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Hepatoprotective Effect of *Ferula assafoetida* Against Arsenic Induced Toxicity in Swiss Albino Mice

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Abstract

Groundwater arsenic contamination incidents are increasing with time. Major incidents are in Gangetic plain of India. It has led to various to health related problems in the population of this area. Primarily, arsenate is actively transported into cells by phosphate transporters in liver. Liver and kidneys accumulate arsenic in the presence of repeated exposures and the kidneys are the major route of arsenic excretion. Arsenic causes hepatic and renal degeneration through alteration in various enzymatic pathways. Thus, the present study is designed to evaluate hepatoprotective effect of *Ferula assafoetida* against arsenic toxicity in mice. Sodium arsenite at the dose of 3 mg/kg body weight was administered for 4 weeks followed by the administration of *Ferula assafoetida* for 4 and 6 weeks at dose of 100 mg/kg body weight. Animals were sacrificed after the completion of the treatment and their blood samples were collected for biochemical assays while liver tissue for histopathological study. Arsenic administration causes more than 10 fold increase in Serum Glutamte Pyruvate Transaminase (SGPT) and Serum Glutamte Oxalate Transaminase (SGOT) levels while alkaline phosphate and bilirubin increased upto three to four folds in arsenic administered group. But, after *Ferula assafoetida* administration for 4 and 6 weeks there was significant restoration in these liver function enzymes. The histopathological study shows significant restoration at cellular level. Therefore. From the present study it can be concluded that arsenic causes increase in liver function enzymes many folds. *Ferula assafoetida* caused significant at biochemical and histological level. This indicates that *Ferula assafoetida* acts as effective hepatoprotective antidote against arsenic induced toxicity.

Keywords: Arsenic; Hepatotoxicity; *Ferula asafoetida*; Hepatoprotective

Introduction

In India, groundwater contamination incidents are increasing with time and the major incidents are in Gangetic plains. Groundwater arsenic poisoning in northern India has been studied in dugwells, hand pumps and spring water [1] and was reported in 1976 from Chandigarh and different villages of Punjab, Haryana and Himachal Pradesh. Earlier, tubewell strainers, pesticides, insecticides and other anthropogenic sources were considered as the source of groundwater arsenic contamination in West Bengal [2]. Arsenic absorption takes place mainly in the small intestines; also a minimal absorption occurs from skin contact and inhalation [3]. After its absorption, arsenic can be found in different organs, especially in the liver [4].

Liver is the organ which not only carries out the metabolic functions but also detoxifies the toxins. In arsenic exposure, arsenate is actively transported into cells by phosphate transporters in liver [5]. Kidneys accumulate arsenic in the presence of repeated exposures. The kidneys are the major route of arsenic excretion, as well as major site of conversion of pentavalent arsenic into the more toxic and less soluble trivalent arsenic. Sites of arsenic damage in the kidney include capillaries, tubules, and glomeruli [6].

Ferula assafoetida also called as Hing is a popular household remedies and its components are used for many prescriptions in traditional healing [7,8]. Assafoetida is used as a flavouring agent and forms a constituent of many spice mixtures. It is used to flavour, curries, meatballs, dal and pickles [9]. The whole plant is used as a fresh vegetable. The herb is also used as an antidote of opium.

Thus, the present study is designed to evaluate hepatoprotective effect of *Ferula assafoetida* against arsenic toxicity in mice.

Materials and Methods

Animals

Swiss albino mice *(Mus musculus)*, weighing 30g to 35g of 8 weeks old, were obtained from animal house of Mahavir Cancer Institute and Research Centre, Patna, India (CPCSEA Regd-No. 1129/bc/07/CPCSEA). The research work was approved by the IAEC (Institutional Animal Ethics Committee) with IAEC No. 2015/3E-16/12/15. Food and water to mice were provided *ad libitum* (prepared mixed formulated food by the laboratory itself). The experimental animals were housed in conventional polypropylene cages in small groups (2 each). The rats were randomly assigned to control and treatment groups. The temperature in the experimental animal room was maintained at 22 ± 2θC with 12 h light/dark cycle.

Chemicals

Sodium Arsenite (98.5%) manufactured by Sigma-Aldrich, USA (CAS Number: 7784-46-5), was obtained from the Scientific store of Patna of Bihar India.

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Medicinal plant used

Gum of *Ferula assafoetida* was used as antidote.

Preparation of *Ferula assafoetida* aqueous extract: In the present study, gum of *Ferula assafoetida* were procured locally from Patna, Bihar, India The identity of the medicinal plant was confirmed by Dr.Ramakant Pandey (Botanist), Department of Biochemistry, Patna University, Patna, Bihar, India. The collected gum of *Ferula assafoetida* were dried and were grinded to fine powder. The aqueous extract dose was calculated after LD_{50} estimation which was found to be 1600mg kg^{-1} body weight and the final dose was fixed to 100 mg kg^{-1} body weight.

Chronic toxicity study

Selected pathogen-free mice were sorted and sodium arsenate was administered at the dose of 3 mg/kg body weight dose for 4 weeks by Gavage method. Sacrifices were done at the end of 4th week of Sodium arsenite administration in each group.

Bioremediation

Sodium arsenate administration 3 mg/kg body weight for 4 weeks was followed by the administration of *Ferula assafoetida* for 4 and 6 weeks at the dose of 100 mg/kg body weight. Animals were sacrificed on 4th and 6th weeks of administration.

Biochemical assessment

Blood samples were collected by orbital puncture and centrifuged to separate the serum to carry out biochemical analysis. Biochemical analysis were performed through serum by standard kit process (Coral crest) through U.V Vis spectrophotometer.

Histopathological study

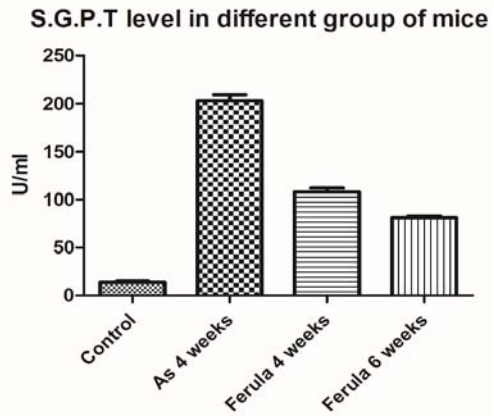
All mice were sacrificed after the scheduled period. A midsaggital incision was made and liver tissue from all the mice were removed and fixed in 10% neutral formalin. For the light microscopic study the Haemotoxylin- Eosin stained slides were prepared and the sections were viewed under light microscope.

Statistical analysis

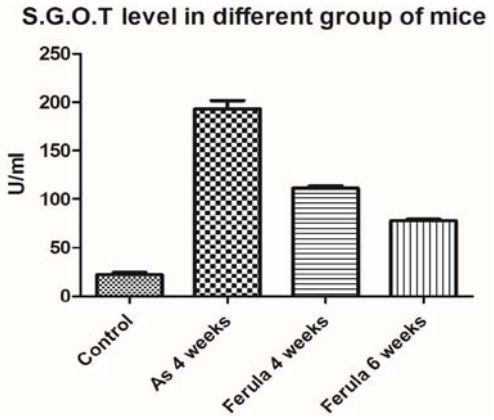
Results are presented as mean ± S.D and total variation present in a set of data was analysed through one-way Analysis of Variance (ANOVA). Difference among means has been analysed by applying Dunnett's 't' test at 99.9% ($p < 0.05$) confidence level. Calculations were performed with the GraphPad Prism Program (GraphPad Software, Inc., San Diego, USA).

Results

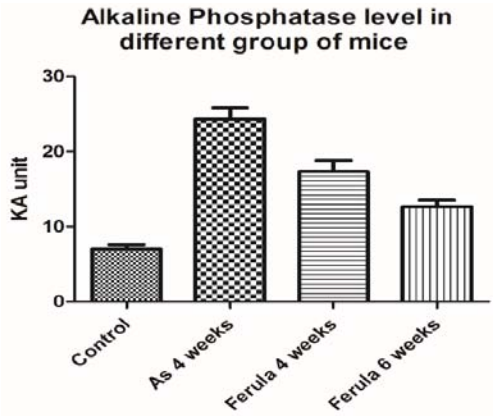
The biochemical assay showed the following findings - in control group of mice SGPT level was 17 ± 2.17 U/ml and 210 ± 7.26 U/ml after 4 weeks of arsenic administration. While, it was 108 ± 2.71 U/ml and 82 ± 1.24 U/ml after 4 weeks and 6 weeks of *Ferula assafoetida* administration (Graph 1). In control group of mice SGOT level was 18 ± 1.14 U/ml and 198 ± 4.78 U/ml after 4 weeks of arsenic administration. While, it was 112 ± 1.93 U/ml and 78 ± 1.07 U/ml after 4 weeks and 6 weeks of *Ferula assafoetida* administration (Graph 2). In control group of mice Alkaline Phosphate (ALP) level was 7 ± 0.98 KA Units and 24 ± 1.91 KA Units after 4 weeks of arsenic administration. While, it was 17 ± 0.85 KA Units and 13 ± 0.51 KA Unit after 4 weeks and 6 weeks of *Ferula assafoetida* administered group (Graph 3). In control group of mice bilirubin level was 0.75 ± 0.10 mg/dl and 2.43 ± 0.48 mg/dl after 4 weeks of arsenic administration, while it was 1.67 ± 0.08mg/dl and 1.30 ± 0.03mg/dl after 4 weeks and 6 weeks of *Ferula assafoetida* administered group (Graph 4).



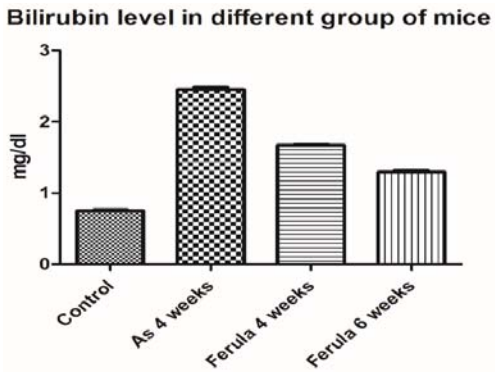
Graph 1: Effect of *Ferula assafoetida* on Arsenic induced toxicity showing SGPT activity (n=6, values are mean ± S.D).



Graph 2: Effect of *Ferula assafoetida* on Arsenic induced toxicity showing SGOT activity (n=6, values are mean ± S.D).



Graph 3: Effect of *Ferula assafoetida* on Arsenic induced toxicity showing ALP activity (n=6, values are mean ± S.D).



Graph 4: Effect of *Ferula assafoetida* on Arsenic induced toxicity showing Bilirubin activity (n=6, values are mean ± S.D)

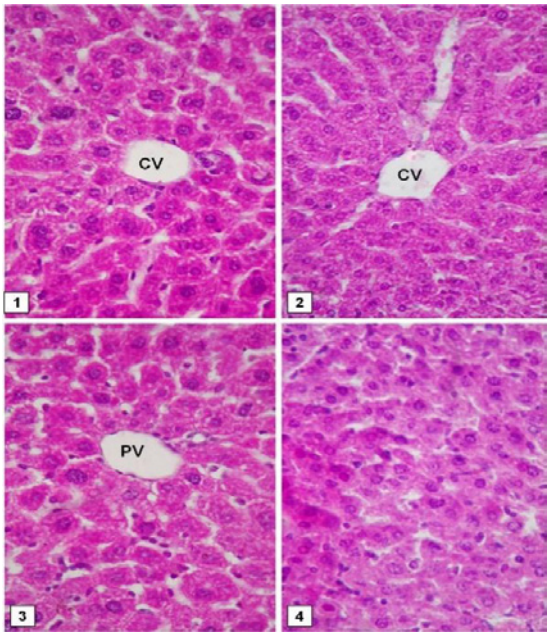


Figure 1: Microphotographs section of liver tissue of control mice stained with haematoxylene and eosin showing polygonal hepatocytes with centrally placed nucleus with intact dense cytoplasm. Sinusoids (S) are clearly seen which are opening in the Central Vein (CV). Portal Vein (PV) X500.

Discussion

Arsenite binding to protein serves as a reservoir and takes place after initial increase in arsenite concentration. When methylation enzymes start to become effective, the reservoir may slowly release small amounts of arsenite for methylation [10]. The methylation of arsenite is catalyzed by a specific methyltransferase using Sadenosylmethionine as a Methyl donating cofactor (SAM). The trivalent Arsenic compounds are more cytotoxic then their pentavalent forms. However, various studies in animals and cell cultures have shown the adverse effects of methylated Arsenic, such as DMAV as a tumor promoter or direct genotoxic action of MMAIII and DMAIII *in vitro* [11]. The main excretion route of Arsenic is through the urine and bile. However, the various Arsenic metabolites do not excrete in the same farsenichion in different animals and humans. In present study we observed increase in bilirubin and alkaline phosphate many folds.

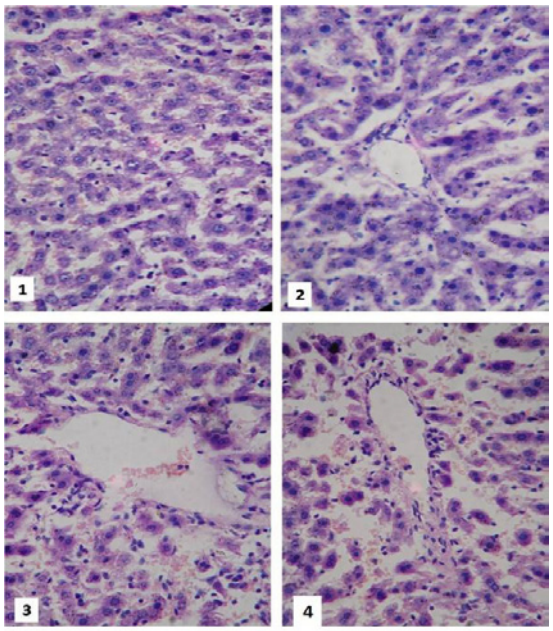


Figure 2: Microphotographs section of liver tissue of 4 weeks arsenic treated mice stained with haematoxylene and eosin showing degenerated hepatocytes with multilobed nucleus and degenerated cytoplasm. Degeneration in the endothelial cells of the central vein and portal veins was observed. X500.

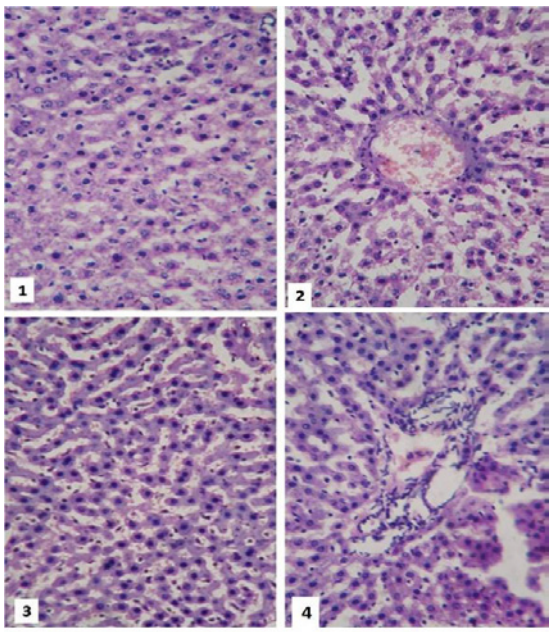


Figure 3: Microphotographs section of liver tissue of 4 weeks (Fig.1&2) & 6 weeks (Fig. 3&4) *Ferula assafoetida* administered upon 4 weeks arsenic treated mice stained with haematoxylene and eosin showing amelioration in the hepatocytes as very least degeneration is observed. Granulated nuclei observed in hepatic cells with only few vacuolated spaces. Sinusoids and central vein are also restored at much extent along with nuclear material. X500.

The common thinking is that tri-valent arsenic metabolites

inhibit Pyruvate Dehydrogenase (PDH), which leads to disruption of the energy system of the cell, [12] which in turn may release an Apoptosis-Inducing Factor (AIF) resulting in cell damage and death. Inhalation causes lung tumors, while oral exposure causes skin tumors. Individuals chronically consuming arsenic contaminated water also exhibit cancer in other organs including the bladder, liver and kidney [13,9]. Since, the liver tends to accumulate arsenic with repeated exposures, hepatic involvement has been reported most commonly as a complication of chronic exposures over periods of months or years [14]. In present study we observed more than 10 folds increase in SGPT and SGOT level in arsenic administered group.

There is clear evidence that arsenic can disrupt gene expression, particularly through its effects on signal transduction. Arsenic can interact directly with the Glucocorticoid Receptor (GR), selectively inhibiting GR-mediated transcription. It has been suggested that arsenic can disrupt cell division by deranging the spindle apparatus [15], chromosome damage and aneuploidy, and causes micronucleus formation, DNA–protein cross-linking, and sister chromatid exchange. It is known to inhibit DNA repair and even to exacerbate the effects of other mutagenic agents, thereby increasing susceptibility to multiple diseases [16].

Ferula assafoetida, administered orally to rats at a dose of 2500 mg% for 8 weeks, decreased the levels of phosphatases and sucrase in the small intestine [17]. In present study, Ferula administration causes significant restoration in SGPT and SGOT while bilirubin and alkaline phosphate were restored more effectively. The resin portion is known to contain asaresinotannols 'A' and 'B', ferulic acid, umbelliferone which probably plays the vital role to combat the arsenic induced hepatotoxicity in mice [18,19].

However, the histopathological study reveals the amelioration in the liver tissue of the *Ferula asafoetida* treated group. This denotes that there is remarked restoration at the histopathological level. But, at the biochemical level the restoration is in the process [20]. have well studied the chemopreventive effect of asafoetida at histopathological level in DMH induced colon carcinogenesis in rats. Similar studies like [21,14] have also observed the antinociceptive effect of *Ferula assafoetida* oleo-gum-resin in mice at histopathological level.

Therefore, the above study shows that *Ferula assafoetida* plays the vital role to combat the toxic effects of arsenic in liver of mice.

Conclusion

It is concluded from the study that arsenic causes increase in liver function enzymes many folds. *Ferula assafoetida* causes effective restoration in SGPT and SGOT levels, while alkaline phosphatase and billirubin were more restored after *Ferula assafoetida* administration. The histopathological study also correlates that asafoetida restores the cellularity of the hepatocytes damaged by the arsenic induced toxicity. Thus, indicates that *Ferula assafoetida* possesses hepato-protective effect against arsenic induced toxicity.

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