

The Effect of Arsenic on Liver Tissue of Experimental Animals (Fishes and Mice) - A Review article

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Abstract- Toxic metals are widely found in our environment and are mainly caused by the use of the pesticides, industrial activities and mining operations. One of them is arsenic that accumulates in the liver tissue to toxic levels and cause changes in the activities of several liver enzymes and cellular damage. Enzymes like aspartate aminotransferase and alanine aminotransferase are found predominantly in liver tissue and cellular damage as a result of arsenic exposure releases these enzymes into the blood stream and the plasma levels of these enzymes indicate hepatotoxicity. The objective of this project is to review the several research works on the effect of arsenic on liver tissue of fishes and rats at different time of exposure. The resources used for this review were obtained from published work in several peer review journals. ALT activity has shown an increase of 6.03%, 13.61% and 27.75% at different doses of exposure and the AST has shown also an increase of 9.04%, 16.32% and 38.08% at different doses in fishes. The GDH activity has shows an increased level of 9.61%, 23.72% and 34.62% at different doses when compared to control groups of fishes. Varied degrees of changes (mild to severe) were also observed in groups of fishes and mice exposed to different doses of arsenic and results in necrosis of the hepatocytes, central vein and sinusoidal spaces expansion due to shrinkage. Other result has shown that fish exposed to different concentrations of NaAsO_2 have shown varied degrees of changes i.e. death in high concentration; however, as the concentrations decreased, the survival period increased gradually. The FTIR spectra revealed also significant differences in absorbance intensities in the amide bands between control and arsenic intoxicated liver tissues. Among the results reported most of which have shown increment and some of them have shown decrement when compared to the control groups up on the exposure of different concentration of arsenic i.e. (28.30 mg/L of arsenic trioxide (As_2O_3), 4.2 mg/kg sodium arsenate, (96 ug/L, 144 ug/L), 1/10 LC50 of As, 1/20 LC50 of As, 75mg/L arsenic trioxide (As_2O_3), (0.5,0.1 and 0.2mM of NaAsO_2) and (41.5 ppb) of As_2O_3 . Eventually, Arsenic administration increased serum AST and ALT activities of fishes reflecting a situation of tissue damage. This indicates that ALT and AST can be used as biomarkers of cellular damage in blood plasma, protein degradation and liver damage. In all the investigations various activities of arsenic on the enzymes may be related to the arsenic concentration, duration of the exposure, species differences and the methodology used

Index Terms- Fishes, Mice, hepatotoxicity, Toxic, Metal

I. INTRODUCTION

Toxic metals are widely found in our environment and humans are exposed to these metals from numerous sources, including contaminated air, water, soil and food; several studies have indicated that metals, such as lead, arsenic, cadmium, mercury and others deplete cells major antioxidants and enzymes; toxic metals mentioned above cause an increase in production of reactive oxygen species (ROS) such as hydroxyl radical (HO), superoxide radical (O_2^-) or hydrogen peroxide (H_2O_2) (1). Here we intend to review the extent of toxicity of arsenic on liver tissue of Mice, Rats and Fish at different times as indicated in various research works.

Non-degradable heavy metals are regarded as hazardous to aquatic ecosystems because of their environmental persistence and their tendency for bioaccumulation. Different species of elements can exert diverse toxicological effects in animal and human system and it has been reported that heavy metals affect various biochemical parameters of the fish liver (2).

Arsenic, one of these heavy metals is a naturally occurring metalloid with atomic number 33 located on Group V of the periodic table. It exists in four oxidation states: -3, 0, +3, and +5. The more commonly known arsenic compounds are arsenate and arsenite (3)(4). Arsenic occurs as two allotropic forms, yellow and metallic gray. The metallic gray form is the stable form under ordinary conditions (3). Arsenic is a protoplasmic poison due to its effect on sulphhydryl group of cells interfering with cells, enzymes, cell respiration and mitosis (2).

It has been reported that exposure to arsenic is via drinking water, air, food and beverage in many places in the world and exposure through drinking water is increasing due to contamination from industrial operation and over withdrawal of ground water for irrigation (5)(2). Exposure to high levels of arsenic through drinking water has been recognized for many decades in some regions of the world, i.e. China, India, and some countries in Central and South America (4).

Arsenic is a metalloid that is widely found in water, soil, air and also usually found in the environment combined with other elements such as oxygen, chlorine and sulfur. Arsenic combined with these elements is called inorganic arsenic and arsenic combined with carbon and hydrogen is referred to as organic arsenic. Organic arsenic is usually less harmful than the inorganic forms (3).

Arsenic in drinking water is typically inorganic and can be present either as $\text{As}+3$ (arsenite) or $\text{As}+5$ (arsenate). In Bangladesh, arsenic in the ground water is primarily in the $\text{As}+3$ form and is more cytotoxic and genotoxic than $\text{As}+5$ (6). The

Legal limits of arsenic vary between 0.1 mg kg⁻¹ (Venezuela) and 10 mg kg⁻¹ (Hong Kong), in addition the Joint world health organization expert Committee (1983) has also set a limit of 0.1mg kg⁻¹ or 10 parts per billion (ppb); however, in some countries this norm is related to the total arsenic concentration, whereas in other countries it expresses the inorganic arsenic fractions; therefore the meaning of these norms is not straightforward (7)(3)(8). A decreasing toxicity order can be set as: arsenite - arsenate - dimethylarsinic acid - monomethylarsonic acid - arsenobetaine - arsenocholine - trimethylarsine oxide (8). Individuals who accumulate the trivalent intermediates are thought to be at greater risk of arsenic-induced diseases (6).

Arsenic level found in marine organisms are much higher than those found in terrestrial organisms thus an important question relates to the ability of marine organisms to concentrate arsenic (9)(8). Therefore fishes are usually considered as organism of choice for assessing the effects of environmental pollution on aquatic ecosystem and the body blood parameters of the fish have been used as indicators of environmental risk and also, the assay of the enzymes activities aspartate aminotransferase (AST), alanine aminotransferase (ALT) & lactate dehydrogenase (LDH) in the blood and tissues of the fish frequently used as a diagnostic tool in human and animals (9). Arsenic toxicity is associated with the formation of reactive oxygen species, which may cause severe damage to several biological systems and based on these studies, it is hypothesized that these metals could also accumulate in the liver to toxic level and cause pathological alterations (10).

Arsenic contamination is mainly caused by the use of the arsenic pesticides, industrial activities and mining operations (1). Due to increasing levels of arsenic in the ground water in Bangladesh and West Bengal considerable attention has been given to the study of the effect of arsenic on human beings and selected mammals (11). Continuous exposure of freshwater organisms to low concentrations of heavy metals may result in bioaccumulation, causing changes in the activities of several liver enzymes. In addition fish as living bio indicator species play an increasingly important role in monitoring of water pollution because they respond with great sensitivity to changes in the aquatic environment (12).

II. THE LIVER AS A TARGET ORGAN FOR METABOLISM

Most ingestible substances are ultimately taken up to the liver for metabolic activities. This exposes the liver to several toxicity. Toxic metals are widely found in our environment and are mainly caused by the use of the pesticides, industrial activities and mining operations. One of them is arsenic that accumulates in the liver tissue to toxic levels and cause changes in the activities of several liver enzymes and cellular damage. Enzymes like aspartate aminotransferase and alanine aminotransferase are found predominantly in liver tissue and cellular damage as a result of arsenic exposure releases these enzymes into the blood stream and the plasma levels of these enzymes indicate hepatotoxicity. A number of researches have been conducted concerning the effect of arsenic on the liver tissue of fishes and mice by various investigators in different

species in response to variable doses of arsenic and time of exposure and are presented as follows:- for example Serum ALT level of *labeo Rohita* species of fish exposed to 28.30 mg/L arsenic trioxide has shown an activity of 641.18 IU/L at 24 h and 798.11 IU/L at 96 h exposure and from the control 487.25 IU/L at 24 h and 399.7 IU/L at 96 h, was recorded respectively. Similar trends were also observed in serum AST of fish exposed to arsenic that has shown an activity of 1532.77 IU/L at 24 h and 1622.39 IU/L at 96 h exposure and from the control has shown 1085.72 IU/L at 24 h and 861.58 IU/L at 96 h, respectively. These results indicated that arsenic toxicity increase the level of liver enzymes of fish (*Labeo rohita*) upon the exposure of the same dose of arsenic as the time of exposure increase(10)

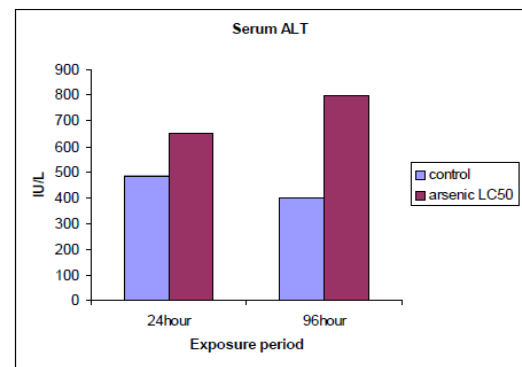


Figure 1: The toxic effect of arsenic trioxide (28.30 mg/L) on the ALT activity of *Labeo rohita* at the end of 24 and 96 h exposure periods (P<0.01)

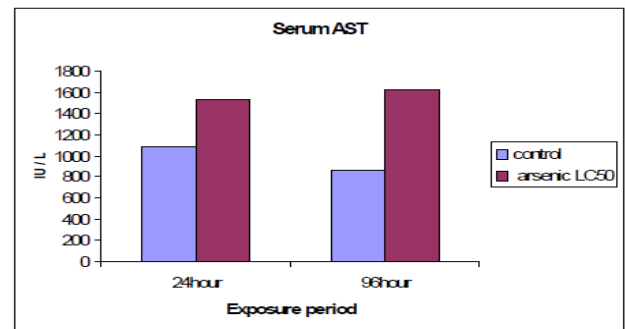


Figure 2: The toxic effect of arsenic trioxide (28.30 mg/L) on the AST activity of *Labeo rohita* at the end of 24 and 96 h exposure periods (P<0.01)

Similarly, Devaraju *et al.* have pointed out that administration of sub lethal dose of sodium arsenate i.e. 4.2 mg/kg/body weight was given to albino mice as single, double and multiple doses at stipulated period i.e 3rd, 5th and 9th days respectively. Isolated liver tissue for enzymes analysis and histopathological has shown that; the alanine amino transferease (ALT) activity has shown an increase of 6.03% in single dose, 13.61% in double dose and 27.75% in multiple doses. The activity level of aspartate amino transferase (AST) has shown an elevation of 9.04% in single, 16.32% in double and 38.08% in multiple dose when compared to control. The glutamate dehydrogenase (GDH) activity has shown an increased level of 9.61% in single, 23.72% in double and 34.62% in multiple doses when compared to control and results Severe pathological

changes in all dose of sodium arsenate such as necrosis of hepatocytes, nuclear degeneration and vacuoles(12) as shown in table1 and figure A – E

Table 1; alterations in alanine and aspartate aminotransferases and glutamate dehydrogenase activity levels in liver tissue of sodium arsenate treated albino mice

Name of enzymes	Single dose		Double dose		Multiple dose	
	Control	Experiment	Control	experiment	Control	experiment
ALT (uMoles of pyruvate formed/mg protein/hr	1.492±0.033	1.582±0.044 (6.03)	1.510±0.032	1.695±0.023 (13.61)	1.498±0.029	1.906±0.029 (27.75)
AST(umoles of pyruvate formed/mg protein/hr	1.305±0.027	1.423±0.044 (9.04)	1.312±0.026	1.520±0.029 (16.32)	1.308±0.025	1.802±0.023 (38.08)
GDH(umoles)	0.156±0.020	0.171±0.031 (9.61)	0.158±0.025	0.193±0.024 (23.72)	1.160±0.022	0.210±0.013 (34.62)

Values in parenthesis indicate the percentage change over control
 Values are mean ±SD. Of six separate observation

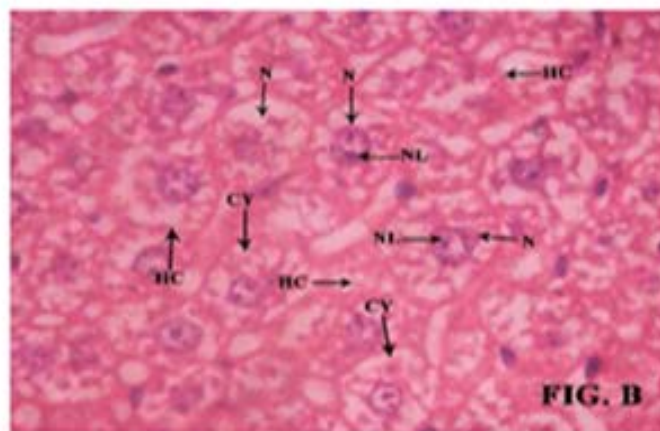
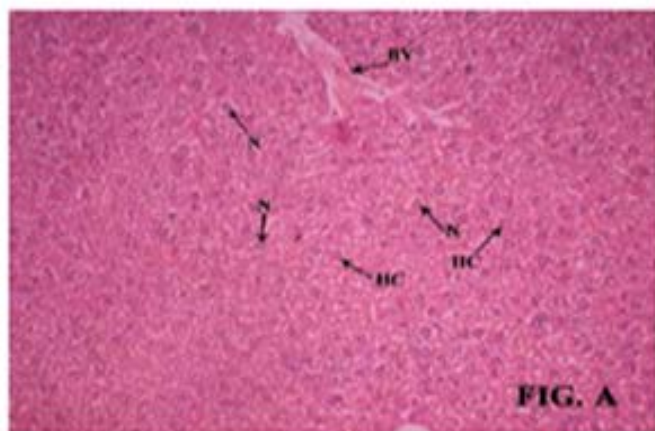


Fig.A: Mice Liver showing hepatocytes (HC) with centrally placed nucleus – H & E. 100 X.

Fig.B.The mice liver under single dose did not show significant pathological changes with one or more nucleoli (NL) and cytoplasm (C)-H & E.400 X.

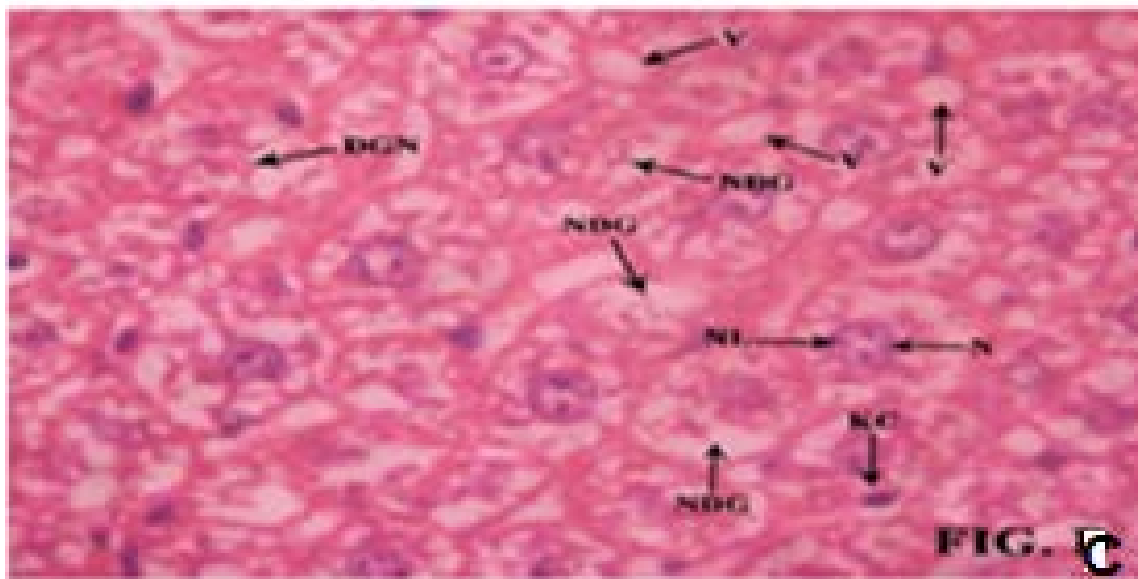
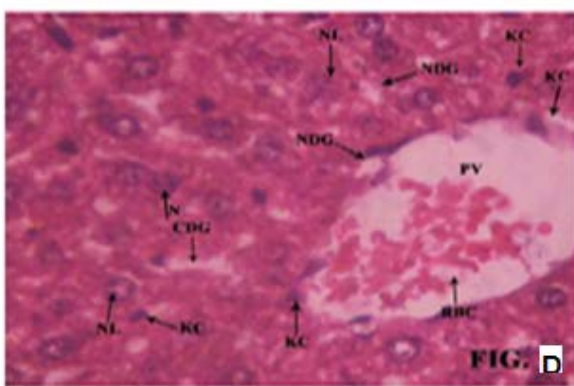


Fig.C: Mice liver under double dose of sodium arsenate showing nuclear degeneration (NDG) and appearance of vacuoles (V) in hepatocytes – H & E. 400 X.



Figs. D & E: Mice liver under multiple dose of sodium arsenate showing few RBC in portal vein (PV), nuclear degenerative changes (NDG) and cytoplasmic degenerative changes in cytoplasm (CDG), emptied portal vein (EPV), appearance of severe necrosis in cytoplasm (NCC),

Significant decrease in all enzymatic activity was observed in the liver of the juvenile *Labeo rohita* exposed to the concentration of arsenic (144 µg/L) and (96 µg/L) for one month period of exposure, and results in the disturbance in the structure and integrity of cell organelles, like ERC and membrane transport system. But the decrement was not significant at the lower concentration (11) as shown in table2.

Table 2; Enzyme activities in the Liver of *Labeo rohita* after exposure to arsenic, activity is expressed as µMoles pyruvate formed per mg protein in 30 minutes

Labeo rohita Groups	Arsenic conc. (µg/l)	GOT µMpyruvate formed in 60minutes	GPT µM pyruvate formed in 30 mins	ACP µM pyruvate formed in 30mins	ALP µM pyruvate formed in 30mins
Control	0	19.44±3.34	9.50±3.29	0.27±0.14	0.76±0.31
First Group	96	18.46±4.15	6.91±1.10	0.07±0.01	0.74±0.07
Second Group	144	13.09±6.46	1.88±1.29	0.04±0.06	0.64±0.05

GOT; glutamate oxaloacetate transaminase; GPT; glutamate pyruvate transaminase; ACP; acid phosphatase; ALP; alkaline phosphatase

According to the investigation reported by Allah and Hameid, in 2009 the plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) in the *Clarias gariepinus* (a specie of fish) exposed to 1/10 LC50 and 1/20 LC50 of arsenic for 20 days were significantly increased and this report indicated that as the dose of arsenic increases it leads to varied degree of liver cell damage such as shape deformation, vacuolization, enlargement, necrosis and degeneration of hepatocyte. As shown in Table 3 and figure F

Table 3; Changes in the activities (Units/min/g fresh tissue) of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the liver tissue of the Nile cat-fish (*Clarias gariepinus*) exposed to two levels of arsenic (As) for 20 days.

Groups	AST	ALT
Control	48.432±5.121	40.592±6.927
1/10 LC50 of As	65.513±4.152	62.692±4.212
1/20 LC50 of As	58.724±5.136	51.937±5.214

The data are expressed as mean of fish's ±standard deviation. (P<0.05) indicate significant differences from the control.

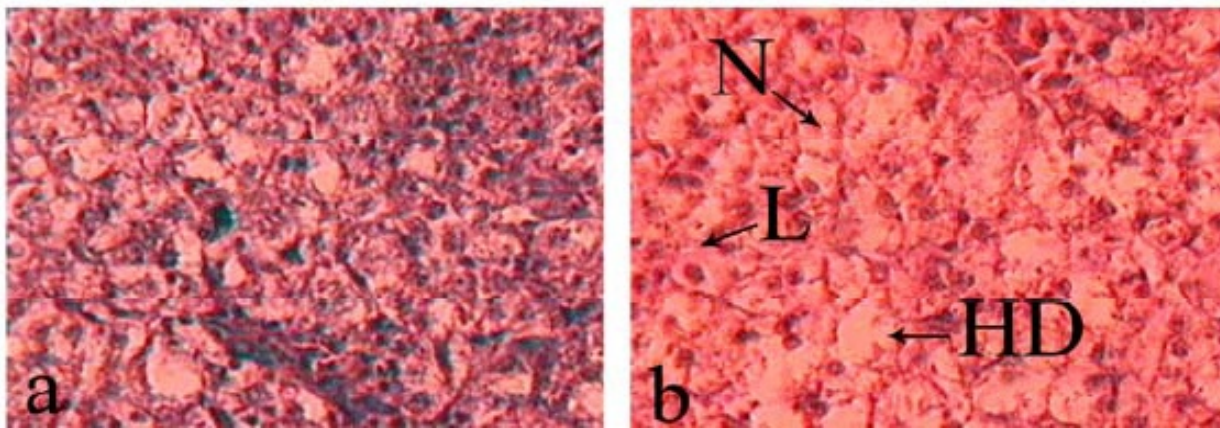


Figure F. Photomicrograph of the liver section of *Clarias Gariepinus* stained with haematoxylin and eosin (400X): (a) Fish exposed only to water (control); b) Fish exposed to 1/10 LC50 of As, showing necrosis (N), enlarged hepatocyte (L) and hepatocyte degeneration (HD).

Ferzand *et al.*, in 2008 have reported that varied degrees of change (mild to severe) were observed in 30, 150 and 300 ppb arsenic exposed groups for 40 days and results various pathological changes such as Necrosis of hepatocytes, central vein, cytoplasmic, nucleus blabbing and sinusoidal spaces expansion in the tissue of liver mice. fig.(G-J).

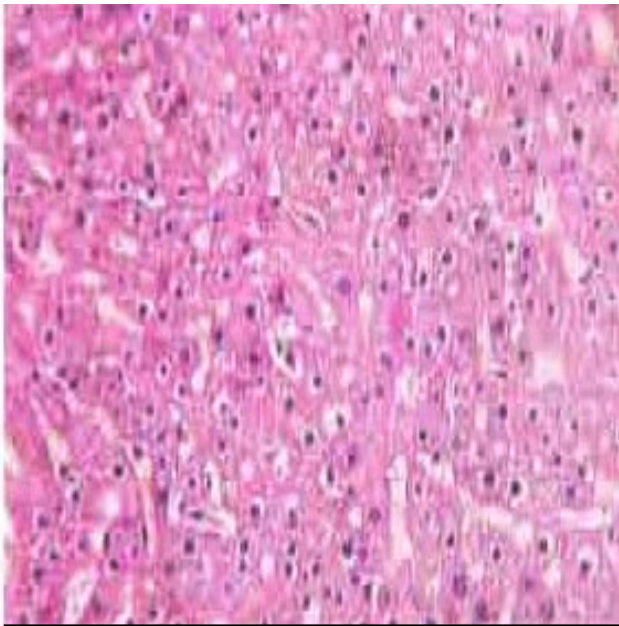


Figure G; Liver of Mice of control group, no necrotic and degenerative changes, normal histology (1600X H and E

FigH; mice liver showing mild necrotic and degenerative changes due to arsenic exposure through water. A, mild necrotic hepatocytes, B; free nuclei, C: mild degree of nuclei blabbing, D: mild cytoplasmic blabbing and hydropic fatty degeneration

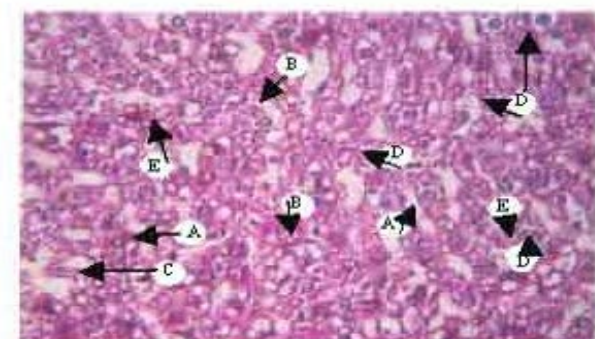
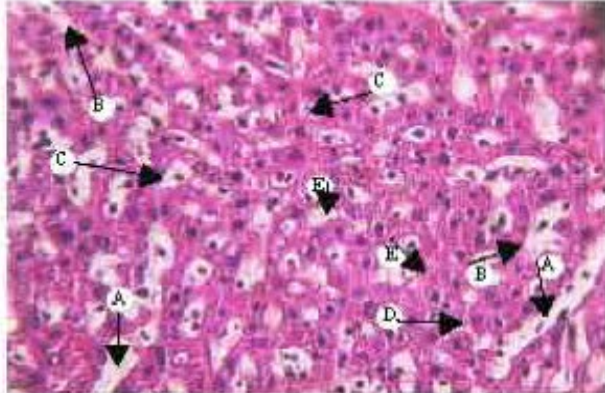
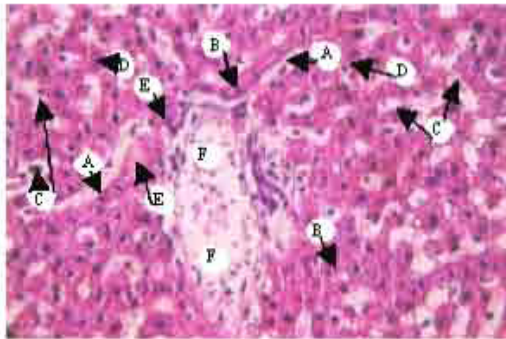


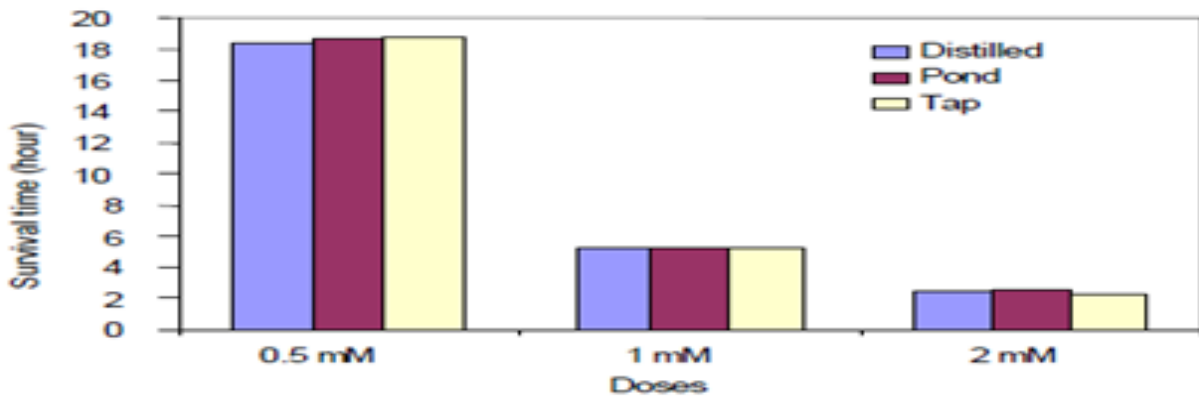
Fig I; Mice liver showing moderate degree of necrotic and degenerative changes due to exposure to 150ppb of arsenic



FigJ; mice liver exposed to 300ppb of arsenic in daily water

nuclei (C), nucleus vacoulation or blabbing (D), severe cytoplasmic vacoulation (blabbing) due to hydropic and fatty degeneration (E), central vein in showing necrosis of endothelium (1600X H and E)

According to Ahmed *et al.*, 2008 different concentrations of NaAsO₂ ranging from 0.5 mM up to 2 mM were used and when the fishes (*Channa straitus*) exposed to high concentration (2 mM) of NaAsO₂, they died within 2 and half hour. However, as the concentrations decreased, the survival period increased gradually. For 1mM and 0.5 mM of NaAsO₂ the survival time was over 5 hours and 18 hours respectively; however, Survival durations of the exposed fishes did not vary according to different water sources. Figure K



FigureK: comparison of survival period of fish after exposure to different concentrations of NaAsO₂ in different water types

III. DISCUSSION

Liver is a target organ and primary site of detoxification and is generally the major site of intense metabolism and is therefore prone to various disorders as a consequence of exposure to the toxins of extrinsic as well as intrinsic forms. Liver plays important role in metabolism to maintain energy level and structural stability of the body (16). It is also the site of biotransformation by which a toxic compound has been transformed in less harmful form to reduce toxicity; however, it is exposed to damage and produce hepatotoxicity (17). According to (10) though the liver plays an important role in metabolic processes and detoxification of many antibiotics, acute exposures to arsenic may lead to accumulate in the liver and cause pathological alteration. Moreover, cell injury of certain organs like liver leads to the release of tissue specific enzymes into the bloodstream. Significant increase in transaminases (AST and ALT) activity in fish exposed to arsenic could be due to possible leakage of enzymes across damaged plasma membranes and/or the increased synthesis of enzymes by the liver. Arsenic administration increased serum AST and ALT activities of fishes reflecting a situation of tissue damage.

Enzymes are biochemical macromolecules that control metabolic processes of organisms, thus a slight variation in enzyme activities would affect the organism (11). Common environmental contaminates such as metals pose serious risks to biochemical parameters and enzyme activities of fish and it is proved that fish subjected to metals have a reduced protein, glycogen level and enhanced enzymes (ALT,AST and ALP) activity (18).

The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are two important enzymes working as an important link between carbohydrates and protein metabolism in addition AST catalyses the inter conversion of aspartic acid and α -ketoglutaric acid to oxaloacetic acid and glutamic acid. While ALT catalyses the inter conversion of alanine and α -ketoglutaric acid to pyruvic acid and glutamic acid (16)(13). ALT and AST participate in transamination reactions and found predominantly in liver, cardiac cells and striated muscle tissue. Cellular damage releases the ALT and AST into the blood stream and the levels of these enzymes have the potential to indicate hepatotoxicity (16)(6). Serum ALT and AST are usually elevated in serious hepatic damage and the extent of organ damage is

dependent on the type of toxicant, its mechanism of action and duration of exposure (6). This elevation in Serum ALT and AST has been well supported by(13) that is, examined sample of subjects in India demonstrated that arsenic exposure induced liver enlargement with concomitant elevation in levels of alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase. Other investigations conducted in Bangladesh have shown that significant difference in alkaline phosphatase activity in a sample exposed to arsenic compared to that of a non-exposed sample and another study of arsenic-endemic and non endemic population in India have shown that arsenic elevated the activity of blood proteins/enzymes assessed by liver function tests (6).

A number of studies in humans exposed to inorganic arsenic by the oral route have noted signs of hepatic injury. Clinical examination often revealed that the liver is swollen and tender and analysis of blood shows elevated levels of hepatic enzymes; these effects are most often observed after repeated exposure to doses of 0.01–0.1 mg As/kg/day though doses as low as 0.006 mg As/kg/day have been reported to be effective with chronic exposure along with this histological examination of the liver tissue chronically exposed to similar doses has revealed a consistent finding of portal tract fibrosis, leading in some cases to portal hypertension (3). Several studies are reporting arsenic-induced liver fibrosis, hepatocellular damage, inflammation, focal necrosis in addition to hepatocellular carcinoma (9). Histopathological changes in different animals by heavy metals have been reported by several investigators thus the liver under sodium arsenate showed necrosis, appearance of vacuoles, nuclear degenerative changes in experimental animals (13). Chronic arsenic poisoning can cause serious health effects including cancers, melanosis (hyperpigmentation or hypopigmentation), hyperkeratosis (harden skin), restrictive lung disease, peripheral vascular, gangrene, diabetes mellitus, hypertension and ischaemic heart disease (14). Hepatic cancer and other hepatic disorders are considered to be the major causes of arsenic-related mortality (6).

According to epidemiologic studies and clinical observations, arsenic is associated with increased risk for certain types of human cancers, including epidermoid carcinomas of skin, lung cancers, and possibly liver cancers (19). General adverse health effects associated with human exposure to arsenic include cardiovascular diseases, developmental abnormalities,

neurologic and behavioral disorders, diabetes, hearing loss, fibrosis of the liver and lung and hematological (4).

In this review liver enzymes such as ALT, AST and GDH have shown marked increment and on the other hand some antioxidants like GSH, MDA, SOD, SH and ALP, ACP have shown decrement under the exposure of different concentration of arsenic; for example the toxic effects of arsenic trioxide (As_2O_3) on the survival and biochemical profiles i.e. serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity of *Labeo rohita* have shown increment upon exposure to lethal concentrations of arsenic (28.30 mg/L), i.e. serum alanine aminotransferase (ALT) level of *L. rohita* exposed to arsenic trioxide showed an activity of 641.18 IU/L at 24 h and 798.11 IU/L at 96 h exposure (Figure 1), this result was significant when compared with the control that have shown 487.25 IU/L at 24 h and 399.7 IU/L at 96 h, respectively. Similar trends were also observed in serum AST of fish exposed to arsenic that showed an activity of 1532.77 IU/L at 24 h and 1622.39 IU/L at 96 h exposure. And the control has shown 1085.72 IU/L at 24 h and 861.58 IU/L at 96 h, respectively. (Figure 2). These results indicated that arsenic toxicity increase the level of liver enzymes of fish (*Labeo rohita*) up on the exposure of the same dose of arsenic as the time of exposure increase.

It is also reported that the plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) were significantly increased in fishes (*Clarias gariepinus*) exposed to 1/10 lethal concentration (LC50) and 1/20 lethal concentration (LC50) of arsenic, i.e. in serum AST and ALT of fish exposed to arsenic that have shown an activity of $(65.513 \pm 4.152, 58.724 \pm 5.136)$ and $(62.692 \pm 4.212, 51.937 \pm 5.214)$ respectively, and have shown significant variation when compared with the control that showed the activities of serum (AST and ALT), i.e. 48.432 ± 5.121 and 40.592 ± 6.927 respectively. Table 3, in those reports the activities (AST & ALT) in the treatment groups were increased significantly over the recorded value of control group, that is the increment was also significantly higher in fishes (*Clarias gariepinus*) exposed to 1/10 LC50 of arsenic (which is the higher dose), whereas it was non-significantly differed for fishes exposed to 1/20 LC50 of arsenic. This report indicated that as the dose of arsenic increases it leads to varied degree of liver cell damage that is shape deformation, vacuolization, enlargement, necrosis and degeneration of hepatocyte. Figure 3.

It has been reported that Serum alanine amino transferase (ALT) activity has shown an increase of 6.03% in single dose, 13.61% in double dose and 27.75% in multiple doses. Similarly the levels of aspartate amino transferase (AST) has shown an elevation of 9.04% in single, 16.32% in double and 38.08% in multiple dose when compared to control groups. Similarly the glutamate dehydrogenase (GDH) activity has shown an increased level of 9.61% in single, 23.72% in double and 34.62% in multiple doses when compared to control groups, upon the administration of 4.2 mg/kg sodium arsenate in albino mice (13). table 1.

Severe pathological changes were observed in the tissue mice liver exposed to all dose of sodium arsenate like necrosis of hepatocytes, nuclear degeneration and vacuoles (fig. A-E). Relatively more pronounced changes like cytoplasmic degeneration, emptied portal vein and binucleated has been

absorbed in mice liver tissue exposed to multiple dose of sodium arsenate when compared to that of single and double doses (Fig. D & E). This indicated that as the concentration of arsenic increases cytoarchitectural changes in liver tissue increases and this has been supported by (6)(7) and (14).

The liver tissue of fish has shown significant decrease in all enzymatic activity (i.e. on acid phosphatase (ACP), alkaline phosphatase (ALP), glutamate pyruvate transaminase, (GPT) and glutamate-oxaloacetate transaminase (GOT)) up on exposure to the 144 $\mu\text{g/L}$ and 96 $\mu\text{g/L}$ arsenic concentration. But the decrement was not significant at the lower concentration (96 $\mu\text{g/L}$) (11). Table 2.

According to (11) the variation in enzyme activities in heavy metal treated fish is due to increased permeability of the cell as well as the direct effect of the arsenic on the tissue; therefore, significant deletion of enzymes in fishes exposed to arsenic observed can be attributed to increased arsenic levels in the tissue. Furthermore, accumulation of arsenic in liver could be the possible reason for variation of enzyme activities. The decreased activities of GOT, GPT, ACP and ALP indicated disturbance in the structure and integrity of cell organelles, like endoplasmic reticulum and membrane transport system. As arsenic toxicity induces oxidative stress, the antioxidant enzymes (especially the glutathione – dependent enzymes), react to defend against arsenic toxicity. It has shown that activities of glutathione-S-transferases, glutathione peroxidase, glutathione reductase and catalase decreased in the liver as a result of arsenic; this can be correlated with the decrease in GOT and GPT activities in the fishes exposed to arsenic.

It has been reported that Varied degrees of pathological changes (mild to severe) in the liver tissue of mice were observed in 30, 150 and 300 ppb exposed groups and results necrosis of hepatocytes, central vein, cytoplasmic, nucleus blabbing and sinusoidal spaces expansion due to shrinkage and necrosis of hepatocytes. fig. (G-J). The cells of the liver were showing mild hydropic and fatty degeneration of cells (Fig. H). The degenerated cells were showing mild cytoplasmic vacuolation, cytoplasmic blabbing and necrosis of the hepatocytes. Necrosed patches were in small number; hemorrhages were not frequent throughout the organ cytoplasm and have granular appearance due to the hydropic and fatty degeneration, showing vacuoles.

The group exposed to water containing 150 and 300 ppb of arsenic revealed moderate and severe type of histopathological changes respectively. Degenerated cells has shown severe cytoplasmic vacuolation, cytoplasmic blabbing and necrosis of the hepatocytes and the sinusoidal spaces were expanded due to shrinkage and necrosis of hepatic cells. (Fig I-J). (19)(6) and (7). According to Ahmed *et al.*, in 2008 different concentrations of $NaAsO_2$ ranging from 0.5 mM up to 2 mM were used and when the fishes (*Channa straitus*) exposed to high concentration (2 mM) of Na_2AsO_2 ; they died within 2 and half hour. However, as the concentration decreased, the survival period increased gradually. For 1mM and 0.5 mM of $NaAsO_2$ the survival time was over 5 hours and 18 hours respectively; however, Survival durations of the exposed fishes did not vary according to different water sources. (Fig. K).

During exposure a large amount of slime was produced by the fishes due to toxic effects of arsenic and compared with the control fishes and the exposed fishes were found to suffer from

suffocation and respiratory problems that might cause them to die. Fishes liver exposed to high concentrations of arsenic caused cell death in large numbers, whereas low concentrations induced a lower rate of cell death. The control liver cells were almost all live (98% viable cells). However, viable cell number decreased drastically (38%) after exposure of the fishes to 2 mM of NaAsO₂ and Viable cell number gradually increased with decreasing concentrations of NaAsO₂ (for 1 mM= 68% viable cells and for 0.5 mM=92% viable cell) (14). Arsenic is a potential sulfhydryl-reactive compound that aggregates with a number of cell surface proteins. Aggregation of cellular proteins, increases production of reactive oxygen species and activation of protein tyrosine kinases by arsenic might be together or individually involved in the process of cell death (14). This report indicated that as the dose of arsenic increases with increasing time of exposure the severity of hepatic cell damage increased.

Generally, in all the reports of study, the variation in the activates of the enzymes may be related to the toxicant concentration, duration of the exposure, species differences and the methodology used e.g, variation in the physico-chemical characteristics of the water used for holding and experiments such as pH, temperature, alkalinity, sulphates and chlorides.

IV. CONCLUSION

Generally, this review is to reveal the extent of toxicity of arsenic on liver tissue of mice and fishes and different concentration of arsenic has shown toxic effect in activities of different enzymes of liver tissue of fishes and mice. I.e. in most cases the result showed increment in most activities of enzymes and decrement in some other types of enzymes and showed different pathological changes in the tissue of experimental animals. This variation in the activities of the enzymes may be related to the toxicant concentration, duration of the exposure, species differences and the methodology used. Measuring the serum levels of the different enzymes in fishes and mice in response to arsenic toxicity are potential biomarkers of hepatotoxicity.

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