



Arsenic exposure induced Histopathological changes in different Tissues of Male Albino rats

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ABSTRACT

Long term Arsenic exposure induced Histopathological changes in different Tissues of Male Albino rats. Normal hepatocytes are observed with prominent nuclei. Cytoplasm, Bile duct, Portal vein and Central vein are normal. Bile duct and clear sinusoidal spaces are observed. Histopathological studies helps in detecting the extent of tissue and organ damage under arsenic stress conditions. Histopathology helps in diagnosing the cytoarchitectural changes occurred in the animal under chemical induced toxic stress. Extent of tissue damage depends upon the degree of exposure, type of toxicant, concentration of toxicant and also varies among different animal models. Studies of Hossain, 2012b showed apoptotic and necrotic cells along with structural alterations, fatty infiltration, hemosiderin granules, cytoplasmic vacuolation and fibrous bodies in heart, liver and intestine. In the present study arsenic treatment for a period of 15, 30 and 45 days showed changes in architecture and altered the functional activity. The test tissues (Liver, Kidney, Testis, Lung, Heart and Small intestine) used in the present study almost showed apoptotic and necrotic changes, inflammatory cells infiltration, cytoplasmic vacuolation and cell death due to toxic stress. The changes in tissues are prominent in 45 days of treatment when compared to 15 and 30 days.

Keywords: Histopathological changes, Male Albino rats, Arsenic, Liver, Kidney, Testis, Heart, small intestine, Lung.

INTRODUCTION

Arsenic is widely used in homeopathic preparations, Ayurvedic medicines and haematological malignancies in herbal medicines upto some extent, but usage beyond the permissible levels might promote tissue and organ damage. Arsenic administration to rats was associated with histopathological changes in the form of organ and tissues toxicity in the test groups. Anthropogenic activities due to agricultural practices,

urbanization and industrialization increased release of chemicals and toxicants largely into the environment (Dautremepuits *et al.*, 2004). Arsenic gets deposited mostly in the liver, kidney, lungs, hair and nails after ingestion, inorganic arsenic appears rapidly in the circulation that binds primarily to haemoglobin and exerts many histopathological and structural changes (Bradbury and Gordon, 1990).

Heavy metals including arsenic, chromium, cadmium, manganese and lead when taken beyond the permissible limit according to the WHO and FAO showed disparities in histo-architecture of vital organs. The term 'heavy metal' refers to the metal or metalloid that has relative atomic density greater than 4g/cm^3 or 5g/cm^3 and is toxic even at very low concentrations (Lenntech, 2004) and gets distributed in different tissues depending upon mode of exposure. Arsenic is a toxic metalloid contaminant found in two forms soluble arsenate or arsenite that is well absorbed upto 80% in animals due to exposure by oral route. Absorption occurs by passive diffusion and occurs throughout the body (ATSDR, 1989). Maximum arsenic was found in liver as it is the main organ that helps in arsenic metabolism and promote histological changes (Vahter and Marafanate, 1987).

The liver is most susceptible organ to heavy metal toxicity and it forms a variety of toxicants since it is involved in detoxification and biotransformation. Kidneys help to partially regulate xenobiotic metabolism, metabolic waste excretion from blood, and water and salt equilibrium. Arsenic is a well-known pulmonary irritant in smelter workers exposed to arsenic pollution due to inhalation and accidental ingestion of insecticides and pesticides. Collapse of sinusoidal spaces, hepatocytes disruption and vacuolization, nuclear degeneration, presence of pyknotic nuclei, necrosis and hyper-vacuolization, blood vessel rupturing and hemorrhage is observed in liver (Kesavulu, 2021).

Control liver showed normal hexagonal lobules, vascular congestion in sinusoids, infiltration of mononuclear cells and ballooning degeneration is observed under arsenic stress (Klibet *et al.*, 2016). The histopathological study of hepatic cells of arsenic group rats was characterized by severe steatosis, infiltration of cytoplasm and necrosis which are characteristics of the severe pathological lesion (Owoade *et al.*, 2022). Dilation and vascular congestion in sinusoids,

infiltration of mononuclear cells and cells necrosis is observed in liver under arsenic stress (Danyelle & Kenneth, 2003). Kupffer cells activation, cytoplasmic degeneration, dilatation and hepatic sinusoids congestion, karyomegaly, Leukocytes infiltration in sinusoids, and hepatocytes vacuolar degeneration is observed under arsenic toxicity (Korany *et al.*, 2019).

Glomeruli of kidney showed normal appearance with a regular Bowman's space under normal conditions but arsenic induced toxic insult promoted tubular degeneration, intra tubular degeneration, atrophy of glomeruli with increased Bowman's space, reduction in the glomerular filtration rate, obstruction to urine elimination and sclerosis (Noman *et al.*, 2015; Salahudin *et al.*, 2021). Kidneys showed congestion of vessels, peritubular infiltration by inflammatory cells and mild tubular necrosis under the toxicity of sodium arsenite.

Reduction in the glomerular size, mild vascular congestion, enlarged periglomerular space, mononuclear cells inflammation and haemorrhagic foci in connective tissue at low doses of arsenic under high dose of arsenic kidney showed loss of brush border in PCT cells, cloudy swelling, cells loughing and desquamation along with haemorrhagic foci and mononuclear infiltrate (Gupte *et al.*, 2020).

Testicular architecture contains seminiferous tubules in lumen and Sertoli cells are seen within the lumen, spermatogonial cells are seen to differentiate from primary, secondary and tertiary spermatocytes in a progressive order. Lumen and interstitial space contains interstitial cells (Akinboro *et al.*, 2022). Toxicity induced by heavy metals promotes reproductive changes by impairing spermatogenesis, atrophy of Leydig cells, seminiferous tubules dysfunction (Sarkar *et al.*, 2008). Decreased male organ weight, serum testosterone levels, gonadal dysfunction by decreasing testosterone biosynthesis, sperm number, viability, and motility gets altered under arsenic toxicity (Neves, 2022).

Under the disruption of endocrine activity hypospadias, prostate, testicular cancer and crypt orchidism may occur. At cell differentiation stages spermatogenesis gets affected and toxicant accumulation in different reproductive organs such as prostate, epididymis and seminal vesicles reduces the progressive sperm motility. Disturbances in male reproductive hormones testosterone, Gonadotropin-

Releasing Hormone, Follicle-Stimulating Hormone and Luteinizing Hormone are observed under arsenic toxicity (Renu *et al.*, 2018; Ahmad *et al.*, 2021). Reduction in sperm count, sperm DNA damage, cessation of spermatogenesis and impaired testicular steroidogenesis are observed.

Heart tissue showed degenerative changes in tubular cells, tubular necrosis, degeneration of hepatocytes, severe haemorrhage and formation of Kupffer cells nuclei (Nozohour and Amin, 2019). Sodium arsenite showed infiltration of mononuclear inflammatory cell, mildly congested blood vessels, mild myocardial edema and degeneration of muscle fibers in heart tissue along with mild to severe myokinesis, dilated heart, coronary vessel congestion and necrosis of myocardial cells as well as loss of cardiac architecture (Das *et al.*, 2021). Myocardial mitochondria dysfunction promotes autophagy and decreasing mitochondrial respiration and implicated in the pathogenesis of cardiovascular disease (Siwen *et al.*, 2019).

The myocardial tissue structure was disordered, myocytes were swollen, and cell membranes were damaged (Liang *et al.*, 2020). Hypertension, is a heart disease, atherosclerosis with increased morbidity and mortality from cardiovascular disease may occur under arsenic toxicity (States *et al.*, 2009). Myocardial injury, cardiac arrhythmias and cardiomyopathy are associated with reduction in the antioxidants to arsenic toxicity (Muthumani and Prabu, 2014). Cardiac repolarization resulting in a fatal arrhythmia and the effect of arsenic promotes more cardiac disruptions including coronary heart disease and peripheral vascular disease in humans. Organ dysfunction correlates with the imbalance between ROS and antioxidants status and results in the damage of biological system (Nozohour and Amin, 2019).

The main exposure to arsenic occurs by drinking contaminated water resulting in chronic cough, chronic bronchitis, obstructive lung diseases and bronchiectasis (Ramsey *et al.*, 2013b). Bronchiolar epithelium showed histopathological changes in architecture with declined alveolar space, increased alveolar macrophages, and alveolar hyperplasia, infiltration of the parenchyma by inflammatory cells, fragmented genomic DNA in lung tissue which indicates oxidative stress mediated by genotoxicity (Kaushal *et al.*, 2017). Arsenic treated lung showed

alveolar macrophages enhancement, peri-bronchiolar infiltration, alveolar hyperplasia bronchiolar epithelium degeneration, reduced alveolar space with conjunction of alveolar duct and inflammatory responses (Kaushal *et al.*, 2017; Adeyi *et al.*, 2021).

Arsenic induced lung tissue gives rise to three major types of cancer, namely small cell lung cancer (SCLC), squamous cell carcinoma (SqCC), and adenocarcinoma (AC). SqCC and AC belongs to the group of non-small cell lung cancers (NSCLC) (Taeger *et al.*, 2009). Decreased lung function, respiratory symptoms and signs, increased rate of pneumonia, tuberculosis, bronchiectasis and chronic obstructive pulmonary disease (COPD) are reported in rat upon exposure to sodium arsenite and characterized by chronic bacterial lung infection (Henderson *et al.*, 2017).

Small intestine is the primary site of digestion and nutrients where toxicants get absorbed from the lumen and deliver into the blood stream and causes ill effects to the body. Epithelium of intestine is organized into crypt/villus and differentiated into four main types of cells - enterocytes, enteroendocrine (EEC), goblet, and Paneth cells (Kellett *et al.*, 2022). To protect from injury or toxicants intestine has several mechanisms that secrete mucins from goblet cells and provide a mucosal barrier for the villus epithelium (Kellett, 2020), intestinal epithelium is the first barrier that arsenic must cross to be absorbed into the bloodstream. Arsenic high concentrations in the feces might be moderately associated with the intestinal reabsorption (Wang *et al.*, 2020).

Control intestine tissues show well-defined mucosa, submucosa, goblet cells and serosa. Mucosal and submucosal layer of the intestine show hemorrhage and blood congestion in the blood vessels, reduced villus lengths, necrosis and disintegration or atrophied intestinal villi are observed in the toxic insult. Intestinal stromal cells, pericryptal lamina propria, intestinal trophocytes and telocytes get altered under arsenic exposure and impair intestinal stem cell differentiation (Kellett *et al.*, 2022). Inflammatory factors IL-6, TNF- α , and IL-1 β in the small intestine of rat get up regulated and Myeloperoxidase (MPO) expression gets enhanced under arsenic induced toxic stress (Zhao *et al.*, 2023).

Hence in the present study we paved a way to determine the toxic impact of sodium arsenite in

different tissues including Liver, Kidney, Testis, Lung, Heart and Small intestine for a period of 15, 30 and 45 days and evaluated the histopathological studies to determine the extent of organ damage.

MATERIAL AND METHODS

The test tissues Liver, Kidney, Lung, Heart, Small intestine and Testis were excised, washed with ice cold saline and a portion of tissue fixed in 5 % formalin. Tissues were embedded in paraffin wax, processed tissues were sectioned (6 μ m) and taken on the clean glass slides and stained with haematoxylin and eosin, and observed under the light microscope at 400x magnifications. Histopathological examination of tissues was followed according to Humanson (1972).

Light Microscopy:

Different test tissues were isolated from the control rats and experimental rats. Gently rinse the tissues with physiological saline solution (0.9% NaCl) in order to remove blood particles and debris adhered to the tissue samples. Then fix the samples in 5% formalin for about 24 hours. Remove the fixative by washing thoroughly with running tap water for overnight. Dehydrate the tissues through a graded series of alcohol, and cleared in methyl benzoate, and embedded in paraffin wax. Cut sections at 6 μ m thicknesses and stained with Harris hematoxylin (Harris, 1900) and counter stained with eosin dissolved in 95% alcohol. After dehydrating and clearing the sections, they were mounted in Canada balsam and made ready for observation under the microscope at 400x magnifications.

VALIDITY OF EXPERIMENTAL PROCEDURE:

General:

For all the enzyme studies in the present study, the assays were standardized by conducting preliminary test to determine the optimal pH, temperature, enzyme and substrate concentration and these optimal conditions were subsequently followed for each enzyme assay.

Aliquots for assay:

For the test, aliquots were chosen so that the beginning rates were as close to the actual values as possible, while still yielding enough product to fall within a practical range for spectrophotometric measurement.

Enzyme units:

The tissue soluble protein content in the homogenates / supernatants (enzyme source) was estimated using folin phenol reagent (Lowry *et al.*, 1951) and used for expression of enzyme activity. Enzyme activities were expressed in standard units, i.e., μ moles of product formed or substrate cleaved per milligram protein/hr.

Substrate requirements:

All the enzyme activity levels were determined at saturating substrate concentrations i.e., in zero order kinetics.

Lambert Beer Law:

Spectrophotometric techniques, which measure the optical densities (absorbance) of the resultant colored complexes in relation to the reaction product concentration, were used to measure nearly all of the reaction products. Every estimation between the substance's concentration (product or substrate) and the optical density of the enzymes was computed using standard graphs.

Enzyme nomenclature

The nomenclature of the enzymes used in the present context was according to the report of enzyme commission "International Union of Biochemistry (IUB)".

STATISTICAL ANALYSIS:

Subject the data to statistical analysis such as mean, standard deviation (SD), and analysis of variance (ANOVA) using standard statistical software, Statistical Package for Social Sciences (SPSS; version 16). All values are expressed as Mean $\pm$ SD of six individual observations.

+ and - percent increase and decrease respectively over control.

a- $p < 0.001$,

b- $p < 0.01$,

a. $p < 0.05$ indicates the level of significance.

b. Non significant changes

RESULTS:

Liver Histopathology

Fig 6.1: Control Liver

Normal hepatocytes are observed with prominent nuclei. Cytoplasm, Bile duct, Portal vein and Central vein are normal. Bile duct and clear sinusoidal spaces are observed.

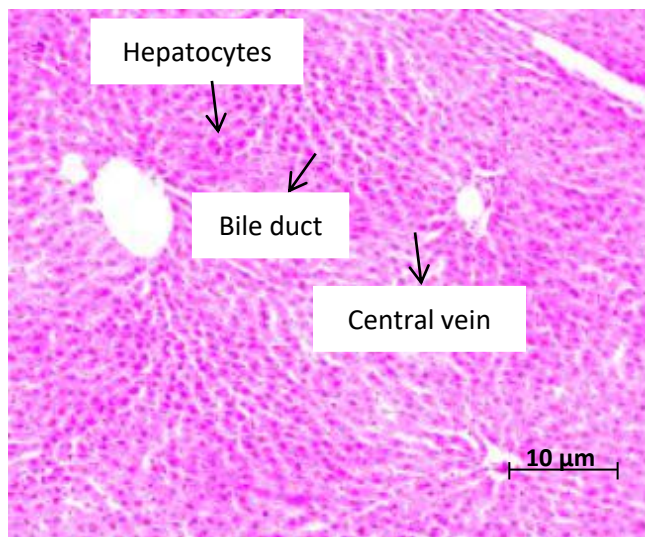


Figure 6.1: Control Liver

Normal hepatocytes are observed with prominent nuclei. Cytoplasm, Bile duct, Portal vein and Central vein are normal. Bile duct and clear sinusoidal spaces are observed. (H & E 10x40X)

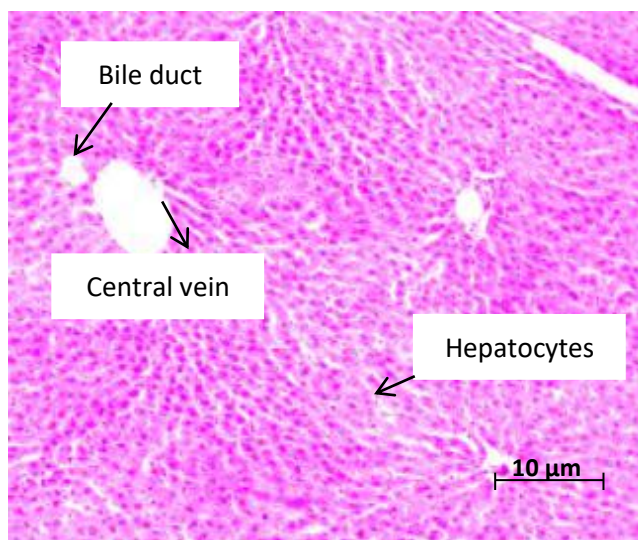


Figure 6.2: Arsenic Liver 15 days

Hepatocytes are slightly enlarged, and central vein showed slight enlargement. Infiltrates are not observed. Cytoplasm is also normal and no haemorrhages are seen. Sinusoidal spaces are observed. (H & E 10x40X)

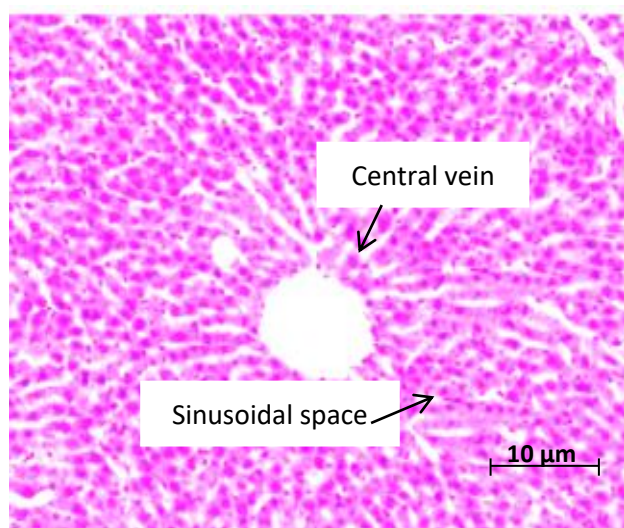


Figure 6.3: Arsenic Liver 30 days

Central vein is enlarged, nucleus moved to peripheral and slight fragmentation is seen, bile duct showed hyperplasia. Sinusoidal spaces are dilated. Cytoplasm is foamy and slight degree of vacuolization is observed. (H & E 10x40X)

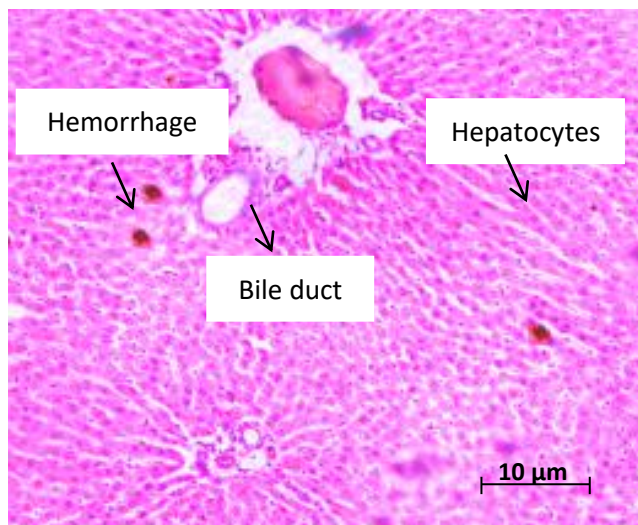


Figure 6.4: Arsenic Liver 45 days

Central vein enlarged and nuclear fragmentation is seen. Haemorrhage is seen and cytoplasm is foamy. Sinusoidal spaces are enlarged. Bile duct is conspicuous and showed slight congestion. (H & E 10x40X)

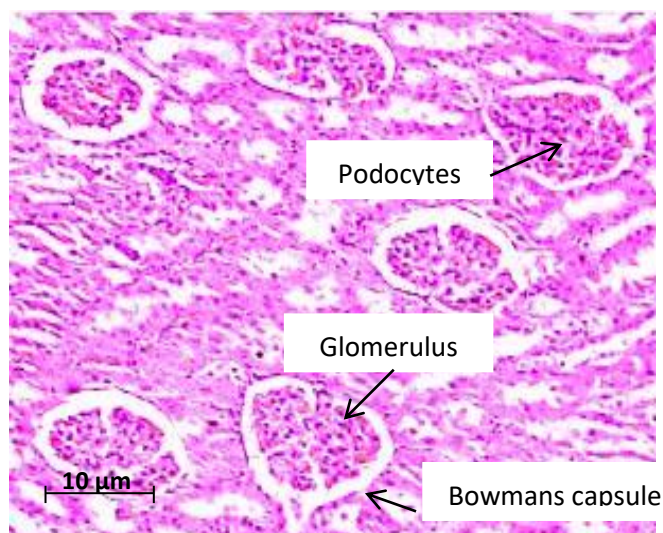


Figure 6.5: Control Kidney

Renal corpuscle is normal with prominent Glomerulus and Bowman's capsule. Collecting tubules are normal without any histopathological changes. Epithelium is with podocytes and capillaries are filled with many blood vessels (H & E 10x40X)

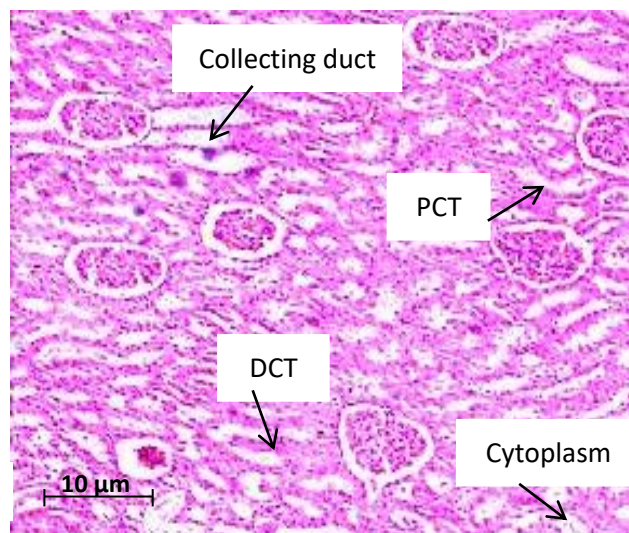


Figure 6.6: Arsenic Kidney 15 days

Renal corpuscle is normal with slight swelling of glomerulus, hemorrhages in glomerulus tufts, pale cytoplasm due to vacuolization, No edema is observed in Proximal and distal convoluted tubules. (H & E 10x40X)

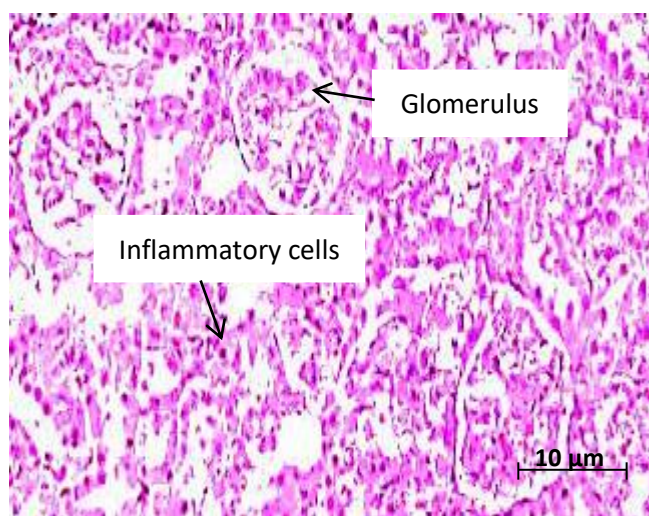


Figure 6.7: Arsenic Kidney 30 days

Fatty degenerative changes and cell edema, are observed. Intrinsic lesions within glomeruli, necrotic changes in glomerulus, podocytes are damaged, collecting duct loses its histology. (H & E 10x40X)

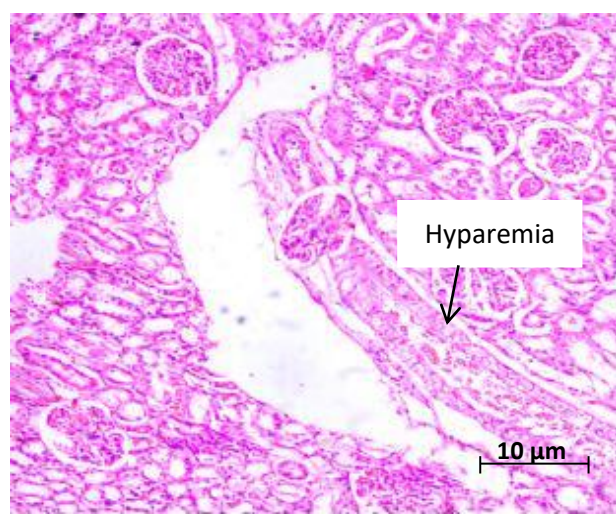


Figure 6.8: Arsenic Kidney 45 days

Tissue necrosis is high, fatty degenerative changes and hypaemia is observed. Renal corpuscle lost its histology with ruptured glomerulus and distorted Bowman's capsule. (H & E 10x40X)

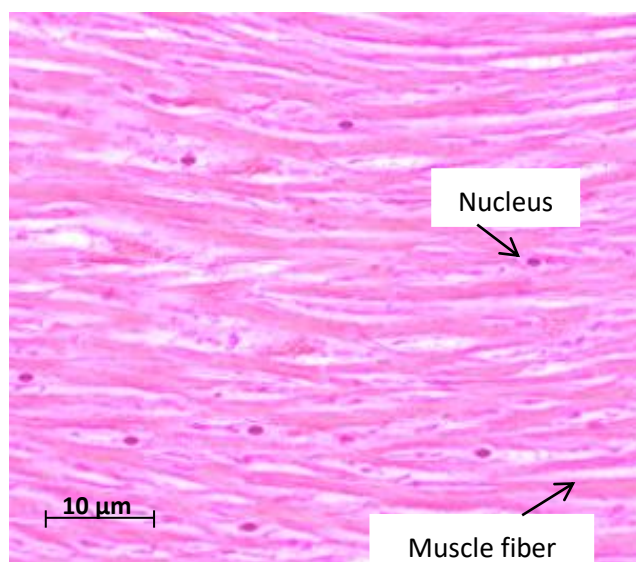


Figure 6.9: Control Heart

Cardiac muscle is prominent with actin and myosin filaments arranged in repeated units called sarcomeres. Intercalated discs are prominent. Nucleus is centrally placed and Lipofuscin granules may be seen near the nuclei.(H & E 10x40X)

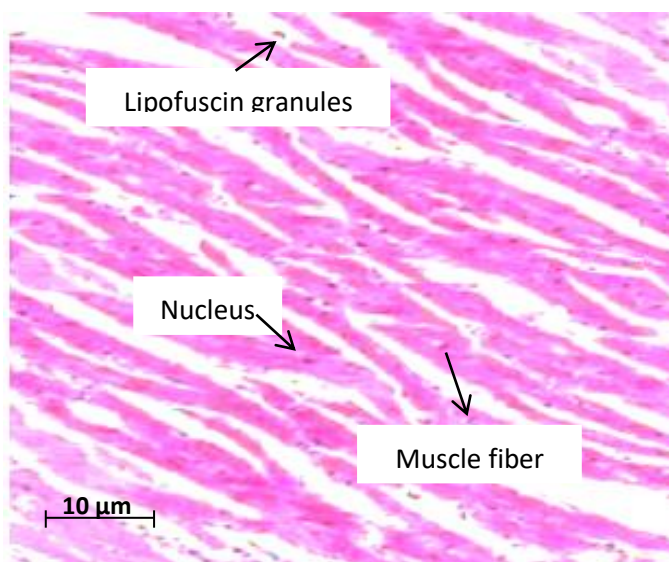


Figure 6.10: Arsenic Heart 15 days

Congestion of inter muscular bundles and disruption of myocardial fibrils. Nucleus is centrally placed. Lipofuscin granules are observed near the nuclei.(H & E 10x40X)

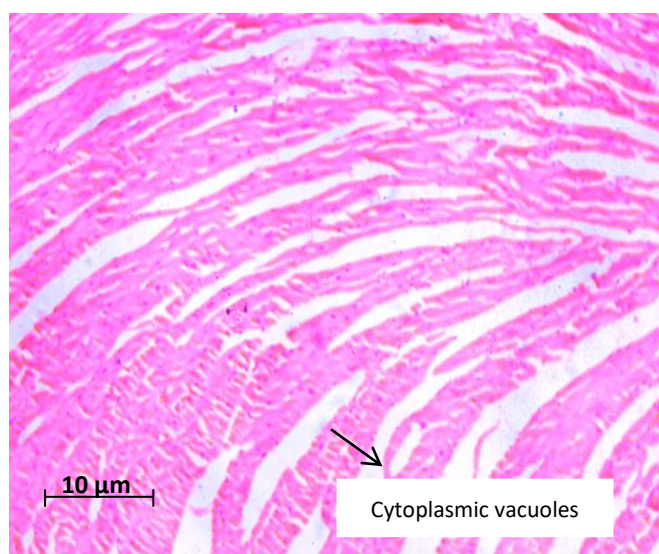


Figure 6.11: Arsenic Heart 30 days

Myocytes are damaged and their architecture changed with loss of cellular organization, inflammatory infiltration is observed, nucleus is disrupted.(H & E 10x40X)

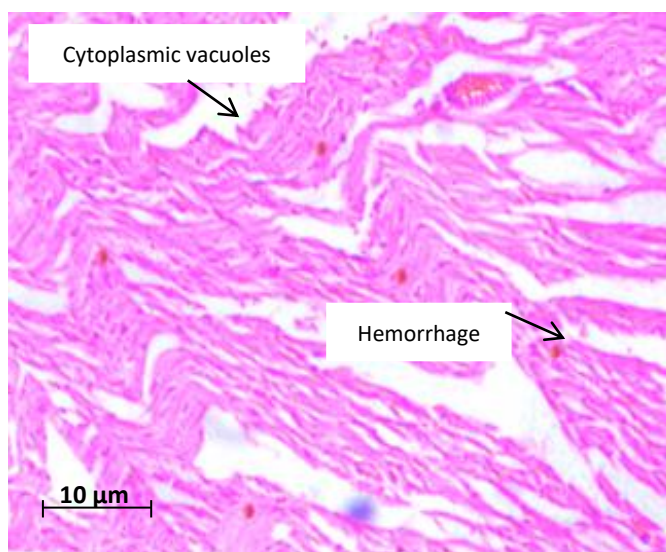


Figure 6.12: Arsenic Heart 45 days

Myocytes damaged heavily and much congestion is observed, myocardial fibers with cytoplasmic vacuoles are seen and slight haemorrhage is observed with disrupted nuclei. (H & E 10x40X)

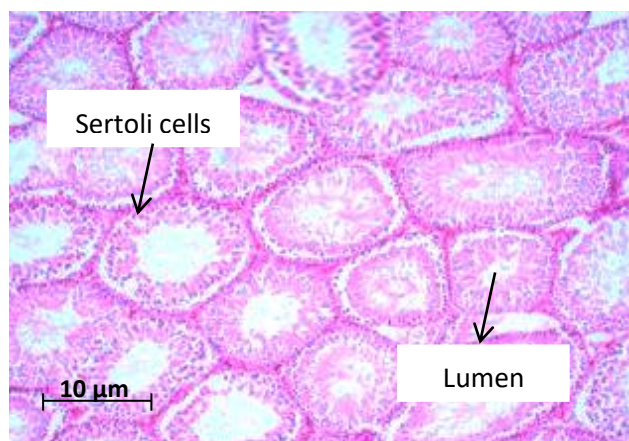


Figure 6.13: Control Testis

Control rat Testis showed normal Seminiferous tubules with prominent lumen and clear spermatids, interstitial space with leydig cells, spermatozoa and sertoli cells. (H & E 10x40X)

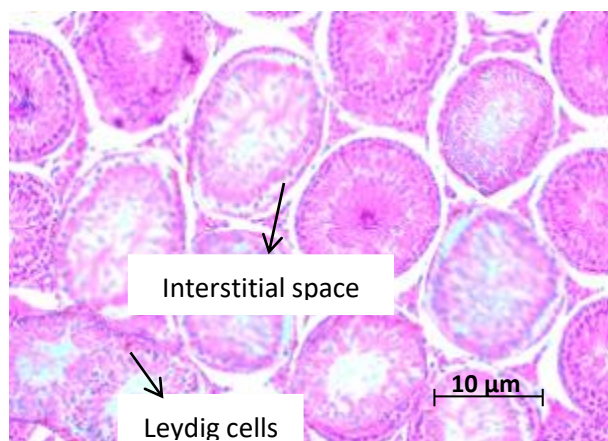


Figure 6.14: Arsenic Testis 15 days

Seminiferous tubules do not show any histopathological changes. Interstitial space increased slightly between seminiferous tubules. Sertoli cells and Leydig cells are normal. (H & E 10x40X)

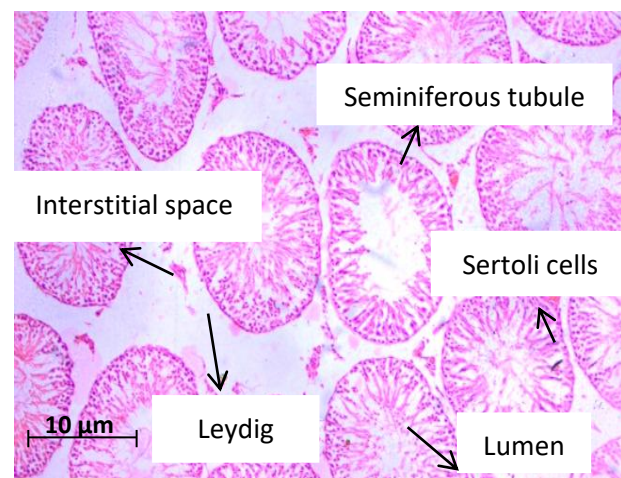


Figure 6.15: Arsenic Testis 30 days

Degenerated seminiferous tubules with changes in histology, scattered Sertoli cells atrophied leydig cells, Interstitial space increased, cytoplasmic vacuolization and nuclear fragmentation of spermatids is observed. (H & E 10x40X)

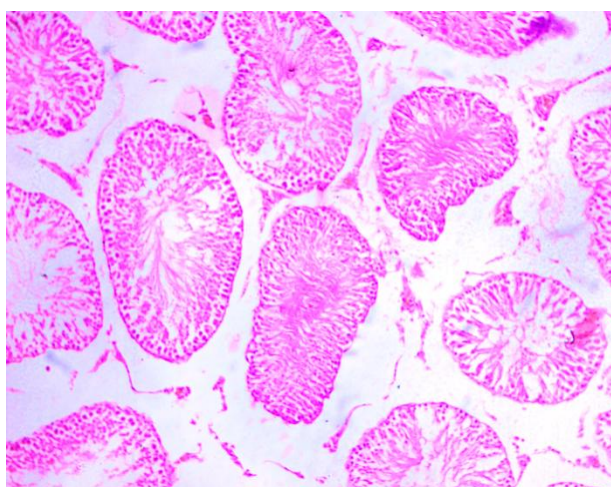


Figure 6.16: Arsenic Testis 45 days

Seminiferous tubules are shrunk with congested Lumen space, Sertoli cells got scattered, withered leydig cells with compact germinal epithelium, interstitial space has enlarged, nuclear fragmentation of spermatids is observed. (H & E 10x40X)

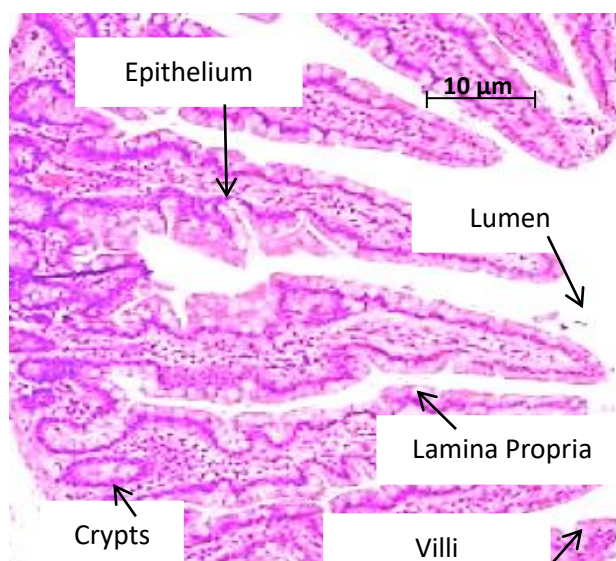


Figure 6.17: Small intestine Control

Mucosa of Small intestine is normal and the columnar epithelial cells are normal in histology with repeated patterns of villi. The Lamina propria is underneath the epithelium. (H & E 10x40X)

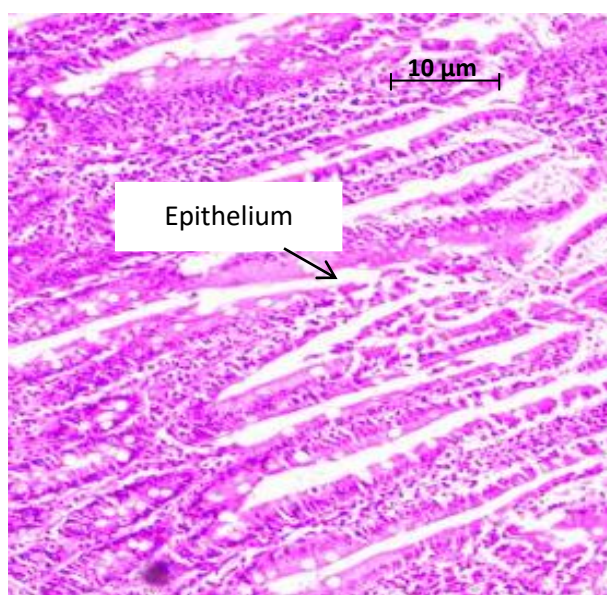


Figure 6.18: Arsenic Small intestine 15 days

Crypts are normal but sloughing of the epithelium from the villi is observed. Inflammatory cells are seen in between the crypts. Space between the villi is clear and do not show any infiltrates. (H & E 10x40X)

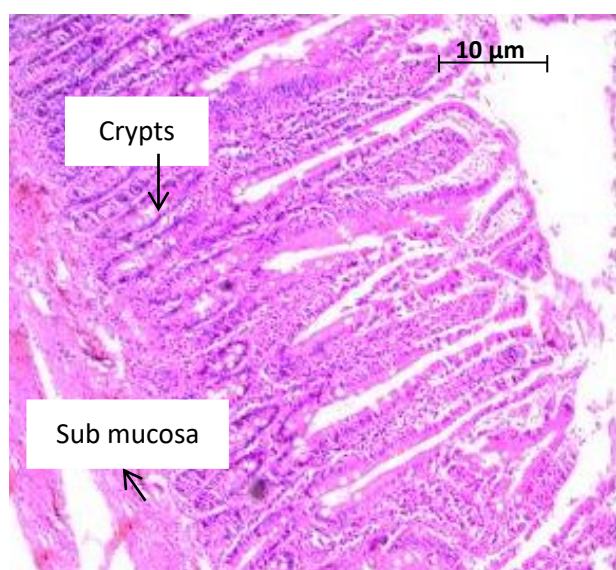


Figure 6.19: Arsenic Small intestine 30 days

Aggregation of inflammatory cells in the submucosa. Cytoplasmic vacuolization is observed. Infiltration of inflammatory cells between the crypts is observed. Luminal space is unclear with tissue coagulation. (H & E 10x40X)

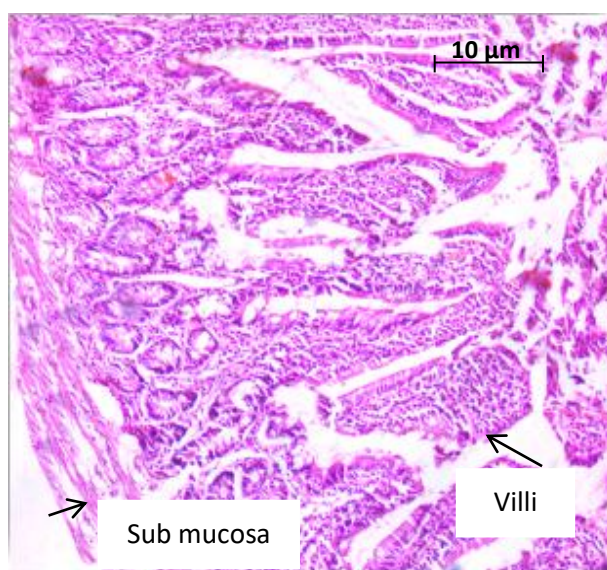


Figure 6.20: Arsenic Small intestine 45 days

Degenerative changes are observed in the Intestinal Mucosa and Submucosa. Coagulation of tissue is seen in the luminal space. Villi lost its histopathology and epithelial sloughing from the villi increased and got damaged. (H & E 10x40X)

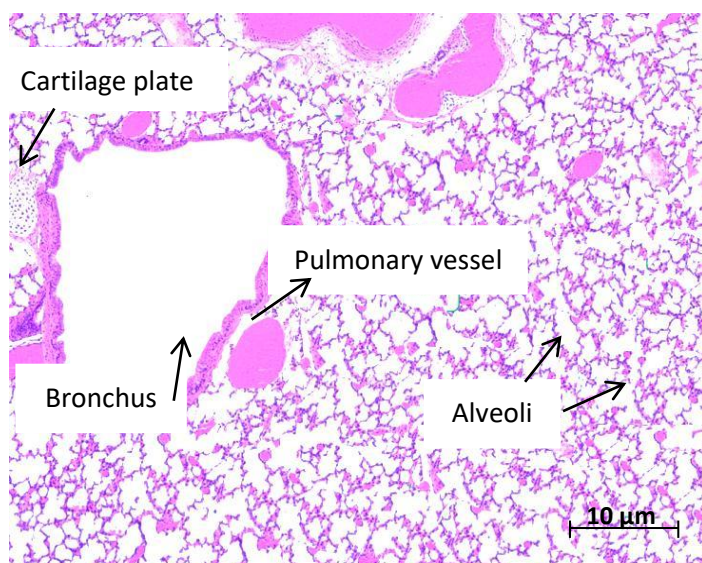


Figure 6.21: Lung Control

Respiratory system showed normal alveolar sac and alveoli with cuboidal cells. Bronchus is clear in shape and surrounded by epithelium. Control lung showed clear pulmonary vessel and cartilage plate.
(H & E 10x40X)

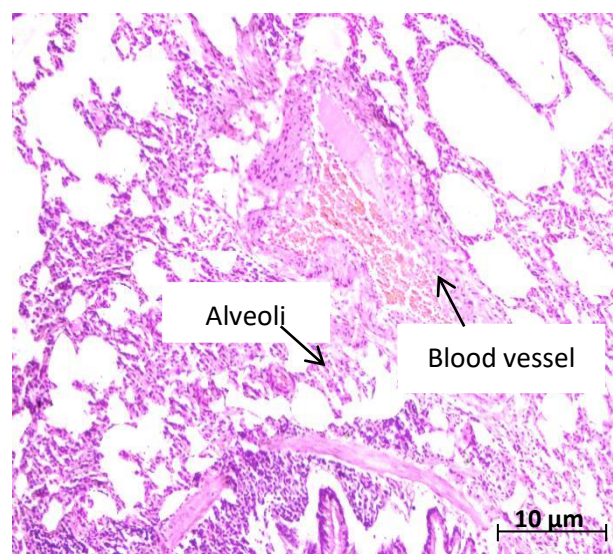


Figure 6.22: Arsenic Lung 15 days

Mild alveolar fibrosis is observable and septa of alveoli showed thickening. Blood capillaries showed dilation and slight haemorrhage is observed. Bronchiole and pulmonary vessel are normal. (H & E 10x40X)

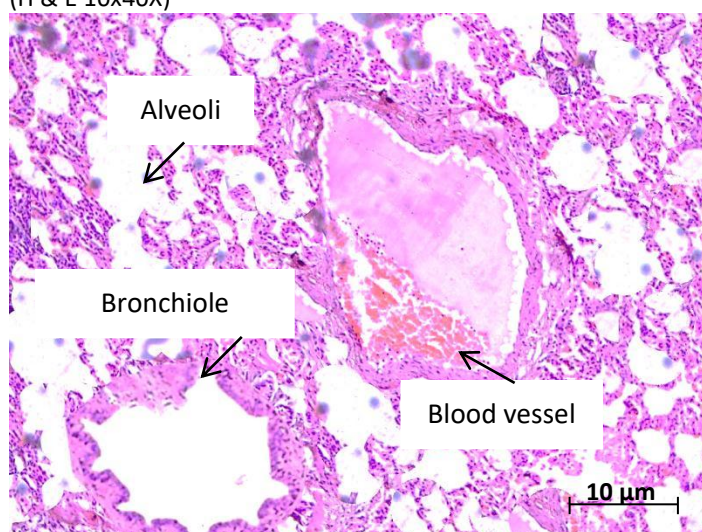


Figure 6.23: Arsenic Lung 30 days

Alveolar wall with few numbers of inflammatory cells. Hyperplasia is observable. Decline in alveolar number and thickening of alveolar septa by mononuclear inflammatory cells infiltration. Bronchiole showed slight damage. (H & E 10x40X)

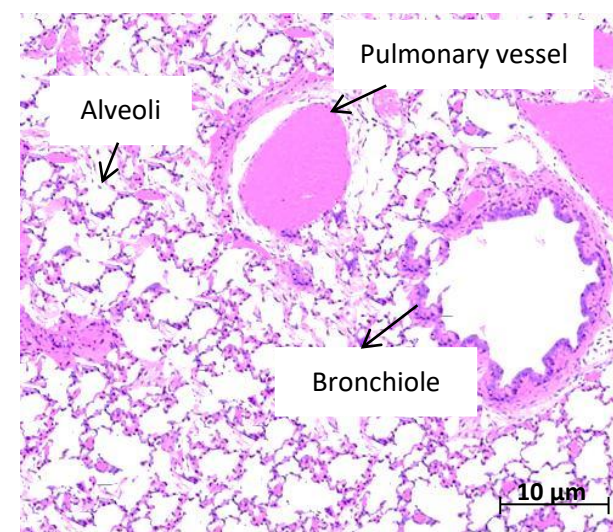


Figure 6.24: Arsenic Lung 45 days

Pulmonary vessel showed slight swelling, Mononuclear inflammatory cells is observed. Alveoli decreased and slight thickening of alveolar wall, Bronchiole and its epithelium got damaged. (H & E 10x40X)

Fig 6.2: Arsenic Liver 15 days

Hepatocytes are slightly enlarged, and the central vein showed slight enlargement. Infiltrates are not observed. Cytoplasm is also normal and no haemorrhages are seen. Sinusoidal spaces are slightly expanded.

Fig 6.3: Arsenic Liver 30 days

The Central vein is enlarged, nucleus moved to peripheral and slight fragmentation is seen. the bile duct showed hyperplasia. Sinusoidal spaces are dilated. Cytoplasm is foamy and a slight degree of vacuolization is observed

Fig 6.4: Arsenic Liver 45 days

The Central vein is enlarged and nuclear fragmentation is seen. Haemorrhage is seen and cytoplasm is foamy. Sinusoidal spaces are enlarged. Bile duct is conspicuous and showed slight congestion. Degenerative changes in hepatocytes and central vein is observed.

Kidney Histopathology

Fig 6.5: Control Kidney

Renal corpuscle is normal with a prominent Glomerulus and Bowman's capsule or renal spaces. Collecting tubules are normal without any histopathological changes. The Epithelium is with podocytes and capillaries are filled with many blood vessels.

Fig 6.6: Arsenic Kidney 15 days

The Renal corpuscle is normal with slight swelling or expansion of the glomerulus, hemorrhages in glomerulus tufts, pale cytoplasm due to vacuolization, No edema is observed in Proximal and distal convoluted tubules, moderate fatty degenerative changes in tubules.

Fig 6.7: Arsenic Kidney 30 days

Fatty degenerative changes and cell edema, are observed. Intrinsic lesions with in glomeruli, necrotic changes in glomerulus, proximal tubular congestion, podocytes are damaged, collecting duct loses its histology, Interstitial fibrosis and nephropathy is observed.

Fig 6.8: Arsenic Kidney 45 days

Tissue necrosis is high, cytoplasmic vacuolation, fatty degenerative changes, brush borders of convoluted tubules were deciliated and hypereimia is observed. The Renal corpuscle lost its histology with a ruptured glomerulus and a distorted Bowman's capsule due to shrinkage of glomerular cells.

Heart Histopathology

Fig 6.9: Control Heart

Cardiac muscle is prominent with actin and myosin filaments arranged in repeated units called sarcomeres. Intercalated discs are prominent. The Nucleus is centrally placed and Lipofuscin granules may be seen near the nuclei.

Fig 6.10: Arsenic Heart 15 days

Congestion of inter muscular bundles and disruption of myocardial fibrils. The Nucleus is centrally placed. Lipofuscin granules are observed near the nuclei.

Fig 6.11: Arsenic Heart 30 days

Myocytes are damaged and their architecture changed with loss of cellular organization, inflammatory infiltration is observed, the nucleus is disrupted.

Fig 6.12: Arsenic Heart 45 days

Myocytes are damaged heavily and much congestion is observed, myocardial fibers with cytoplasmic vacuoles are seen and slight haemorrhage is observed with disrupted nuclei

Testis Histopathology

Fig 6.13: Control Testis

The testis of the control rat displayed typical seminiferous tubules with a clear lumen and spermatids, as well as an interstitial area containing Leydig cells, spermatozoa, and Sertoli cells.

Fig 6.14: Arsenic Testis 15 days

Seminiferous tubules do not show any histopathological changes. Interstitial space increased slightly between seminiferous tubules. Sertoli cells and Leydig cells are normal.

Fig 6.15: Arsenic Testis 30 days

Degenerated seminiferous tubules with changes in histology, scattered Sertoli cells atrophied Leydig cells, Interstitial space increased, cytoplasmic vacuolization and nuclear fragmentation of spermatids is observed.

Fig 6.16: Arsenic Testis 45 days

Seminiferous tubules are shrunk with congested lumen space, Sertoli cells got scattered, with red Leydig cells with compact germinal epithelium, interstitial space has enlarged, nuclear fragmentation of spermatids is observed.

Small intestine Histopathology

Fig 6.17: Small intestine Control

Mucosa of Small intestine is normal and the columnar epithelial cells are normal in histology with repeated patterns of villi. The lamina propria is underneath the epithelium.

Fig 6.18: Arsenic Small intestine 15 days

Crypts are normal but sloughing of the epithelium from the villi is observed. Inflammatory cells are seen in between the crypts. Space between the villi is clear and does not show any infiltrates.

Fig 6.19: Arsenic Small intestine 30 days

Aggregation of inflammatory cells in the submucosa. Cytoplasmic vacuolization is observed. Infiltration of inflammatory cells between the crypts is observed. Luminal space is unclear with tissue coagulation.

Fig 6.20: Arsenic Small intestine 45 days

Degenerative changes are observed in the Intestinal Mucosa and Submucosa. Coagulation of tissue is seen in the luminal space. Villi lost its histopathology and epithelial sloughing from the villi increased and got damaged.

Lung Histopathology

Fig 6.21: Lung Control

Respiratory system showed normal alveolar sac and alveoli with cuboidal cells lining bronchiolar epithelium, smaller bronchioles lined by simple cuboidal epithelium. Bronchus is clear in shape and surrounded by an epithelium. The Control lung showed clear pulmonary vessels and cartilage plate.

Fig 6.22: Arsenic Lung 15 days

Mild alveolar fibrosis is observable and septa of alveoli showed thickening. Blood capillaries showed dilation and slight haemorrhage is observed. Bronchiole and pulmonary vessel are normal.

Fig 6.23: Arsenic Lung 30 days

Alveolar wall with few numbers of inflammatory cells. Hyperplasia is observable. Decline in alveolar number and thickening of alveolar septa by mononuclear inflammatory cells infiltration. Bronchiole showed slight damage.

Fig 6.24: Arsenic Lung 45 days

Pulmonary vessel showed slight swelling, mononuclear inflammatory cells, hyperplasia of pneumocyte were observed. Alveoli decreased and slight thickening of alveolar wall, Bronchiole and its epithelium got damaged.

DISCUSSION

Tissues histological examination was recorded in control and experimental groups of Liver, Kidney, Testis, Heart, Lung and Small intestine preserved in formalin for routine histopathological studies. Fixed tissues were processed by routine paraffin embedding technique. Sections of 5-6 μ thickness were cut and stained with Haematoxylin and Eosin method (H & E) and observed the histopathological changes. The present study results shown that organs showed structural and morphological changes in all organs under sodium arsenite exposure for a period of 15, 30 and 45 days.

Sodium arsenite resulted in hepatocytes vacuolation, congestion, and cellular infiltration by mononuclear cells under 45 days treatment but 15 and 30 days treatment showed mild vacuolar degeneration of hepatocytes. Liver promoted pervasive hepatocytes congestion, disarrangement of hepatic structure, fatty degenerative changes, vacuolization, inflammatory cells infiltration, and necrosis (Rajani and Purnima, 2009; Ola-Davies and Akinrinde, 2016). Hepatocytes arranged into hepatic cords running radiantly from the central vein and RBC congestion and absence of intact nuclei are involved in the initiation of fibrosis (Jalaludeen *et al.*, 2016).

Reduction in severity and pathological changes was seen under 15 days of treatment in Liver of rats. Hepatocytes degeneration, sinusoids dissociation and destruction, irregularly shaped nuclei, marginated chromatin fatty degeneration, marked focal necrosis in liver are observed under arsenic toxicity and changes are more prominent in 30 and 45 days of treatment (Kaya and Karapehlivan, 2017). Liver showed inflammation, steatosis, fibrosis and hepatocyte degeneration under toxic stress (Wu *et al.*, 2008). Sodium arsenite treatment showed hepatic tissue degeneration promoting necrosis around central vein, interstitial hemorrhages and hepatocytes degeneration (Nozohour and Amin, 2019).

Histopathological studies showed that vascular congestion, swollen kupffer cells, liver degenerative changes, massive haemorrhages Fatty degeneration of hepatic cells and necrosis is observed in liver by the findings of Gordon and Lough, (1972), Guicciardi *et al.*, 2013. Hemosiderin-brownish pigment present in the hepatocytes cytoplasm is observed. Histopathological

lesions such as lymphonuclear cells infiltration, hepatic parenchyma degeneration and hepatocytes deformation due to heavy metals, in liver of *L. rohita* (Kaur *et al.*, 2018).

Fibroplasia with infiltration of mononuclear cells, hepatocytes vacuolation, collagen deposition in portal areas, hyperplasia of bile ducts and congestion of portal blood vessels is observed under 45 days of treatment but 15 days treatment showed slight hepatocytes vacuolation, congestion of portal blood vessels and less infiltration of mononuclear cells in portal area. Portal fibrosis and collagen deposition in portal areas is also observed under arsenic toxicity.

Kidney is more prone to damage due to perfusion and increased concentration of renal tubular wastes. Arsenic gets excreted through kidney and damages capillaries, glomeruli, and kidney tubules by arsenic binding with sulfhydryl group of proteins of glomerular filtration membrane and in turn damage proteins (Akter *et al.*, 2022). Kidneys showed congestion, tubular epithelium sloughing from basement membrane and epithelial necrosis (Basile *et al.*, 2012). Arsenic toxicity resulted in ROS generation and promoted cell injury and necrosis and caused Bowman's capsule reduction with histological changes in the glomeruli, glomerular capillaries (Chakraborty *et al.*, 2013).

Kidney showed disruption of renal tubule with loss of brush border lining the tubule, coagulative necrosis, edema, irregular diameters, increased cellularity in the glomerulus and atrophy of renal tubules (Kaur *et al.*, 2018). Increased Bowman's capsule space due to glomerular cells shrinkage, Proximal and Distal convoluted tubules of lumen showed eosinophilic material, cytoplasmic vacuolation and degradation are observed under arsenic induced toxic stress (Tripathi *et al.*, 2021).

Testis of Control rat shown normal Seminiferous tubules with prominent lumen with spermatids, Leydig cells present in clear interstitial, Sertoli cells and developing spermatogonia. Disintegration of peritubular membrane, germ cells disorganization, loss of germ cells, seminiferous epithelium vacuolization is observed in rats on treating with sodium arsenite for a period of 30, 45 and 60 days. The studies of Sarkar *et al.*, 2008 are in consonance with the present study supporting the changes in the

testicular organ. Declined seminiferous tubule diameter, alterations in structural and functional integrity of seminiferous tubules, testosterone synthesis (Ahmad *et al.*, 2021; Choudhuri *et al.*, 2021). Arsenic toxicity caused variations in functionality and morphology of testis including decreased testicular weights, low sperm count, damaged spermatogonia, degeneration of germ cells at the 7th stage of the spermatogenic cycle, impairment of Leydig cells, leading to poor sperm production is observed in rats (Pant *et al.*, 2001; Pant *et al.*, 2004; Ali *et al.*, 2013). Elevated luteinizing hormone, Decreased testosterone level, decreased activity of sorbitol dehydrogenase, acid phosphatase, and 17 β -hydroxy steroid dehydrogenase, down regulation of Ddx3y expressions in the testis and epididymis, that alters spermatogenesis, leading to male reproductive toxicity (17 β -HSD) with up-regulation of ERK1/2, PI3K, AKT, IKK γ and NF- κ B gene expression, decreasing the expression levels of SPACA1, ACE and SMCP in rat testis (Pant *et al.*, 2004; Kumar *et al.*, 2013).

Heart tissue histopathological observations showed cytoplasmic degeneration, severe necrosis, pyknosis and nuclear degeneration. Arsenic treated rat Heart for 45 days showed severe infiltration of mononuclear inflammatory cells, cytoplasmic vacuolization of sarcoplasm in myocytes, haemorrhages in myocardium, degeneration and separation of muscle bundles, myocytes with focal Zenker's necrosis and myocardial blood vessels congestion, but the signs and symptoms are lesser in 15 and 30 days of arsenic treatment (Korany *et al.*, 2019). The present changes in the histopathology of heart are in consonance with the previous studies of Liang *et al.*, 2020; Benowitz, 1992; Nozohour and Amin, 2019. Fragmentation and degeneration of muscle fibers, Mononuclear inflammatory cell infiltration around myocardial blood vessels in cardiac tissue, diminished systemic vascular resistance, ventricular dysarrhythmia, congested blood vessels, disturb cardiac contraction and relaxation, impair heart morphogenesis and development are the supporting evidences that indicates arsenic induced histopathological changes in heart (Huang *et al.*, 2017).

Induction of heart muscles, necrosis of liver cells, necrosis, pyknotic nucleus, bile stagnation is observed in fish (Hossain, 2012b). Myocytes were identified by presence of inflammatory cells within them in a focal pattern, nuclei are irregular and showed hypertrophy,

eosinophilic granules are found in the cytoplasm. Similar changes are observed in liver tissue upon sodium arsenite treatment indicating nuclear and cellular hypertrophy, vacuolation of cytoplasm with distinguished eosinophilic granules and melanomacrophages aggregates (Hossain, 2012b). Myocardial and epicardial edema, capillary leakage, disruption of muscle fiber and hemorrhage in heart of ducklings was proven by the studies of Das *et al.*, 2021. Fibre swelling and separations, capillary congestion in cardiac muscle fibres, interstitial edema, and micro-haemorrhages are observed under arsenic toxicity (Varghese *et al.*, 2017).

Lungs under Sodium arsenate treatment at lower and higher doses 0.05 ppm & 5 ppm respectively caused necrosis and bronchiolar epithelium degeneration, mild alveolar collapse and alveolar septa thickening in lungs (Wu *et al.*, 2008; Cheng *et al.*, 2013). Lungs under arsenic treatment for 45 days showed alveolar wall thickening, Interstitial pneumonia, infiltration of mononuclear cells and perialveolar blood capillaries dilation, bronchiolitis, slight thickening of alveolar wall. Lung tissues showed interstitial pneumonia and light infiltration of mononuclear cells and congestion of perialveolar blood capillaries, few mononuclear cells infiltration are observed under 15 and 30 days of treatment (Henderson *et al.*, 2017).

Lung tissue exhibited squamous cell carcinoma in German uranium miners with exposure to arsenic and proportion of adenocarcinoma increased with rising arsenic exposure (Taeger *et al.*, 2009). 5,000 ppb arsenic for 46 weeks treated arsenic mouse promoted the first lung tumor, a bronchiolo-alveolar carcinoma. Lung adenoma, alveolar hyperplasia, carcinoma, lung fibrosis, alveolar histiocytic infiltration, lymphoid hyperplasia occurred in arsenic treated groups. Lung bronchiolo-alveolar carcinomas consisted areas of tumor cells that occupied large regions of lung lobes and caused histoarchitectural and pathological changes around the surrounding tissue (Waalkes *et al.*, 2014).

Small intestine of Broiler chicks showed epithelium sloughing from the villi, tubular dilatation, loss of brush border. In the epitheliums of PCT and inflammatory cells infiltration between crypts (Khan *et al.*, 2014). Degenerative and necrotic changes are observed in intestine of fish in the intestinal mucosa as well as submucosa, inflammatory cells accumulation in

the mucosa and submucosa with distinguishable edema, cytoplasm showed vacuolization, atrophy is observed in the muscularis externa and submucosa. Intestine showed increased submucosal with, edema, fibrosis, lumen and serosa width enhanced. Dilation of vascular elements, fibrosis, edema, and increased width of the serosa, submucosa and lumen (Hossain, 2012b). Degeneration of mucosal layer, Fusion of muscularis and submucosal layer, Hemorrhage in the mucosa and submucosal layer, Exhaustion of intestinal villi, Necrosis and disintegration of intestinal villi are observed in fish under arsenic induced toxic effects (Rabbane *et al.*, 2022).

Submucosa and submucosal edema, degeneration of epithelium, and inflammatory cells infiltration in the intestine of fish *Channa punctata* is observed under the toxicity of carbofuran (Ram and Singh, 1988). Irregular mucosal epithelial cells proliferation, nuclear hyperchromasia, Villi lost its histopathology and epithelial sloughing from the villi increased and got damaged, hyperplasia of the crypts, increased nucleus-to-cytoplasmic ratios are observed in intestine upon arsenic toxicity (Wang *et al.*, 2020). Cytoplasmic vacuolization, volumes of crypts, submucosa and muscularis externa reduced, mucosal barrier damage, reduced villus lengths, impaired intestinal epithelial tight junctions, inflammatory cells infiltration are common and evident by the studies of Akinrinde *et al.*, 2015; Pagrut *et al.*, 2018; Wang *et al.*, 2019; Kellett, 2020; Zhao *et al.*, 2023 in the small intestine of ducks, rats and chickens under the toxicity of arsenic.

In small intestines it gets absorbed and rapidly distributed to liver and other tissues through portal circulation of the body via systemic circulation and exhibits histopathological changes, the studies of Hossain, 2012b showed apoptotic and necrotic cells along with structural alterations, fatty infiltration, hemosiderin granules, cytoplasmic vacuolation and fibrous bodies in heart, liver and intestine. Degenerative changes in liver, kidney, testis, lung, heart and intestine were observed with treatment of sodium arsenite @ 10 mg/kg b. wt orally for 4 weeks (Pagrut *et al.*, 2018). In the present study all the changes are evident up to maximum extent in all the test tissues including Liver, Kidney, Testis, Lung, Heart and Small intestine with cytoplasmic vacuolization, inflammatory cells infiltration, apoptotic and necrotic changes under arsenic induced toxicity.

SUMMARY AND CONCLUSION:

Histopathological studies helps in detecting the extent of tissue and organ damage under arsenic induced stress conditions. Histopathology helps in diagnosing the cytoarchitectural changes occurred in the animal under chemical induced toxic stress. Extent of tissue damage depends upon the degree of exposure, type of toxicant, concentration of toxicant and also varies among different animal models. Studies of Hossain, 2012b showed apoptotic and necrotic cells along with structural alterations, fatty infiltration, hemosiderin granules, cytoplasmic vacuolation and fibrous bodies in heart, liver and intestine. In the present study arsenic treatment for a period of 15, 30 and 45 days showed changes in architecture and altered the functional activity. The test tissues (Liver, Kidney, Testis, Lung, Heart and Small intestine) used in the present study almost showed apoptotic and necrotic changes, inflammatory cells infiltration, cytoplasmic vacuolation and cell death due to highly toxic stress. The changes in tissues are prominent in 45 days of treatment when compared to 15 and 30 days.

Based on the present results, we can draw the conclusion that arsenic is toxic and that it affects both animals and humans. Arsenic toxicity is a growing major toxicant closely linked to animal and human exposure primarily through drinking water and diet. Hence Arsenic toxicity showed adverse effects on the metabolism of carbohydrates, lipids and proteins. In addition levels of antioxidant enzymes and blood biochemical properties also confirmed the adverse effects of arsenic toxicity.

Researches of arindicate that differential susceptibility plays an important role in arsenic-induced disease manifestation. Multiple physiological systems are impacted by chronic arsenic toxicity, which can also result in malignancies and death. To tackle this threat, holistic multidisciplinary tactics must be used together with a few viable yet affordable options, such as alternative water sources, arsenic-water treatment, new irrigation system adaptations, straight forward changes in cooking technique, and dietary supplements.

Arsenic adversely affected Carbohydrate, Protein and Lipid metabolism promoting organ damage. Levels of antioxidant enzymes and protein carbonyl content

altered in different tissues that mediate arsenic toxic effects and proven by Histopathological examination.

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