. They also reported that liver arsenic concentration were only markedly greater in animals from areas with soil arsenic levels more than 20mg/kg. (Mitranescu et al., 2003). The maximum concentration of arsenic in tissue reaches about 8 hrs after ingestion and the animals that survive for 2-3 days may have levels as low as 3mg/kg. The toxic dose of inorganic arsenic poisoning in cattle varies with an average of 36mg/kg (Radostits et al. 2000). The animals dying of acute or subacute poisoning might have contained from 2 to 100 ppm of As on a wet weight basis in two vital organs such as liver and kidney. And the levels above 10 ppm on a wet weight basis would be the considered confirmatory of arsenic poisoning (Buck et al., 1976). Animals are able to tolerate low levels of arsenic and the normal level in cattle tissues was less than 0.5 ppm. Faires (2004). also argued that arsenic level was more than 10 to 15 ppm in the liver, accompanied by clinical signs and that was considered diagnostic of acute arsenic toxicosis. In chronic experimental study, arsenic (ppm). burden in blood, liver, kidney were estimated as 3.49±0.10, 5.45±0.35 and 4.87±0.17 in chronic arsenic (10 ppm). intoxicated rat after 12 weeks (Nandi et al., 2005).

Health effects in human and animals due to chronic exposure to arsenic

Contamination of arsenic in drinking water is a major health problem throughout the world. Inorganic arsenic has a pronounced acute toxicity in human and experimental animals (NRC, 1999). and epidemiological studies provide clear evidence that it is also a carcinogen in human beings (Bates et al., 1992). Human exposure to arsenic in drinking water has been associated with cancers (lung, bladder and skin), chronic diseases of skin, heart, lungs, nervous system and diabetic effects (Abernathy et al., 2003; Yoshida et al., 2004). It is commonly concentrated in sulphur-bearing mineral deposits. Arsenic can enter the food chain, causing widespread distribution throughout the plant and animal kingdom (IARC, 2004). Exposure to arsenic may occur from natural source (anthropogenic nature), from industrial source, or from administered i.e. accidental source. Self-administration of arsenic, unintentionally i.e. accidental consumption by children or deliberate i.e., homicidal or suicidal in attempts by adults, represents the rare causes of acute poisoning (Flora et al., 2008; Guha, 2008).

Acute arsenic toxicity in human being causes diarrhoea characterised by Rice water stool, garlic like smell in breath, abdominal pain, laryngitis, dehydration and shock (Guha Mazumder, 2003). The pigmentation of chronic arsenic toxicity commonly appears as a finely freckled "raindrop" pattern that is particularly pronounced on the trunk and extremities distributed in bilaterally symmetrical pattern. Pigmentation and leucomelonesis appeared to occur in arsenicosis patients following stoppage of drinking arsenic contaminated water for some duration (NRC, 1999; Guha Mazumder, 2008). Moderate forms are multiple raised keratosis (2-5 mm). while severe forms are large discrete or confluent keratotic elevations (>5mm). on palms and soles, with nodular, wart-like or horn like apperance (NRC, 1999; WHO, 2003; Guha Mazumder, 2008). The clinical characteristic of acute arsenic poisoning includes intense abdominal discomfort, vomiting and diarrhoea followed by rapid circulatory collapse in animals. Death may occur within a few days and sometimes in less than one hour (WHO, 2003).

Irritant chemicals like arsenic, lead, copper, thallium, phenol etc. cause gastritis in monogastric animals (Chakrabarti et al., 2003). Arsenic poisoning is characterised by dysentery, toxaemia, normal temperature and nervous signs in animals (Radostits et al. 2000). The chronic form of arsenic toxicity in cattle includes particular fibrosis producing stiffness and asymmetrical enlargement of hocks or other joints of the limbs (Smith et al. 2000). Ascending degeneration of the peripheral nerve occurs in arsanilic acid poisoning in pigs. Authors also reported that chronic arsenic poisoning will result on the long haired coat which is scaly and the horse is emaciated (Radostits et al., 2000). Toxicity results if feed levels greater than 250 ppm are fed for several weeks. They also reported that toxicity leads to incoordination with ataxia and posterior paresis but alertness and appetite remain normal (Radostits et al., 2000).

Skin pigmentation of arsenical poisoning is due to melanin and it has a characteristic raindrop appearance in human with most of the melanin disposed peripherally. They also stated that arsenical keratoses occur on the palms, soles, and trunk and are premalignant and often multiple (Guha Mazumder, 2003; Guha Mazumder, 2008). Arsenic causes toxic hepatitis, chronic dermatitis with excessive pigmentation and hyperkeratosis & neuritis that ultimately results in atrophy of the optic nerve and blindness (Majumder et al., 2009). Acute and subacute arsenic toxicity in experimentally induced goat were characterised by increased heart rate, respiration rate, absence of ruminal motility, diarrhoea, drooling of saliva, stiff gait, paresis of hindquarter, lameness, tremor, convulsion, coffee coloured urine congested mucous membrane, paresis of limb and death (Biswas et al., 2000). Chronic arsenic in experimentally produced animals causes reduced body weight, coffee coloured urine, congested mucous membrane and polyuria (Biswas et al., 2000). Arsenic is a nephrotoxic agent in bovine showing complication of weakness, trembling, ataxia, depression, colic, rumen atony, diarrhoea, and prostration. Course of

the disease varies from hours to several days and case mortality is high (Guha Mazumder, 2003).

Inorganic arsenic is absorbed from GIT and skin and arsine gas is absorbed from lungs. Guha Mazumder (2003). also reported that chronic arsenic poisoning leads to skin irritation and colour changes, hair loss, nausea, GIT disturbance and bone marrow depression. Arsine causes massive haemaglobinuria and acute renal failure and it is also established as a carcinogen, which can cause cancer in lungs and skin. Acute arsenic poisoning causes gastro-enteritis dehydration, laryngitis and shock. A sweet garlicky odour in breath and of stool is indicative of arsenic poisoning in human (Radostits et al., 2000).

Metabolism of arsenic

Nandi et al. (2005). reported that in acute poisoning and in chronic arsenic ingestion, the highest concentration of arsenic accumulates in the kidneys, liver and liver, kidneys, heart, lungs, muscles, nervous system, gastrointestinal tract, and spleen (small amount). respectively. The residual amount remains in the keratin-rich tissues, hair and skin. In human and in most experimental animals inorganic arsenic is methylated to monomethyl arsonic acid (MMA). and dimethyl arseonic aid (DMA). and the relative compounds of species in urine are generally 10-30% inorganic arsenic, 10-20% MMA and 60-80% DMA (NRC, 1999; WHO, 2003). In comparison to inorganic arsenic, the methylatated metabolites containing pentavalent arsenic (MMAV and DMA V). are less cytotoxic, less reactive with tissue constituents and more readily excreted in the urine (NRC 1999, 2001; El-Demerdash et al., 2009). The sequence of events in arsenic biotransformation remains unknown, but it appears that S-adenosylmethiomic (SAM). is the main source of methyl groups for the methylation dependent upon methyl tranferases (El-Demerdash et al., 2009). Arsenic binds with-SH groups of several enzymes and inhibits biochemical reactions, e.g. pyruvate dehydrogenase. It causes coagulation of proteins and blockage of ATP generation (function as an uncoupler). (NRC 1999, 2001; El-Demerdash et al., 2009). Increasing arsenic intake results in elevation of arsenic content in urine (Rana et al., 2008; Rana et al., 2009). Urinary As excretion rises with increasing As intake so that total urinary As excretion provides a useful index of exposure (Browning, 1969). It also occurs within 2 to 8 hrs after oral administration and continuous for 8-10 days (Radostits et al., 2007).

Pathophysiology of arsenic toxicity

The arsenate was less toxic than the arsenite form in both species (arsenite and arsenate). and few lesions were found with decreased growth rate. In rats distension of common bile duct with hyperplasia of granular elements, and focal necrosis and fibrosis of the liver were observed (Das et al., 2005 Das et al., 2010). But the lethal oral dose of sodium arsenite for most species of animals was found to be from 1 to 25 mg/kg body weight (Buck et al., 1976). Experimental arsenic toxicity occurs in calves following oral administration with 25 mg of sodium arsenite/kg of body weight (Radostits et al., 2000). Chronic arsenic toxicity was induced in goats by oral administration of sodium arsenite @ 25.0 mg/kg body weight daily for 12 weeks and the animals showed gastrointestinal and renal signs with 100% mortality. Intoxicated goats had leukopenia, anaemia and increased erythrocyte fragility rate (Biswas et al., 2000). On oral exposure to arsenic, rabbit shows an oxidative stress causing deleterious effects on the total endocrine pancreas (Mukherjee et al., 2003). Rat and mice are the common experimental models for arsenic toxicity as rodents are most susceptible to arsenic poisoning.

Arsenic causes several toxicity in laboratory animals like field animals (Das et al., 2005; Nandi et al., 2005; Kadirvel et al., 2007; Santra et al., 2007; Ei-Demerdash et al., 2009). Acute toxicity, of trivalent arsenic is greater than the pentavalent form (Kadirvel et al., 2007). The LD50 of arsenic trioxide for mice by oral route varies from 15-293 mg/kg body weights and 111-150 mg/kg body weight in other laboratory animal (WHO, 2000). The fatal dose of ingested arsenic (III). oxide for man has been reported to range from 70-180 mg/kg body weight (WHO, 1993). The biological effect of chronic arsenic toxicity has been extensively reviewed (IARC, 2004). In chronic toxicity arsenic inhibits cellular respiration at the level of mitochondria. Disruption of oxidative phosphorylation and concomitant decrease in cellular levels of ATP are important in causing cellular injury and cell death, because ultrastructural morphometric alteration of mitochondria and alteration of cellular respiratory function are closely correlated. Recent studies accompanied by a loss of the mitochondrial transmembrane potential (Guha Mazumder, 2003; Santra et al., 2007). Arsenic in human beings appears to be a chromosomal mutagen. It appears to have a limited ability to induce point mutations. Increased frequencies of micronuclei, chromosomal aberrations and aneuploidy are detected in the peripheral lymphocytes or urothelial cells, or both in people exposed to elevated levels of arsenic (IARC, 2004). Liver fibrosis occurs as a later stage of chronic arsenic hepatotoxicity, and its persistence may progress to cirrhosis and even to liver cancers. In human beings exposed to chronic arsenic toxicity through domestic burning of arsenic coal in unvented stoves for heating and cooking, liver cirrhosis, ascites, and liver cancers are the main causes of arsenic-related mortality (Pal et al., 2007). So the gross lesions in the arsenic toxicity includes ulceration of mucous membrane, abdominal and intestinal erosions & ulceration, fatty liver, and pale, swollen kidneys (Santra et al., 2000; Das et al., 2005; Santra et al., 2007). The liver is enlarged & heavier than normal, doughy in consistency, uniformly light yellow in colour & reddish yellow congestion that lead to saffron yellow coloured liver due to arsenic toxicity (Santra et al., 2000; Das et al., 2005; Santra et al., 2007).

It was previously reported that arsenic toxicity in goat showed vascular congestion, cloudy swelling, fatty degeneration and massive haemorrhages of specially in liver and kidney (Biswas et al., 2000). Capillary degeneration and degenerative changes observed in specially in liver and kidney gut, skin, lungs and other organs range from cloudy swelling to necrosis in the gut

mucosa, liver, kidney and heart (Santra et al., 2000; Das et al., 2010). In experimental animals, chronic administration of inorganic arsenic through the drinking water in mice causes inflammation and oxidative damage to the liver.

Arsenic-induced oxidative liver damage is often associated with increase in inflammatory cytokines and depletion of glutathione-related antioxidant. Accumulation of the wide spread environmental toxin arsenic in liver results in hepatotoxcity. The toxic insult to the liver caused by arsenic in the drinking water eventually results in fatty liver (steatosis). and hepatic fibrosis (Lieu et al., 2001). Non-cirrhotic fibrosis of the liver is common in subjects chronically consuming ground water geologically contaminated with arsenic (Santra et al., 2000). Histopathology (H&E and Masson stain). revealed liver inflammation, steatosis (fatty liver), hepatocyte degeneration and fibrosis. Exposure to arsenite and other arsenicals has been previously shown to induce apoptosis in certain tumor cell lines at low (1-3 microM). concentration in rat liver following repeated 60 days exposure. (Ferzand et al., 2008). The kidney and spleen showed varied degree of the gross lesion of haemorrhages and milder to dark plum color appearances. The renocytes and splenocytes exhibited hydropic and fatty degeneration, cytolasmic vacuolation, cytoplamic blebbing and necrosis (Ferzand et al., 2008).

Induction of oxidative stress by arsenic

Oxidative stress has been implicated to play important role in the aetiopathogenesis of various degenerative and chronic diseases (Irshad and Chaudhuri, 2002, El-Demerdash et al., 2009). Inorganic arsenic is a generalized poison with a special predilection for the vascular endothelium. It is a notorious environmental toxicant known to be carcinogenic for the skin, lung and urinary bladder in man and causes oxidative stress to animals (Guha Mazumder, 2008; Majumdar et al., 2009). On acute toxicity of sodium arsenite in experimental rat the levels of glutathione, lipid peroxydation and cytochrome P450, catalase and superoxide desmutase were decreased but glutathione peroxidase level increased significantly (Bashir et. al., 2006). Recent studies have shown that arsenic-induced oxidative stress could be reversible mechanism for some of the toxic effects of arsenic in cultured cells and experimental animals (Kitchin et al., 2001; Pie et al., 2002; Shi et al., 2004;Rana et. Al., 2010;Rana et al., 2013).

There are many evidences suggesting that arsenic toxicity involves oxidative damage (Izquierdo-Vega et al., 2006). that plays a vital role for biochemical and molecular alteration (Kadirvel et al., 2007). Decreased levels of antioxidants, increased levels of oxidation products in blood were reported in human population exposed to arsenic (Wu et al., 2001). Many biological processes have been identified as involved in arsenic-induced toxicity and carcinogenicity. Various studies reported that arsenic could participate in the cellular oxidation-reduction reactions resulting in the formation of excess ROS such as superoxide anion (O.2). and hydroxyl radical (OH-). via a chain reaction (Liu et al., 2001; Garcia-Shavez et al., 2006). The alterations of the activities of several enzymes and toxicity biomarkers, viz., aspartate amino transferase (AST), alanine amino transferase (ALT), acid phosphatase (AcP), alkaline phosphatase (AlkP), lipid peroxidation (LPO). and reduced glutathione (GSH). were observed after administration of the arsenic in human (Khuda-Bukhsh et al., 2005). Besides, the long term arsenic exposure increased gluthathione -S _transferase (GST). activity and cellular glutathione level (Kojima et al., 2006.). Superoxide desmutase (SOD). and catalase (CAT). activities increased initially ($P<0.05$). in all the tissues followed by a declining trend and at the end of 12 weeks, the activities were non-significantly ($P>0.05$). lower than respective controls (Nandi et al., 2005; Nandi et al., 2006; Nandi et al., 2008). Superoxide desmutase (SOD_2). is the principal defense against the toxicity of superoxide anions generated by the oxidative phosphorylation (Nandi et al., 2006; Nandi et al., 2008).

It was previously narrated that arsenic increases the level of the lipid peroxides and protein carbonyl by inducing free radical generation or by inhibition of antioxidant enzymes (Ramos et al., 1995; Das et al., 2005; Kadirvel et al., 2007; Sohini and Rana, 2007;Bera et al., 2010). Sengupta and Bishayi (2002). reported that arsenic reduces phagocytic activity of cell due to suppressing effect of arsenic. The arsenic treated cells migrate slower to the source of infection, poorly recognize the foreign pathogenic organism, cannot release optimally several free oxygen radicals and proteases and thereby unable to destroy or eliminate the micro organism from the host (Sengupta and Bishayi, 2002; Ghosh et al., 2007).

Arsenic induces cell proliferation at low levels which might be due to inhibition of transcription and translation processes (Liu et al., 2001 Noreault et al., 2005). Besides, nitric oxide (NO). is cytotoxic agent involved as a mediator in inflammatory disorders and it is cytotoxic, its overproduction is deleterious to cell (Krippeit-Drews et al., 1995). Administration of sodium arsenite found to cause a significant increase in NO production that is responsible for cellular damage and inflammatory changes (Pie et al., 2002; Mukherjee et al., 2007; Kumergai and Jingbo, 2004; Bera et al., 2010). In addition, cascade of cysteine proteases or caspases is a common and critical component of apoptotic cell death pathway (Alnemri et al., 1996; Datta et al., 2007). Arsenic increased TUNEL positive nuclei which is caspase-3 mediated and is related to oxidative stress (Datta et al., 2007; Santra et al., 2007).

Chronic low level arsenic exposure on rat liver epithelial cells produce highly aggressive malignant cells and hypomethylation of DNA detected using α satellite DNA (Zhao et al., 2001). Arsenic-induced toxicity and carcinogenicity include induction of micronuclei, alterations in gene expression, induction of oxidative stress, alteration in enzyme activities, change in carbohydrate metabolism, inhibition of DNA repair, perturbation of DNA methylation, alteration of signal transduction pathways, altered cell cycle control, aberrant differentiation, and altered apoptosis (Bagnyukova et al., 2007; Manna et al., 2007). Free radicals and reactive oxygen species are produced in the metabolic processing of arsenical compounds (Yamanaka et al., 1990; Yamanak

et al., 2001) which may lead to DNA single-strand breakage and DNA protein cross-link via the formation of apurinic/ apyrimidinic (AP). slices through a Schiff based reaction between amino groups of nuclear proteins and aldehyde groups of AP sites in DNA (Yamanaka et al., 2001).

Genotoxicity

Detection of stress protecting marker gene

Arsenic compounds may generate reactive oxygen species (ROS). during its metabolism in cells. Several studies indicated that genotoxicity of arsenic may be mediated by ROS (Yamanaka et al., 1991; Wang et al., 1996).

Superoxide desmutase (SODs), antioxidant enzyme, catalyse the desmutation of superoxide into hydrogen peroxide. The liver injury occurs when there is imbalance between reactive oxygen species (ROS). and antioxidant enzymes. ROS are scavenged by antioxidant enzymes such as SOD, catalase (CAT). and glutathione peroxidase (GSH-Px). Superoxide dismutase (SODs). are thought to be one of the first line of antioxidant defence and are highly efficient in protecting cells and tissues against oxidative stress by catalyzing the desmutation of superoxide radicals to form hydrogen peroxide and molecular oxygen. There are three kinds of isoenzymes extracellular superoxide dismutase (EC SOD), Manganese-containing superoxide desmutase (Mn-SOD) and copper and zinc containing superoxide dismuttase (Cu-Zn-SOD). The mitochondrial enzyme (Mn-SOD), involved in ROS detoxification, catalyse the dismutation of superoxide radical (O_2). MnSOD is a nuclear-encoded antioxidant enzyme that localizes to the mitochondria (Zhao et al., 2001). Aberrant expressions of several genes were consistent with the results of array analysis of chronic arsenic-exposed mouse livers and chronic arsenic-transformed rat liver cells. Clearly, a variety of gene expression changes may play an integral role in arsenic hepatotoxicity and possibly carcinogenesis (Lu et al., 2001). The presence of SOD_2 gene in mitochondria can influence the role of mitochondria as a source of ROS removal and alteration of SOD_2 gene level might contribute to cancer susceptibility and resistance to cancer therapeutic agents (Yamanaka et al., 1990;Yamanaka et al., 1991). The native molecular weight of the Cu-Zn-SOD isolated from the cytosolic and mitochondrial fractions were determined by analytical sedimentation equilibrium. They were found to be identical within the limits of precision of the method, i.e. 31,800 and 31,400 daltons (Matsumato and Fridovich, 2001).

Manganese Superoxide dismutase (MnSOD). enzyme activity and SOD_2 gene expression have often been reported to decrease during the development of cancer. SOD_2 has also been implicated as a candidate tumor suppressor gene for human malignant melanoma. Genomic DNA methylation patterns are also known to change during carcinogenesis and serve as a mechanism for tumor suppressor gene inactivation. Decreased SOD_2 gene expression in some malignant cell populations may be due, at least in part, to methylation of upstream transcriptional regulatory sequences in the SOD_2 gene (Huang et. al., 2004). Chronic arsenic exposure has been shown to induce malignant transformation of mammalian cells and 1. Induction in the cell proliferation and 2. Decrease in DNA repair capacity results in the accumulation of mutation and 3. Changes in the DNA methylation pattern affecting regulation genes are hallmark of cancer development (Huang et. al., 2009). Besides, exposure of arsenic at hepato carcinogenic dose induces alteration in DNA methylation and a complex set of aberrant gene expression in liver (Xie et al., 2007). It was also reported that liver mitochondria from homozygous mutant mice, with a complete deficiency in MnSOD, exhibited substantial respiration inhibition and marked sensitization of the mitochondrial permeability transition pore. Mitochondria from heterozygous mice, with a partial deficiency in MnSOD, showed evidence of increased proton leak, inhibition of respiration, and early and rapid accumulation of mitochondrial oxidative damage (Kokoszka et al., 2001). MnSOD, a mitochondrial gene overexpression decreases p53-gene expression at the promoter level. These findings raise the hypothesis that p53 and SOD2 genes are mutually regulated leading to the modulation of various cellular processes including apoptosis (Drane et al., 2001).

Role of anti-oxidant in chronic arsenic toxicosis

Natural antioxidant

Antioxidants have been found to be beneficial in mitigating of chemically induced oxidative damage (Ramanathan et al., 2003; Nandi et al., 2005; Ramanathan et al., 2005). Co-administration of arsenic treated rats with ascorbic acid and alpha-tocopherol showed significant reduction in the level of lipid peroxidation and elevation in the levels of ascorbic acid, alpha-tocopherol, glutathione and total sulfhydryls and in the activities of isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, succinate dehydrogenase, NADH-dehydrogenase and cytochrome c oxidase (Ramanathan et al., 2003). The treatment with alpha-tocopherol also showed a protector effect on the polyunsaturated fatty acids of liver mitochondria, microsomes and testis mitochondria of arsenic exposed rat (Ramanathan et al., 2003; Kadirvel et al., 2007). Ascorbic acid treatment in arsenic trioxide treated rats increased arsenic excretion, inhibited lipid peroxidation, improved GSH status, regulated GSSG turnover and also restored glutathione-S-transferases activity in liver and kidney (Sohini and Rana, 2007; Santra et al., 2007). Ascorbic acid, α tocopherol, cysteine have been used for post exposure acute arsenic toxicity in rats (Flora, 1999, Ramanathan et al., 2002). In addition, significant ameliorative efficacy of ascorbic acid and thiamine was observed in experimental lead toxicity occur in rats when given simultaneously as compared to post exposure treatment (Flora and Tandon, 1986). The protective effects of L-ascorbic acid, a standard antioxidant, against inorganic arsenic (As_2O_3) toxicity to

arsenic affected population may prevent the occurrence of fatal human diseases (Singh and Rana, 2007).

It scavenges nitric oxide (NO) and peroxynitrite and also inhibits excessive production of NO by inducible form of NO synthase (iNOS) (Barchowsky et al., 1996; Schindler, 2000;Rana et al., 2012a). This reduction using ascorbic acid may be due to direct oxygen radical scavenging property (Kadirvel et al., 2007; Bera et al., 2010) or by decreasing the constituent levels of both activated NF-β that respond to arsenic generated oxidative stress (Barchowsky et al., 1996).

Mushroom lectin as immunomodulant

Mushroom is one of the important ingredients of Indian traditional folk medicine since ancient times. It is believed to consist of an important dietary and medicinal property, and it is used against number of ailment and diseases (Wang et al., 1996; Wang et al., 1998; Wang et al., 2002; Ho et al., 2004). Mushrooms are nutritionally functional food and a source of physiologically beneficial and non-toxic medicine. It was also narrated that edible mushroom, Pleurotus florida has therapeutic use for prevention and control of cancer and cardiovascular diseases due to antioxidative role (Jose and Janardhanan, 2000; Jose et al., 2004). Mushroom is able to interfere with tumor initiation through a variety of mechanism, such as enhancing the host's antioxidant capacity in upregulating phase I and phase II enzymes involved in the metabolic tranformation and detoxification of mutagenic compounds (Wang et al., 2002).

The most significant medicinal effect of mushrooms and their metabolites which attracted the attention of the public is their antitumor property (Wasser and Weis, 1999; Ho et al., 2004). Mushroom contains polysaccharides and protein- polysaccharides complex of which polysaccharides are considered to be the most important from medical point of view (Jose and Janardhanan, 2000; Zheng et al., 2007). Chief among the most bio-pharmacological activities of polysaccharides are their immunomodulatory and antitumor activities. Numerous reports indicated that most of the polysaccharides or polysaccharide-protein complexes can not exert any direct cytotoxic action on tumor cells. These actions are predominantly considered to be host mediated. (Jose et al., 2004). Mushroom metabolites are usually used as adaptogens and immunostimulant (Jose and Janardhanan, 2000).

A variety of compounds with important pharmacological properties have been isolated from mushroom, which include polysaccharides, polysaccharopeptides, polysaccharide protein with immuno-enhancing and anticancer properties (Wang et al., 1996; Wang et al., 1998, Wang, 2002). Mushroom lectins are capable of activating macrophages and lymphocytes (Wang et al., 1996; Dalloul et al., 2006) whereas some of them posses potent mitogenic activities towards human lymphocytes and thus receiving special attention and they are collectively designated as fungal immunomodulatory proteins (FIP) (Ho et al., 2004).

Mushroom lectins as alternative antioxidants in chronic arsenicosis in animals

Mushrooms are well known for their nutritional and medicinal values. A variety of compounds with important pharmalogical properties have been isolated from mushrooms, which include polysaccharides, polysaccharopeptides, polysaccharide-proteins with immuno-enhancing, anticancer activities, lectins with immunomodulatory, antitumour, antioxidative and hypotensive activities. Lectin from Pleurotus florida, an edible mushroom lectin which fed orally to rat significantly increased body weight with reduction of relative organ weight and restoration of histopathological alteration (Rana et al., 2012a; Rana et al., 2012b). In addition, it was also reported that mushroom lectin has a great role in preventing various metal toxicities (Jose and Jannardhanan, 2000; Jose et al., 2004; Zheng et al., 2007). Zaidman et al. (2005) demonstrated that mushroom lectin prevents and treat many forms of cancer by reducing apoptosis and cell death by increasing the cell proliferation. Mushroom lectin playa a significant role in reducing TUNEL positive nuclei, activity of apoptotic effector caspase-3, cell death by scavenging radical and increasing cell proliferation (Bera et al., 2011 Rana et al., 2013). Ho et al., (2004) indicated that the protective power of mushroom extracts is due to immunomudulatory properties. Miller (2002) stated that mushroom lectin has a capability to reduce arsenic burden. Rana et al. (2012b) reported that superoxide dismutase (SOD) and catalase (CAT). activities were normalized when supplemented with mushroom lectin as it has a crucial role in counteracting free radical induced damage to macromolecules by healing of the free radical mediated cell damage.

Medicinal mushrooms have been reported to have antibacterial, antiviral, antitumor, hypotensive, hepatoprotective, anticholesterolic effects (Wasser and Weis, 1999; Jose and Jannerdhanan, 2000). Mushroom are nutritionally functional food and a source of physiologically beneficial and nontoxic medicines. Mushroom lectin reduces oxidative stress in duration dependent manner with restoration of the activities of antioxidant enzymes i.e. SOD and CAT by preventing overproduction of lipid peroxides (LPO) and protein carbonyl (PC) in arsenic induced rat (Rana et al., 2012b) In another aspect Ho et al. (2004) and Zheng et al. (2007) demonstrated that mushroom lectin is able to scavenge or neutralize free radicals by interacting with oxidative cascade, quenching oxygen by chelating some metal ions and inhibiting peroxidation of membrane lipids thereby maintaining membrane integrity and their functionsAccording to Jose et al. (2004) and Kimura et al. (2007) it is reported that mushroom lectin acts through different mechanisms and in different compartment by scavenging free radicals, reducing peroxide concentration and repairing cell membrane. It has beneficial role by modulating the activity of plasma biomarker enzymes like aspertate transaminase (AST),alanine transaminase (ALT), acid phosphatase (ACP), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH). Yang et al.

(2007) reported that mushroom lectin prevented arsenic induced alteration in enzyme activities. It was established that edible mushroom, Pleurotus florida has therapeutic use in prevention and control of cancer and cardiovascular diseases owing to its antioxidative (Jose and Janardhanan, 2000; Jose et al., 2004) and cytoprotective role (Wang et al., 1998; Wang et al., 2002) Rana et al.(2012a) revealed that mushroom lectin accelerated cell adhesion, cell proliferation and morphological alterations. Zheng et al. (2007) indicated that mushroom lectin exhibited a potential role against cell cytotoxicity and also regulates cell growth, cell adhesion, cell migration, cell apoptosis and immune responses. Wang et al. (1996) reported that the mushroom lectins are capable of activating macrophages and lymphocytes. In addition, Ho et al. (2004) reported that mushroom lectin has fungal immunomodulatory protein (FIP) which activates macrophages and lymphocytes to prevent cellular death. Vandana et al. (2006) indicated that mushroom lectin is able to prevent altered cellular activities in arsenic induced rat. Wang et al. (1996) and Ho et al. (2004) inclined that mushroom lectin has a great role in accelerating cellular activities in infections. Mushroom lectin restored phagocytic activity by normalizing the nitric oxide production induced by arsenic and available literature showed that it plays a great role in scavenging NO and peroxynitrite and also inhibits excessive production of NO by inducible form of NO synthase (iNOS) (Wang et al., 1996; Dalloul et al., 2006; Young et al., 2008). In addition, it was also established that mushroom lectin enhances the phenotypic function of macrophages NO production and cytokine expression (Yang et al., 2007; Young et al., 2008). DNA damage has been recognized as the cause of onset of many diseases like cancer and could be a useful indicator of the oxidative stress and apoptosis. Development of DNA ladder is considered to be hallmark of apoptosis. When the hepatic and renal cells of different groups were analyzed on agarose gel the presence of nucleosomal ladder could be detected. Jose and Jannerdhanan (2000) demonstrated that the beneficial role of mushroom lectin in to prevention of DNA damages which might be due to its free radical scavenging activity. Rana et al. (2012b) noted that mushroom lectin prevented DNA damage which is in acoordance with the confirmatory reports of Koyama et al. (2002) who described that the DNA damages is to acceleration of DNA efficiency in the damaged cells. Rawal et al. (2004) and Paterson (2008) reported that the antioxidant defense by mushroom lectin is due to its amerliorative properties and chelating abilities with trace element contents. Mushroom lectin prevents oxidative stress by restoring relative mRNA SOD_2 expression corresponding to GAPDH in comparison to control cells (Bera et al., 2010; Rana et al., 2012b).

Summary

Arsenic, a sulfydryl-reactive metalloid, is one of the most important global environmental toxicant. This toxicant accumulates in ground water and agricultural products are being polluted due to its anthropogenic activity. The toxicological effects of arsenic on health are multidimensional in both human and animal beings. Liver and kidneys are considered to be primary targets of its toxicopathological manifestations. Mushroom lectin is having a great role in mitigating the toxic effects of arsenic by normalizing arsenic induced histopathological alterations and oxidative indices. This finding provided a clue on antioxidant properties of the mushroom lectin and it's future prospect in combating arsenic toxicity. It may use as alternative antioxidant for providing a novel strategy for designing cancer intervention.

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