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Review Article

Toxico-Pathological Aspects of Arsenic in Birds and Mammals: A Review

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Abstract

Arsenic (As) is a colorless and tasteless naturally occurring metalloid found in water, air and soil. There are two forms of As, i.e., inorganic and organic, the former form is of serious health concern. In Pakistan, mainly in southern and central parts, the ground water level of As is very high (up to 100 µg/L) as against WHO limits (10 µg/L). In Sindh and Punjab, over 36 and 20% of population is exposed to As contamination. The population is exposed to As by poultry and animal products, drinking water, fumes, dietary sources and dust with the highest concentration in seafood, mushrooms and rice. As alters the physiology of the organs leading to various pathological disorders. This review deals with pathophysiology and clinico-histopathological, immuno-pathological and toxico-pathological effects of As in birds and mammals.

Keywords: Arsenic; Pathophysiology; Clinico-histopathology; Immuno-pathology; Toxico-pathology; Birds; Mammals

Introduction

Poultry industry is one of the most important livestock sectors in Pakistan and is expanding very rapidly particularly for the last decade (Javaid *et al*., 2012; Islam *et al*., 2013). This sector has played a vital role in poverty alleviation particularly in the rural areas by generating direct or indirect employment for both male and female community (Islam *et al.,* 2012). Poultry meat is contributing about 19% of the total meat production in the country and is providing affordable production of good quality nutritious animal protein (Adzitey and Huda, 2012). However, intensive poultry farming is still facing many infectious and non-infectious problems like various diseases and different forms of toxicity including arsenic toxicity (As) especially in areas where ground water level of As is much high.

Heavy metal toxicity is one of the major abiotic stress leading to hazardous effects on biota (Jabeen *et al.*, 2012; Javed, 2013). This is because heavy metals bio-accumulates through water and food (Palaniappan and Vijayasundaram, 2009; Javed, 2012; Naz and Javed, 2013). As is a toxic element widely distributed in nature, such as water and soil (Tan *et al.*, 2014). As is a semi-metallic element found in soil, groundwater, surface water, air and various foods. As occurs naturally in the earth's crust with higher concentrations in some geographic areas and in some types of rocks and minerals (Duker *et al.,* 2005; Anonymous, 2005). Inorganic and organic forms of As are present in the environment, of these inorganic form is of serious health concern (Lima *et al.,* 2010). The arsenates ($Na_2HAsO_4.7H_2O$) are thermodynamically considered to be more stable than the arsenites in underground and oxygenated fresh water systems (Irgolic, 1982; Cui and Liu, 1988).

In Pakistan, mainly in southern and central parts, the ground water level of As is very high (up to 100 µg/L) as compared to WHO limits (10 µg/L). Studies conducted by Wadhwa *et al.* (2013) indicated that As contents in drinking water and food were found 3–15 folds greater than permissible limits in southern parts of Pakistan. In Sindh and Punjab, over 36 and 20% of population is exposed to As contamination (Islam *et al*., 2009). The discharge of As in the environment has resulted due to natural and anthropogenic activities and is found in air particles, soil and food (Wang and Mulligan, 2006; Wright and Belitz, 2010). The population is exposed to As by poultry and animal products, drinking water, fumes, dietary sources and dust with the highest concentration in seafood, mushrooms and rice (Datta *et al.,* 2012). Nutritional factors can alter the host response to environment toxicants. Nutritious diet may be able to inhibit or reverse the toxic mechanism of As, whereas a diet with increased concentration increases the susceptibility to adverse effects of As (Vahter, 2007; Lindberg *et al.,* 2008). This review deals with pathophysiology and clinico-histopathological, immuno-pathological and toxico-pathological effects of As in birds and mammals.

Pathophysiology of As toxicity

Arsenic is a colorless, tasteless and naturally present metalloid element found in water, air and soil (Han *et al.*, 2012). As is present both in organic and inorganic forms in environment. Organic As compounds are mostly nontoxic,

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while inorganic As compounds are toxic which are mostly found in surface and ground water (Feng *et al.,* 2001; Lage *et al*., 2006; Lima *et al.,* 2010; Bartel *et al*., 2011). As enters the body via diet and drinking water and its absorption mostly occurs in small intestine. It is also absorbed through inhalation and skin contact (Hertz-Picciotto and Smith 1993; Centeno *et al.,* 2002).

Arsenic accumulates in almost all organs, mainly in the liver (Cullen and Thomas, 2000) where biomethylation of As takes place producing monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) (Buchet and Lauwerys, 1988). MMA and DMA disable many enzymes which are involved in the cellular energy production and repair or synthesis of DNA. As antagonizes phosphate during ATP synthesis and also binds with sulfhydryl groups of numerous enzymes when in reduced form, which are vital for cellular metabolism (Brouwer *et al.,* 1992). Individuals exposed to As have different nucleotide deletion repair mechanism, thus altering the DNA repair process (Andrew *et al.,* 2006). Inorganic As is mostly present in arsenite [trivalent {As(III)}] and arsenate [pentavalent {As(V)}] forms. These can be either methylated as MMA or dimethylated as DMA. The inorganic As metabolism comprises of reduction process in which two-electron reduced from pentavalent to trivalent As and this reaction is catalyzed by glutathione enzyme. By oxidative methylation of MMA and DMA, pentavalent organic As is produced (Jomova *et al.*, 2011). The trivalent forms when react with thiol groups become more toxic, while toxicity of the pentavalent forms is less but hamper oxidative phosphorylation. Almost all organs are affected by As toxicity. Trivalent inorganic As binds with sulfhydryl groups of dihydrolipoamide inhibits pyruvate dehydrogenase. As a result, transformation of pyruvate to acetyl coenzyme-A (CoA) is reduced, citric acid cycle activity is lessened and manufacturing of cellular ATP is diminished. Trivalent As impedes several additional cellular enzymes by binding with sulfhydryl group. Trivalent As hinders the uptake of cellular glucose, fatty acid oxidation, gluconeogenesis, and additional production of acetyl CoA. It also chokes the formation of glutathione, as a result discontinues cellular oxidative damage (Flora, 2011). Pentavalent inorganic As transforms into trivalent As and thus produces toxicity. The important point is that, pentavalent As bears a resemblance to inorganic phosphate and alternates for phosphate in glycolytic and cellular respiration pathways. As a result, formation of high-energy phosphate bonds stop and separation of oxidative phosphorylation takes place. In the company of pentavalent As, adenosine diphosphate (ADP) produces ADP-arsenate, as a result ATP and high-energy phosphate bonds of ATP are vanished (Anonymous, 2012). Reduced state of trivalent As combines with thiol groups of enzymes and proteins, which hinder the catalytic activity of these enzymes (Aposhian *et al.,* 2004). Pyruvate dehydrogenase enzyme is inhibited by As metabolites, which disturb the cellular energy production (Aposhian and Aposhian, 2006). This disruption leads to discharge of an apoptotic inducing factor from mitochondria, ultimately leading to cell death (Akay *et al.,* 2004). Pentavalent As replaces phosphorus in several biochemical reactions. So instead of the production of stable phosphorus anion, less stable AsV anion is produced leading to hydrolysis of ATP. In citric acid cycle, As hampers succinate dehydrogenase enzyme and compete with phosphate to disengage oxidative phosphorylation, thus obstructing mitochondrial respiration, reduction of NAD^+ and ATP creation. For carcinogenicity, potential mechanisms include genotoxicity, oxidative stress, altered cell proliferation, altered DNA methylation, co-carcinogenesis, and tumor formation (Saha *et al.,* 1999; Hughes, 2002; Flora, 2011).

Trivalent As inhibits many cellular enzymes by binding with sulfhydryl group. It also prevents the gluconeogenesis, cellular uptake of glucose, fatty acid oxidation and manufacturing of acetyl CoA. To reveal oxidative stress, trivalent As stops the creation of glutathione, which is a tool for protection of cells against oxidative injury (Miller *et al*., 2002; Watanabe and Hirano, 2013; Wang *et al.,* 2014). As also produces oxidative stress, modifies monocyte superoxide anion formation and prevents nitric oxide production (Flora, 2011). Arsenic trioxide (As_2O_3) also inactivates endothelial nitric oxide synthase enzyme, which reduces the formation and bioavailability of nitric oxide. It also has been related with prompting atherosclerosis, snowballing platelet aggregation and decreasing fibrinolysis (Balakumar and Kaur, 2009).

Inorganic As in drinking water and food items has been associated with lung and bladder cancers in several countries including Pakistan (Wadhwa *et al.*, 2013). As is a carcinogenic metalloid based on the augmented incidences of lung and skin cancer perceived. Inorganic As is methylated in the body by changing reduction of pentavalent As to trivalent and adding a methyl group from S-adenosylmethionine. The prime site of As methylation is liver, although most of the organs display As methylating activity. The finished products are MMA and DMA. Their reactivity with tissues is less and freely evacuated in the urine, though, intermediates may be produced which are further reactive. Arsenate (AsV) is quickly reduced in blood to AsIII, which proposes high toxicity. There are indications that subjects having less MMA in urine have faster removal of ingested As in comparison with more MMA in urine (Hossain *et al.,* 2012). It is known that As toxicity is linked to its chemical nature. As is incorporated by cells through aquaporin (family of membrane channel proteins) in animals, then it biotransforms and its metabolites can also cause lesions of toxicity. So, the biotransformation of As should be taken as a bio-activation pathway which causes As toxicity (Ventura-Lima *et al.,* 2011). Multidrug-resistance proteins conjugate with As and eliminated by glutathione peroxidase (GSH); however, researches reports that the mechanisms of influx and efflux take place in

mammals. As can disturbs signaling pathways in mammals. It has been reported that As can encourage oxidative stress in mammals and also some marine animals (Poersch *et al*., 2006). As_2O_3 has been reported to cause a substantial extension of cardiac action potential length at many stages of repolarization, creates conduction interruption and amplifies triangulation (Raghu *et al*., 2009).

Clinico-pathology of As Toxicity

It is clear from Table 1 and 2 that various forms of As produce a wide range of clinical signs at 0.05 to 300 ppm dose. Toxicity signs also vary from species to species. The As toxicity in chicken causes depression, ataxia, lameness and stunted growth (Nandi *et al*., 2006; Sharaf *et al*., 2013), body weight loss (Gur *et al.*, 1989; Albert *et al*., 2008), less feed consumption, loss of appetite, sour mouth, dullness and neurological disorders (Halder *et al*., 2007). Not only in birds but also in humans, As_2O_3 causes various signs like dullness, depression, increased frequency of defecation, excessive salivation and keratosis (Table 1).

Valentine *et al.* (2007) reported ataxia with intense muscle fasciculation succeeding to recumbency along with bloody diarrhea in As intoxicated cattle. The beginning of clinical signs was at least 12 h after the cattle had gained entrance to the contents of old constructions used for storage, and the greatest of deaths happened within 24 to 48 h after the appearance clinical signs. Rapid and severe autolysis considered more than expected for the postmortem interval.

Body weight lost up to 15% with high doses of MMA has been reported. Diarrhea and respiratory distress were recorded in rats and mice with the treatment of MMA and DMA (Stevens *et al*., 1979). MMA was the major form of As found in the blood plasma whereas DMA was present in the kidney and liver tissues (Nandi *et al*., 2006; Albert *et al*., 2008).

Not only toxicity is observed but also some beneficial effects of As have been reported. There was significantly improvement in feed utilization and egg production in Japanese quails with dietary addition of 50 and 100 mg/kg of arsanilic acid; however, the concentration of As in the tissues and feces in these birds was higher than in control birds (Desheng and Niya, 2006). Broiler birds with feed supplementation of 45.4 mg/kg roxarsone showed gradual and significant development performance; however, a significant As rise in liver was seen. Results advocated that the part of roxarsone could be mainly to change the manifestation levels of cell development, immunity and metabolism of energy related genes, consequently motivating animal development (Li *et al*., 2011). Mainly there are two genes, i.e., PSAP and HNRNPD associated with cell growth recorded during roxarsone treatment. Prosaposin (PSAP) is the precursor of saposins, and the sequential cleavage from the N-terminal region produces four mature saposins, A, B, C and D (Hiraiwa *et al.*, 1993). In the literature, it is evident that PSAP plays an active role in preventing apoptosis, stimulating cell proliferation and survival (Koochekpour *et al*., 2005; Li *et al*., 2011). Second cell growth associated gene HNRNPD is known as adenylate uridylate-rich (AU-rich) element RNA binding protein 1 (AUF1), belonging to subfamily of ubiquitously expressed heterogeneous nuclear ribonucleoproteins (HNRNPs). It plays a role in regulating the stability of mRNA by mediating the degradation of cytokine and proto-oncogene mRNA (Moraes *et al.,* 2003; Li *et al*., 2011). HNRNPD can also increase the metabolism of lipids and as a result affecting the cell growth. Two genes mentioned above showed expression changes due to the supplement of roxarsone, which suggests their involvement in animal growth (Tschernatsch *et al.*, 2006).

Toxico-pathological Effect of As

Arsenic causes both acute and chronic toxicities in a variety of organisms (Table 1; Table 2). Toxic effects of inorganic As included denaturation of cellular enzymes by interacting with sulfhydryl groups (Graeme and Pollack, 1998; Gebel, 2000) that results in cellular damage through increased reactive oxygen species (ROS) (Wang *et al.,* 1996; Ahmad *et al.,* 2000) and altered gene expression (Rossman, 1998; Abernathy *et al.,* 1999). The effects on cellular metabolism have been reported to be distressing mitochondrial respiration (Klaassen, 1996) and synthesis of energy (Winship, 1984). Ellenhorn and Barceloux (1988) reported that due to structural resemblance to phosphate, As replaces phosphorus from bones.

Arsenic usually does not spare any organ of the body. Toxic effects of sodium arsenate (22.5 ppm) in drinking water of mice showed proximal tubular congestion and atrophy along with glomerular swelling and interstitial fibrosis and nephropathy (Yuping *et al*., 2000). Sodium arsenite @ 13.5 mg kg^{-1} also induced acute renal injury in mice (Akihiko *et al*., 2004). Neurotoxicity in the brain of mice treated with As_2O_3 @ 2 ppm/day in drinking water reported as loss of neurons, nuclei, vacuolation in Purkinje cells and degenerative changes in cerebellar cortex (Fengyun *et al*., 2005). Due to toxicity of As liver showed vacuolation, congestion and condensed nuclei (Fig. 1), whereas kidneys exhibited congestion, epithelial necrosis and sloughing of tubular epithelium from basement membrane (Fig. 2). Hemopoietic tissues also showed pathological lesions (Yasmin *et al*., 2011). With the treatment of As, intestines of broiler chicks showed sloughing of epithelium from the villi and infiltration of inflammatory cells between the crypts (Fig. 3).

In fish As toxicity is also a major problem where it has rendered many pathological changes. As_2O_3 has been reported to cause apoptosis of fin cells (Wang *et al.*, 2004), hyperplasia and necrosis of liver (Pedlar *et al.,* 2002), inflammation, edema and fibrosis of gall bladder (Cockell *et al.,* 1991), kidney fibrosis (Kotsanis and Iliopoulou-

Table 1: Clinico-pathological effects caused by arsenic trioxide in various species

Species	Dose	Signs	Lesions	References
Man		Dullness, depression, defecation, salivation, keratosis	Redness of gastric, intestinal and abomasal mucosa, submucosal edema, epithelial necrosis, fluid accumulation	Jun *et al.* (2008)
Buffalo	50 mg/L water	Despair, prostration, loss of weight, weakness, dehydration, anorexia, bloody diarrhea, ruminal inertia, exhaustion, reddish urine, dry dull rough, epilated hair coat and anestrus	Anemia, Congestion and hemorrhage in intestine, liver and in kidneys, dermatosis	Rana *et al.* (2008)
Fish	0.5, 10ppm	Not Reported	Apoptosis of fin cells, fibrosis of kidneys, gall bladder, hepatic vacuolization	Pedlar *et al.* (2002); Wang *et al.* (2004), Saxena and Saxena (2007)
Rat	0.4, 4 and 40ppm	Decrease water, feed intake and growth	Hemorrhage in intestine, Hepatic steatosis, fibrosis, renal tubular necrosis	Nain and Smith, (2012)
	5 & 10 mg/kg b.wt.	Food intake and body weight gain increased	Maternal death, kidney and liver weight decreased, stomach abnormalities (adhesions and eroded areas)	Holson *et al.* (2000)
	10 ppm	Decreased growth	increased levels of As in blood, liver and kidneys	Nandi *et al.* (2006)
		Loss of appetite, increased body temperature, decreased body weight	Ataxia, muscle fasciculation progressing to recumbence.	Dwivedi *et al.* (2011)
Ducklings	100 mg/L of water	Depression, decrease body weight, reduced feed intake, dullness and ruffled feathers	Not Reported	Islam *et al.* (2009)

Georgudaki, 1999), and the generation of various heat shock proteins (Kothary and Candido, 1982). Various morphological changes, as well as increased number of necrotic bodies and vacuolization in hepatocytes of fish has been reported (Sorensen *et al.,* 1985).

Lymphoid organs are also not spared by As toxicity in fish. Saxena and Saxena (2007) reported histopathological lesions in lymphoid organs such as hemorrhages along with congestion and lymphocytic infiltration of liver and kidneys. Yadav and Trivedi (2009) found significantly increased frequency of micronuclei due to As toxicity in fish. The reproductive effects in fishes include disruption of ovarian cell cycles (Wang *et al.,* 2004), inhibition of follicle development, damaging spermatogenesis and degeneration of testes (Shukla and Pandey, 1984).

Nemec *et al.* (1998) reported prominent clinical signs in As intoxicated rabbits as loss of appetite, prostration, constipation and ataxia, whereas, on necropsy there was pale soft liver, molted kidneys, dark area in stomach and congested lungs. In Wistar male rats treated with As trioxide histopathologically, myocardial selling, intestinal edema and lymphocytic infiltration, fibroblastic proliferation and myocardial necrosis in heart were noted (Sherif *et al*., 2005). As toxicity in mice exposed to As containing water at 30, 150 and 300 ppb resulted in histopathological changes that were mild to severe type of necrosis and deteriorating alterations in liver and kidneys, splenocytosis and proliferation of connective tissues (Rubina *et al*., 2008).

Female mice exposed to 51 mg As/kg/day showed decrease and increase in lymphocytes and monocytes, respectively. Non-neoplastic changes were observed in the urinary kidneys and bladder. There was an increase in the vacuolization of urinary bladder. An increase in glomerulonephropathy, nephrocalcinosis and fibrosarcoma of the skin was observed (Gur *et al.*, 1989).

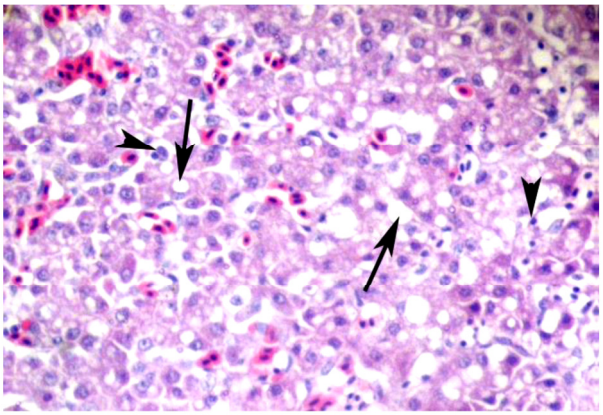

Fig. 1: Liver of As treated broiler chicks showing vacuolation (arrow), congestion and condensed nuclei (arrow head). H & E. 200X (Mashkoor *et al.*, 2013)

Li *et al.* (2010) estimated the oxidative DNA damage and pathologic changes in kidney tissue of mice treated with As_2O_3. Histopathological lesions recorded as cell swelling, tubular dilatation, lymphocytic infiltrations, loss of cell to cell contacts and loss of brush border in the epitheliums of proximal convoluted tubules. As intoxication resulted in the generation of ROS and led to cell injury or necrosis through the ROS signaling pathway. Reduction and vanishing of Bowman's capsule were noted in the glomeruli, glomerular capillaries were dilated and hyperemic and there was mild cellular proliferation detected in the glomeruli. These pathological alterations might be associated to the As-tempted rise in oxidative stress (Chakraborty *et al.*, 2013). The proximal convoluted tubules and podocytes of

Table 2: Clinico-pathological effects caused by sodium arsenate, sodium arsenite and other forms of arsenic in various species

Arsenic type	Species	Dose	Signs	Lesions	References
Sodium arsenate	Goat	25mg/kg	Gastrointestinal and renal disturbance, 100% mortality	Coagulative necrosis in kidneys, liver fibrosis, pneumonia	Biswas *et al.* (2000), Roy *et al.* (2009)
	Rat	0.05ppm, 5ppm	Not Reported	Necrosis and degeneration of bronchiolar epithelium, liver fibrosis	Jadhav *et al.* (2007), Singh *et al.* (2010), Ghatak *et al.* (2011)
	Broiler	0.8 to 6.7 ppm	Decreased body weight, egg production, egg weight, more embryonic mortality	Not Reported	Vodela *et al.* (1997)
		150ppm	Decrease feed intake, low weight gain, increase FCR	Ecchymotic hemorrhages in heart, congestion and hemorrhage in liver, intestine, degenerative spleen	Vodela *et al.* (1997)
	Ducklings	30,100 and 300 mg/kg	Decrease growth, increase mortality, tremors and convulsions	Liver congestion, necrosis and fibrosis, severe degeneration of brain	Camardese *et al.* (1990), Whitworth *et al.* (1991), Hoffman *et al.* (1992)
	Catfish	1 ppm	Not Reported	Wear and tear of Skin, sloughing of the epithelial cells, degeneration of the club cells, mucous cells hyperplasia and hypertrophy, vacuolization of cytoplasm, DNA and RNA contents decreased,	Singh and Banerjee, (2008)
Sodium arsenite	Goats	50 mg/kg b. wt.	GIT disorders and renal insufficiency, 100% mortality,	Hemorrhagic and degenerative necrotic lesions, proliferative pneumonia in lungs, hyperplastic Goiter in thyroid and chronic proliferative lesions of skin, As- residues in all organs and highest in liver.	Biswas *et al.* (2000)
	Rat (male)	100 mg /kg b. wt.	Decreased feed and water intake and body weight gain, increased liver weight	Not Reported	Yu and Beynen, (2001)
	Albino Wister Rats	100 ppm	Not Reported	Hepatomegaly, Splenomegaly,	Jadhav *et al.* (2007)
	Rat		Not Reported	Inflammation of spleen, bladder carcinoma	Kalia *et al*. (2007)
	Mice	200 ppm	Not Reported	Hepatofibrogenesis, liver inflammation, steatosis, and hepatocyte degeneration	Wu *et al*. (2008)
		49 ppm	Not Reported	Increasing the number and size of necro-inflammatory foci, increase in proliferating hepatocytes	Arteel *et al.* (2008)
	Rat	50 ppm	Not Reported	Cytotoxicity, necrosis of the urothelial upper layer, higher cell proliferation and hyperplasia	Suzuki *et al*. (2010)
Arsenic acid	Rabbit	3mg/kg	Anorexia, prostration, constipation, ataxia	Pale liver, molted kidneys, congested lungs	Nemec *et al.* (1998)
Roxarsone	Broiler birds	45.4 mg/kg	Increased chicken growth performance	Increased of As residue in liver had seen. Alter the appearance levels of cell development, immunity and metabolism of energy related genes	Li *et al.* (2011)

Conversions ⇒1 ppm = 1 mg/kg = 1 µg/g, 1 ppm = 1 mg/l = 1 ug /ml = 1000 ug/L= 10^{-6}

Table 3: Immuno-pathological effects caused by As in various species

Arsenic type	Specie	Dose	Effects	References
Sodium arsenite	Rat	0.25 - 2 µM	Impair T-cell activity, cytokines, interferon, decrease antibody response to SRBCs	Qian *et al.* (2010), Yuri *et al.* (2012), Claudie *et al.* (2012)
	Broiler	1-10 Mm	Delayed hypersensitivity, decrease phagocytic activity, cytokines and interferon production	Manoj *et al.* (2008), Subhashree *et al.* (2010)
Arsenic trioxide	Rat		Decreased Neutrophils and macrophages	Rachel *et al.* (2004)
	Mice	50 µg/m^3, 1 mg/m^3	Decrease humoral response	Scott *et al.* (2009)
	Fish	2-10 ppb	Low spleen leukocytes, decrease T and B cells	Debabrata *et al.* (2006), Nayak *et al.* (2007).
Gallium arsenide	Mice	50, 100, 200 g/kg	Decrease production of cytokines, T-cell activity and anti bod response to SRBCs	Sikorski *et al.* (1991)

the Bowman's capsule may be more vulnerable to As-tempted nephrotoxicity due to their anatomical position and high reabsorptive activity (Wang *et al.*, 2014).

In rats intoxication with different doses of As showed that maximum sings were observed in group treated @ 100 ppm AsIII in diet. As induced cytotoxicity and necrosis of the urothelial superficial layer, with increased cell proliferation and hyperplasia (Suzuki *et al*., 2010). Wu et al. (2008) noted inflammation of liver, steatosis (fatty liver), hepatocyte deterioration and fibrosis in sodium arsenate treated mice. Arsenite produced more severe effects than arsenate. It was concluded that chronic inorganic As exposure in mice harvests liver injury and a high fat diet significantly increases As-induced hepatofibrogenesis (Wu *et al.,* 2008). Dietary inclusion of 50 and 100 mg/kg of arsanilic acid resulted in increased egg production and feed

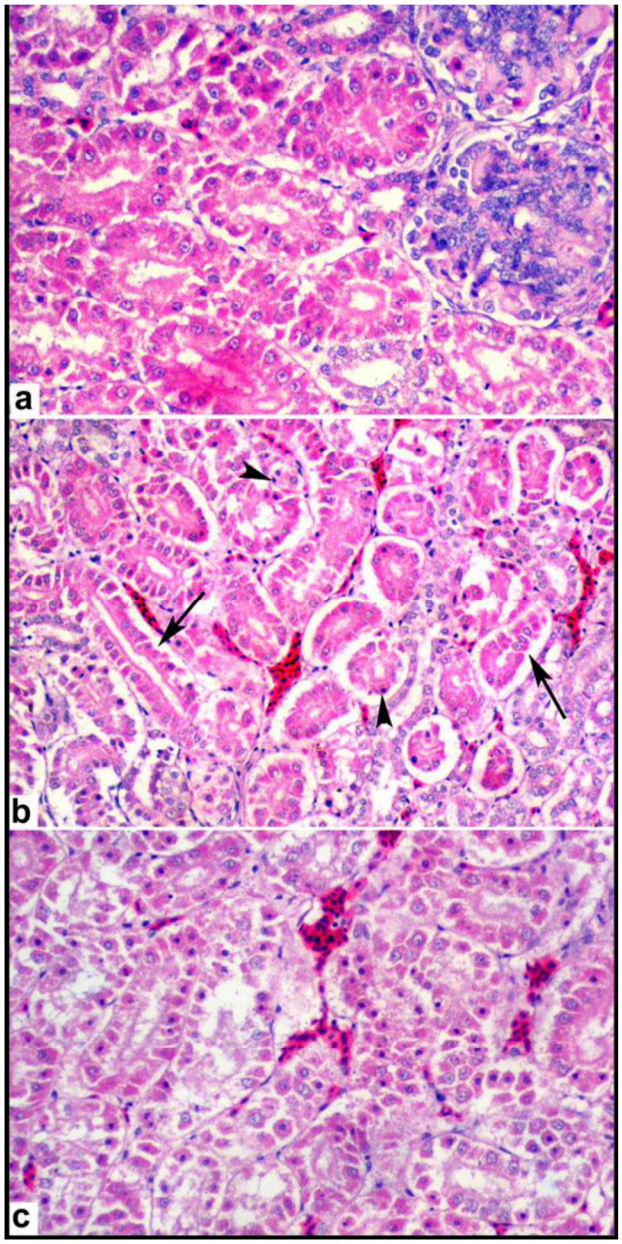

Fig. 2: Histopathology of kidneys. a) Control birds showing normal histological structure, b) As-treated broiler chicken showing congestion, condensed nuclei (arrow heads), epithelial necrosis, sloughing of tubular epithelium from basement membrane (arrows), and c) As+Vit C showing congestion and few condensation nuclei (H and E, X40 for all panels) (Khan *et al.,* 2013)

utilization in Japanese quail with the higher concentration of As in the feces and tissues as compared to control group (Desheng and Niya, 2006). Gross lesions were redness of the gastric, intestinal, and abomasal mucosa, prominent submucosal edema, epithelial necrosis, and massive accumulation of fluids in intestine (Beasley *et al.,* 1994).

Nain and Smith (2012) reported that the subchronic exposure of As in the rats at different doses (0.4, 4.0 and 40.0 ppm) resulted in decrease water and feed intake, whereas, growth rate was not affected. Similarly, Vodela *et al.* (1997) reported that As intake through drinking water resulted in decrease feed intake and weight gain of broiler breeders. Debendranath and Dasgupta (2010) reported the lesions of chronic As toxicity appearing due to drinking of As contaminated ground water included keratosis, bronchitis, chronic obstructive pulmonary edema, non-cirrhotic portal fibrosis, polyneuropathy, non-pitting edema of feet or hands, conjunctiva congestion, weakness and anemia. High concentration of As (200 mg/L) was found to be associated with increased risk of stillbirth, lung cancers, skin and urinary bladder. Lasky *et al.* (2004) reported that As concentration in liver and muscle tissues of poultry birds was highest as compared to other organs.

Camardese *et al.* (1990) fed mallard ducklings on a diet containing 30, 100 or 300 mg/kg (sodium arsenate) for 10 weeks. As was stored considerably in brain and liver fed 100 or 300 mg/kg but did not showed any histopathological lesions. In a similar study, Whitworth *et al.* (1991) reported that the highest concentration caused a significant increase in resting time and abnormal behavior. Ducklings on 300 mg/kg spent more time under the heat lamp. Arsenate had no effect on growth and feeding behavior on a diet containing 200 mg/kg for 4 weeks. However, ducklings grown on diet deficient in protein, the same arsenate dose resulted in significant reduction in survival and growth rate (Hoffman *et al.,* 1992). Stanley *et al.* (1994) reported that 400 mg/kg sodium arsenate has been resulted in significantly decrease in growth rate of ducklings but did not affect survival rate.

Mahaffey *et al.* (1981) reported parenchymal swelling and mild hepatic steatosis, swelling, necrosis and severe fibrosis in periportal areas of affected liver of rat due to As feeding. Sodium arsenate at low (0.05 ppm) and high (5 ppm) doses resulted in necrosis and degeneration of bronchiolar epithelium with emphysema and thickening of alveolar septa of lungs (Singh *et al.,* 2010) and severe liver inflammation, steatosis, fibrosis and hepatocyte degeneration (Wu *et al.,* 2008). However, Kaise *et al.* (1985) reported hemorrhage, convulsions and retching in the intestinal tract of mouse treatment As_2O_3.

In broilers sodium arsenate @150 ppm resulted in decreased feed intake and weight gain with increased feed conversion ratio (FCR). Gross lesions included ecchymotic hemorrhages in heart, congestion and hemorrhages in liver and intestinal mucosa, swollen kidneys and degenerated spleen. Histologically birds showed disruption of cardiac muscle bundles, sinusoidal congestion, focal areas of lymphoid aggregation, disrupted villi, mucosal congestion and infiltration of mononuclear cells in kidney, whereas spleen and bursa of Fabricius revealed depletion of lymphocytes, hemorrhages, and cystic spaces (Vodela *et al.,* 1997; Kalavathi *et al.,* 2011).

Ai-zhi and Zhen-yong (2007) studied the effect of As

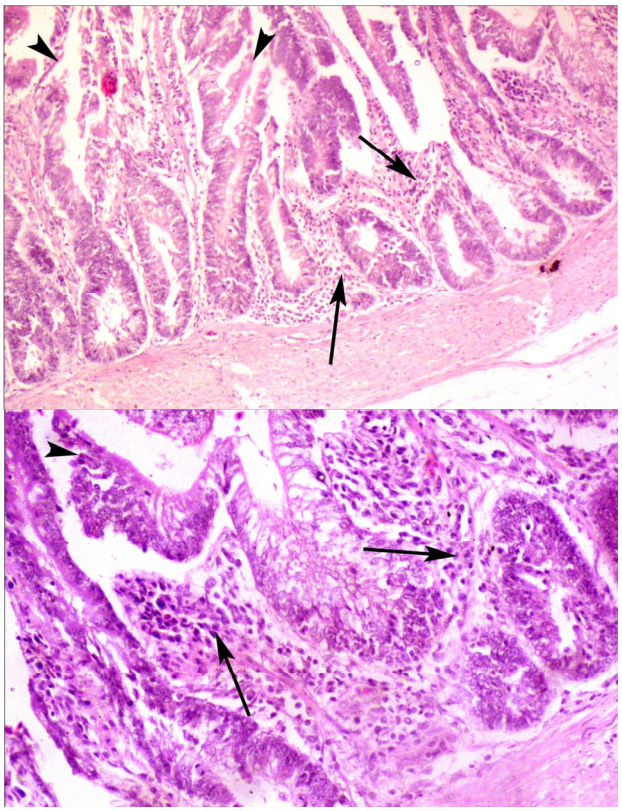

Fig. 3: Photomicrograph of intestines of broiler chicks treated with As showing sloughing of epithelium from the villi (arrow head) and infiltration of inflammatory cells between the crypts (arrow). H & E. upper) 200X and lower) 400X (Sharaf *et al.*, 2013)

product *p*-amino phenylarsenic acid (PAPAA) on body weight and immune organs in chickens. Two hundred and eighty day old male chickens were randomly divided into 7 groups fed with basal diet supplemented with 0, 50,100, 150, 200, 250, 300 mg/kg PAPAA. After 70 days every group was weighed and killed. The main immune organs including spleen, thymus and bursa Fabricius were weighed and their absolute and relative weights were calculated. Conclusively, the groups fed with 150, 200, 250, 300 mg/kg PAPAA had significantly higher body weights and immune organs weights as compared to control group and the group fed with 200 mg/kg had the most significant increase. So PAPAA can enhance chicken's body weights and immune organs weights.

Immuno-pathological effects of As

Arsenic a heavy metal known to cause tissues damage of various systems including the immune system (Table 3). As exposure, alongside of its general toxicity may also affect monocyte, lymphocyte and macrophagic activity in mammals, resulting in immunosuppression (Blakley *et al.,* 1980; Yang and Frenkel, 2002; Duker *et al.,* 2005; Sakurai

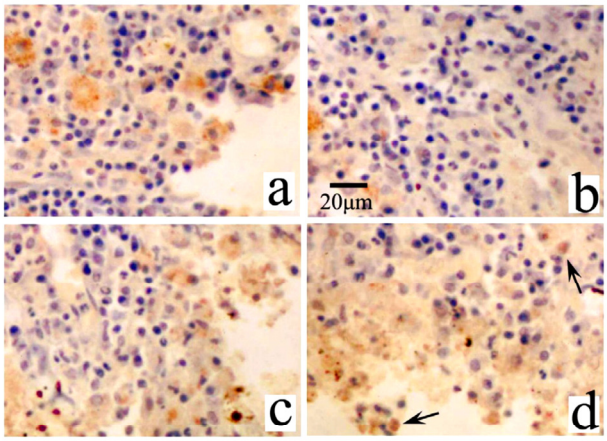

Fig. 4: Down-regulation of survivin expression by arsenic trioxide (ATO). Representative photomicrographs of immunohistochemical staining detected on liver tissue. The arrowhead indicates the representative positive cells. Tumor-peripheral tissue in the control (a) and experimental group (b). Tumor tissue in the control (c) and experimental group (d). Scale bar = 10 μm (Li *et al.*, 2013)

et al., 2006). It acts on mitochondria, where it uncouples mitochondrial oxidative phosphorylation, which in return produces ROS. In published literature, it is well documented that As is immunotoxic (de la Fuente *et al.*, 2002; Chakraborty *et al.*, 2013). It also interferes with splenic macrophages functioning of antigen-presentation, which is then able to alter reaction of antibody-forming cells for IgM and IgG to sheep erythrocytes, and also proliferative response of lymphocytes (Sikorski *et al.*, 1991). Moreover, phagocytic activity of macrophages was also found to be significantly decreased by As exposure in birds (Fairbrother *et al.,* 1994; Vodela *et al.,* 1997). Generally, As can interrupt the glucocorticoid regulation of immune function (Kaltreider *et al.,* 2001). As caused apoptosis which may lead to a reduced immune response in mice (Harrison and McCoy, 2001), rats (Bustamante *et al.,* 1997) and humans (de la Fuente *et al.,* 2002). Furthermore, exposure to As caused the suppression of primary antibody response (Sikorski *et al.,* 1991), reduced macrophage and neutrophil number (Patterson *et al.,* 2004), was more prone to infection (Aranyi *et al.,* 1985), increased death rate due to bacterial infection (Hatch *et al.,* 1985) and decreased chemotactic and phagocytic indices (Sengupta and Bishayi, 2002; Bishayi and Sengupta, 2003).

Arsenic intensified the transforming growth factor-α (TGF-α), granulocyte macrophagic-colony stimulating factor (GM-CSF) and TNF-α in keratinocytes of human (Germolec *et al.,* 1996), and IL-1 and IL-8 in keratinocytes of murine (Yen *et al.,* 1996; Corsini *et al.,* 1999). Moreover, As resulted in the promotion of the expression of receptors (IL-1, IL-6 and IL-7) and inducible nitric oxidase (iNOS) in the epithelial cells of rat liver (Chen *et al.,* 2001). it has also

been shown to decrease the expression of various receptors like IL-2 (Yu *et al.,* 1998), IL-1α, IL-1β, IL-8, IL-12, IL-18, TGF-β1, TGF-β2 and monocyte chemotactic protein-1 (Yang and Frenkel, 2002).

The immune dysfunction in mice treated with arsenite (As^{3+}) resulted in impair T-cell multiplication and production of cytokines in response to subtoxic doses of arsenite in splenocytes of both young and aged mice. Moreover, it also resulted in decreased production of interleukin-2, interleukin-4 and interferon-γ by splenocytes from young mice and IL-10 by splenocytes in aged mice. It was revealed that the production of IL-2 and IL-4 by splenocytes from aged mice was affected by arsenicenite that lead to decrease in immune response (Yuri *et al.,* 2012; Claudie *et al.,* 2012).

Rachel *et al.* (2004) investigated hypersensitivity responses in As-treated mice in the induction and elicitation phases of dermal sensitization. They reported reduction in the number of circulating neutrophils and thioglycollate-induced peritoneal macrophages. The immune cells population and immune responses decreased due to prolonged exposure of sodium arsenite. Acharya *et al.* (2010) investigated the carcinogenetic and immunological effect in As-treated mice. The damaging consequences were assessed by FACS readings that showed specific programmed cell death cascade in lymphocytes. Moreover, neoplastic changes were noted under the influence of As. Qian *et al.* (2010) reported that sodium arsenite had suppressive effect to antibody responses in *in vivo* and *in vitro* studies. Spleen cells were isolated from C57BL/6J wild-type male mice and treated with sodium arsenite. Immunotoxicity assays were used to determine the T-dependent antibody response and antibody response to sheep red blood cells (SRBCs). Spleen cell viability was not changed following 4 days of As treatment, however, the antibody response showed suppression due to As-treatment. From the results of the above studies, it can be extracted that As in one way or the other is immunotoxic and lowers the immunity in the affected individuals.

This interpretation is further substantiated by Scott *et al.* (2009) who reported that immunotoxicity of As_2O_3 in mice resulted in reduction of primary T-dependent antibody response and greater than 70% in humoral immune response towards sheep red blood cells. Sikorski *et al.* (1991) also endorsed such ideas by reporting that GaAs exposure led to decreased capacity of splenic macrophages to process or present the particulate antigen SRBC. In broiler chicks, significantly reduced body weight gain, weight of spleen, thymus and bursa of Fabricius with As-treatment also indicated immunological functions (Manoj *et al.*, 2008). It was further reported that the metalloid significantly depressed the ability of peripheral blood and splenic lymphocytes to proliferate. The delayed type hypersensitivity response was also significantly decreased. The suppression of cellular and humoral immune response has also been reported (Subhashree *et al.*, 2010).

In zebra fish, the toxicity of As from 2 to 10 ppb concentration in drinking water resulted in 50-folds increase in viral load and 17-fold increase in bacterial load in zebra fish. Moreover, bacterial post-As-exposure infection showed at least 2.5 to 4 folds drop in interleukin-1β and tumor necrosis factor-α levels, respectively (Nayak *et al.,* 2007). In another study in catfish, As_2O_3 treatment resulted in significant decrease in splenic leucocyte count while histological studies indicated changes in cellular composition of spleen those led to tissue-specific and time-dependent changes in the function of T and B cells (Debabrata *et al.,* 2006).

As and Carcinogenicity

Other serious concern of As is carcinogenicity (Wadhwa *et al*., 2013). As may alter one or more DNA repair processes. According to Andrew *et al.* (2006), patients exposed to As have different nucleotide deletion repair, which ultimately results in carcinogenesis. Moreover, DMA has been ended in several genotoxic effects, including DNA strands breaks, formation of apyrimidinic and apurinic sites, increase in oxidative stress by oxidation of DNA bases, formation of proteins-DNA cross linkages and chromosomal aberrations (Kitchin, 2001; Coelho *et al.,* 2013; Xie *et al.*, 2014). Clastogenic effects of As have been resulted due to high affinity of As to sulfydryl groups. Not only DMA but roxarsone (3-Nitro-4-hydroxyphenylarsonic acid) also causes mutation and DNA strand breaks (Shen *et al.,* 2014). In male Syrian golden hamsters, arsenic trisulfide and calcium arsenate intoxication resulted pneumonia, metaplastic ossification and emphysema in lungs along with adenoma and malignant tumors (Goran and Nils, 2004).

As mentioned above As toxicity leads to carcinogenicity. In this field, survivin has recently been identified as an inhibitor of apoptosis protein (Hossain *et al.,* 2009; Li *et al.*, 2013) with unclear pathophysiological functioning. Having unique structure, survivin has been reported to be expressed in various cancers and even during developmental stages of embryo (Upadhyaya *et al*., 2007; Hebb *et al.,* 2008). In this way survivin (Fig. 4) might be a new target for the malignant tumors diagnosis (Mita *et al.*, 2008; Hirano *et al.*, 2014). Survivin has also been recently found in the involvement in apoptosis induced by As_2O_3 (Li *et al.,* 2013). So we may anticipate more functions of this protein in future.

In conclusion, As, naturally present in groundwater, air and soil enters in body through diet and drinking water and its absorption takes place mostly through small intestine. In the body, it causes various pathological changes, which are depicted in various forms of clinical signs and lesions. Toxicity signs of As varies from species to species. In chicken causes depression, ataxia, lameness and stunted growth, body weight loss, less feed consumption, loss of appetite, souring of mouth, dullness and neurological disorders. In mammals As causes various signs like dullness, depression, increased frequency of

defecation, excessive salivation and keratosis. As causes both acute and chronic toxicities in a variety of organisms. Toxic effects of inorganic As included denaturation of cellular enzymes, cellular damage through increased reactive oxygen species, oxidative stress, altered gene expression, genotoxicity, carcinogenicity and immunosuppression. As is naturally contaminating ground water of provinces of Sindh and Punjab where at some places its level exceeds (up to 100 µg/L) WHO permissible limits (10 µg/L) and affects over 36 and 20% of population. As it is naturally occurring, therefore, there is dire need to find out some useful chemicals, vitamins, minerals which can ameliorate the toxic effects of As so that productivity of mammals and birds could be increased.

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