RESEARCH ARTICLE

Effect of Morin on Arsenic-induced Hepato-Renal Toxicity in Swiss Albino Mice

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Abstract

Morin is a bioflavonoid with antioxidant properties. This study was aimed to investigate the protective effects of morin against arsenic induced hepatic and renal injury and hematotoxicity in mice. 24 male Swiss albino mice of 5-6 weeks of age were divided into four experimental groups six mice each, Gr-I (control), Gr-II (Arsenic trioxide @ 3 mg/kg b.wt. p.o. for 28 days), Gr-III (morin @ 50 mg/kg b.wt. p.o. + Arsenic trioxide @ 3 mg/kg b.wt. p.o. for 28 days), Gr-IV (morin @ 100 mg/kg b.wt. p.o. + Arsenic trioxide @ 3 mg/kg b.wt. p.o. for 28 days). In Gr-III and Gr-IV Morin was administered 30 min before oral administration of arsenic trioxide. On 29th day 0.5-1.0 mL blood was collected, and serum was separated and used to determine hepatic marker biomolecules AST and ALT and, renal marker biomolecules creatinine and urea. The serum ALT and AST levels in arsenic intoxicated animals increased as compared to control group, which were attenuated by co-administration with morin. Creatinine and urea level in Gr II was significantly high compared to control animals which was decreased by co-administration with morin. TLC was reduced in arsenic-intoxicated animals, which improved due to co-administration with morin @ 100 mg/kg p.o. Histopathology revealed significant improvement in hepatic and renal histoarchitecture in groups treated with morin @ 100 mg/kg p.o. It is suggested that morin @100 mg/kg p.o is more protective than @50 mg/kg/b.wt. p.o against arsenic-induced hepatic and renal toxicity in Swiss albino mice.

Keywords: Arsenic, Hepatic biomarkers, Hepatotoxicity, Morin, Nephropathy.

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Introduction

Human get exposed to inorganic arsenic mostly via pollution from industry and drinking water (Messarah *et al*., 2012). Toxicity to trivalent arsenic is attributed to binding to thiols or sulphur-containing ligands and increased free radical generation (Majhi *et al*., 2011; Patra *et al*., 2012; Dash *et al*., 2013). The epidemiological study reflects that fibrosis of liver, liver carcinoma, hepatomegaly etc. are seen in arsenic exposed areas due to chronic exposure (Wu *et al*., 2008; Dutta *et al*., 2014). Many reports suggested oxidative stress as the main factor behind hepatotoxic events of arsenic

Synthetic antidotes like BAL (British anti-lewisite) and dimercapto propane-1-sulphonate is available for management of arsenicosis which act through chelation. However, these metal chelators are not free from adverse side effects (Mehta & Flora, 2001), therefore dietary intervention or supplementation with phytochemicals may be of interest to population at risk. Morin (3,5,7,2′,4′-pentahydroxyflavone), is a bioflavonoid found in different fruits and herbs. Conventional metal chelators gradually getting replaced with Phyto-antioxidants for combating toxicity of arsenic. Morin, a natural bioflavonoid has been recognized for its pharmacological properties like chemoprotective (Kawabata *et al*., 1999), anticancer (Kuo *et al*., 2007), anti-inflammatory (Fang *et al*., 2003), antioxidant activity (Merwid-Lad *et al*., 2012; Prahalathan *et al*., 2012). Hence, in this study, the therapeutic potential of morin was assessed on arsenic-induced hepatotoxicity in male Swiss albino mice with reference to hepatic and renal markers, hematological parameters and histology.

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Materials and Methods

Preparation of Drugs and Chemicals

Arsenic trioxide stock solution (0.01 g As_2O_3/mL of 1N NaOH) was prepared by dissolving 0.1-g of As_2O_3 in 10 mL 1N NaOH and stored in refrigerator at 4°C. At the time of dosing of animals As_2O_3 of concentration 1-mg/mL was prepared fresh with normal saline (NS) from this stock solution. Morin stock

solution was prepared freshly by dissolving 36 mg of Morin in 150 µL of 1 N NaOH and volume was made to 3 mL by adding NS. The required amount was administered to the animals per oral through a gavage from this solution.

Experimental Animals and Designs

Twenty-four male Swiss albino mice purchased from CPCSEA registered breeder were kept for 7 days acclimatization period inside the Lab Animal house, College of Veterinary Science and AH (Regd.no.433 CPCSEA/CVS/2007) in separate clean polypropylene cage with stainless steel grill with soft bedding material. Pellet feed were made available for the mice. Animals were provided continuous access to fresh drinking water along with 12 hours light and 12 hours darkness.

After 7 days acclimatization mice were divided into four experimental groups having six animals each; Gr-I (untreated control), Gr-II (Arsenic trioxide @ 3 mg/kg b.wt. p.o. for 28 days), Gr-III (morin @ 50 mg/kg b.wt. p.o. + Arsenic trioxide @ 3 mg/kg b.wt. p.o. for 28 days). Gr-IV (morin @ 100 mg/kg b.wt. p.o. + Arsenic trioxide @ 3 mg/kg b.wt. p.o. for 28 days). Morin was administered 30 min before oral administration of arsenic trioxide. All experimental protocols were performed with due approval from Institutional Animal Ethical Committee (Approval No 06/IAEC/dt.09.03.18). Dose of morin and arsenic trioxide was decided as per Shankari *et al*. (2010) and Das *et al*., (2015) respectively.

Haematological and Biochemical Analysis

0.5 mL of whole blood was collected from retro orbital sinus mixed with EDTA in 1.5 mL Eppendorf tube to estimate the haematological parameters (Hb, TLC, and TEC). 1-mL blood was collected in vacutainer to separate serum by centrifugation at 1008 x g for 10 min. The serum was collected aseptically and stored immediately at -20^{o}C. Biochemical parameters (ALT, AST, Creatinine and Urea) were estimated from un-haemolysed serum sample by using the commercially available biochemical kits (CORAL, India). For analysis of each parameter 160-200 µL of serum sample was used in Autoanalyzer.

Histopathological Study

On 29th day the animals from different groups were sacrificed by cervical dislocation. Tissues (liver and kidney) were removed and fixed in 10% buffered neutral formalin (BNF) for 72 hours after gentle rinse with normal saline (NS) to remove blood and debris adhering to them. The liver and kidney tissues were subjected to overnight washing under slow running tap water, subsequently dehydrated through ascending grades of alcohols, cleared in xylene and embedded in molten (temperature 60^{o}C) paraffin wax to obtain paraffin blocks. The tissue paraffin blocks were sectioned through rotary microtome to obtain 5-6 µ thick section and stained with Haematoxylin and Eosin following the standard procedure in practice. The slides were studied under a trinocular research microscope (Leica, DM 2500, Digital camera system DFC 290, Germany)

Statistics

Results were expressed as Mean ± SEM (n= number of animals). Data were analysed by Oneway ANOVA followed by Dunet posthoc test.

Table 1: Effect of Morin @50 mg/kg p.o and @ 100 mg/kg p.o on biochemical parameter in arsenic-intoxicated mice. n=6

Parameters	*Gr I*	*Gr II*	*Gr III*	*Gr IV*
AST (U/L)	145.67 ± 15.21	289.52** ± 33.14	151.68 ± 3.02	156.72 ± 4.80
ALT (IU/L)	45.52 ± 4.38	79.63* ± 8.11	64.35 ± 6.18	73.40 ± 7.95
Creatinine (mg/dl)	0.57 ± 0.04	0.75 ± 0.06	0.68 ± 0.04	0.70 ± 0.07
Urea (mg/dl)	28.43 ± 1.87	38.33** ± 2.36	32.88 ± 2.06	35.63 ± 2.35

[* p < 0.05, **p < 0.01]

Table 2: Effect of Morin @50 mg/kg p.o and @ 100 mg/kg p.o on Haematological parameters in arsenic-intoxicated mice. n=6

		Gr I	*Gr II*	*Gr III*	*Gr IV*
Hb (gm/dl)	0 day	11.05 ± 0.78	11.88 ± 0.43	10.96 ± 0.64	11.13 ± 0.39
	14 day	11.93 ± 0.34	12.33 ± 0.55	11.58 ± 0.29	14.07** ± 0.48
	28 day	11.48 ± 0.78	13.18 ± 0.47	14.27** ± 0.44	13.37 ± 0.93
TLC (no./cu.mm.)	0 day	7866.67 ± 345.12	8088.33 ± 301.45	8183.33 ± 266.35	8416.67 ± 231.54
	14 day	8266.67 ± 197.77	8700.00 ± 437.42	8716.67 ± 411.84	8433.33 ± 189.15
	28 day	8783.33 ± 536.29	4663.33** ± 909.58	4550.00*** ± 464.58	6732.00* ± 412.98
TEC (million/cu.mm.)	0 day	7.08 ± 0.56	6.68 ± 0.59	7.35 ± 0.46	7.20 ± 0.58
	14 day	7.12 ± 0.59	6.77 ± 0.40	5.98 ± 0.66	6.57 ± 0.55
	28 day	7.05 ± 0.53	7.15 ± 0.55	6.90 ± 0.66	6.10 ± 0.34

[* p < 0.05, **p < 0.01, ***p < 0.001]

Results and Discussion

The results on biochemical and hematological alterations due to arsenic intoxication and ameliorative effect of Morin in Swiss albino mice are presented in Tables 1 and 2, respectively.

AST and ALT activities are two sensitive bio-markers of hepatic injury. Enhanced ALT and AST activities in experimental mice exposed to arsenic are attributed to hepatic cell membrane leakage and loss of cellular integrity (Kotyzova *et al*., 2013; Muthumani, 2013). Significantly higher ($p < 0.01$ and $p < 0.05$) levels of AST (289.52 ± 33.14 Vs145.67 ± 15.21 U/L) and ALT (79.63 ± 8.11 Vs 45.52 ± 4.38 IU/L) in mice exposed to arsenic than in control animals (Table 1), may be due to damage to the membrane of hepatocytes because of arsenic intoxication. Morin when administered orally, reduced hepatotoxicity and decreased levels of hepatic markers (Table 1); which might be attributed to their membrane protective effects (Bhattacharjee *et al*., 2014).

Serum creatinine (0.75 ± 0.06 mg/dl) and urea levels (38.33 ± 2.36 mg/dl) were significantly increased by arsenic intoxication (Gr II) compared to control (Gr I) that indicating towards renal injury and reduced glomerular filtration rate (Wei *et al*., 2015). Morin ameliorated these pathological changes in the kidney in a dose-dependent manner (Table 1) might be hindering nitrosative stress or oxidative stress or inflammation (Athira *et al*., 2016).

Hematological parameters are very useful indicators of toxicity due to drugs and environmental toxins in human and animals. There was an initial insignificant rise in TLC value in all the groups during the 14th day of observation (Table 2), which might be attributed to increased immune response due to exposure to foreign substances. It is evident from different studies that TLC increases due to stimulation of body defence mechanism on exposure to foreign entities/toxicants which usually decreases on chronic exposure because of depression of the immune response (Tandan *et al*., 2012, Mondal *et al.,* 2016). In this study exposure to arsenic (Gr II) led to a significant decrease in TLC value by 28th day (4663.33 ± 909.58 no./cu.mm) whereas TEC and total Hb% was not significantly affected (Table 2) compared to control mice, which is in partial agreement with Gora *et al*., (2013). The fall in TLC value in arsenic intoxicated animals is in corroboration with earlier findings by Mittal and Flora, (2007) might be due to bone marrow depression by arsenic intoxication leading to depressed white blood cell production (Mittal and Flora, 2007). As evident from Table 2, by 28th day co-administration of Morin @100 mg/kg p.o (Gr IV) partially protected the TLC value (6732.00 ± 412.98 no./cu.mm) may be attributed to the immunomodulatory property of the naturally occurring flavonoid. Campbell (2014) reported a reduction in erythrocyte count due to arsenic trioxide administration. No significant change in total erythrocyte count was observed due to arsenic administration in this study.

The histoarchitecture of the hepatic parenchyma of the arsenic-intoxicated group (Gr II) revealed lobular degeneration, necrotic changes in the parenchyma, hypertrophy, and mild fatty changes in the hepatocytes with the disintegration of sinusoids (Fig. 1a). Similar findings like vacuolar degeneration followed by hepatic necrosis have been reported in the case of rat intoxicated with arsenic (Gora *et al*., 2014). These damages to liver tissue, further supported by the increased level of hepatic marker enzymes, AST and ALT observed during the experiment may be suggested to an imbalance between the pro-oxidation and antioxidant homeostasis mechanism of liver (Sarkar *et al.,* 2014). In arsenic-intoxicated mice pre-treated with morin @50 mg/kg p.o (Gr III) the liver parenchyma revealed poor lobulation pattern with scanty interlobular connective tissue. The hepatocytes revealed

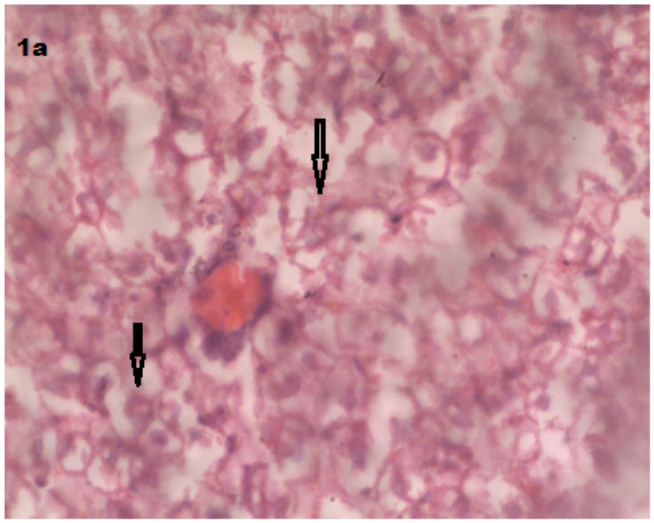

Fig. 1a: Photomicrograph of liver of mice challenged with arsenic trioxide showing fatty change in hepatocytes, desquamation of hepatocytes and disintegration of sinusoids
H & E × 400

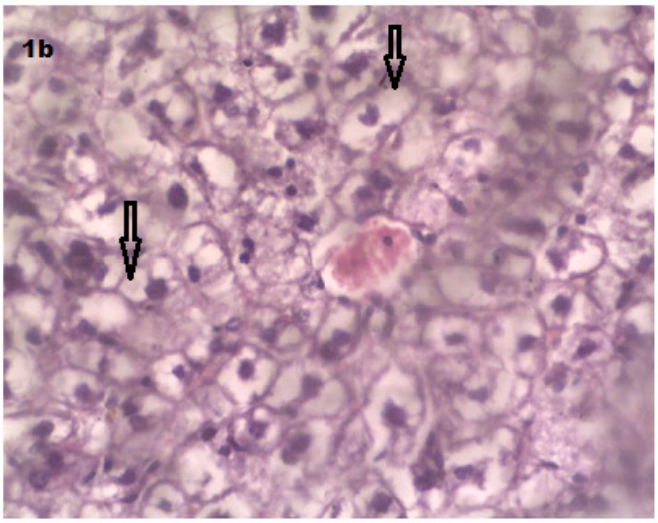

Fig.1b: Photomicrograph of liver of mice treated with morin @ 50 mg/kg bwt and arsenic trioxide @ 3 mg/kg b.wt showing hypertrophy of the hepatocytes. Note fatty change in the cytoplasm of the hepatocytes
H & E × 400

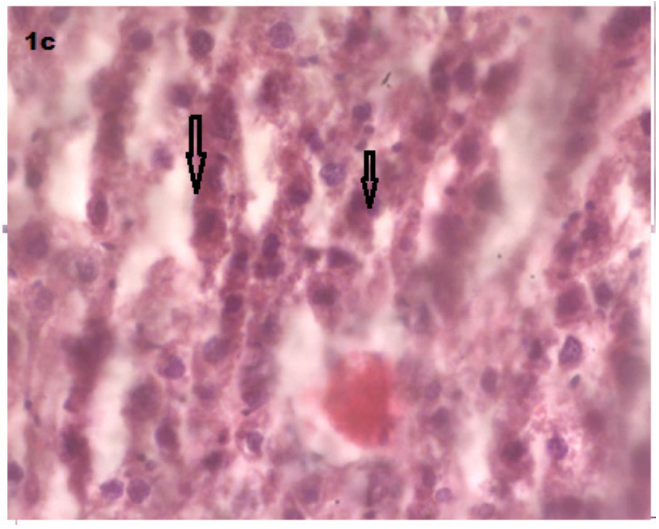

Fig. 1c: Photomicrograph of liver of mice treated with morin @100 mg/kg bwt and arsenic trioxide @ 3 mg/kg b.wt showing normal hepatocytes with moderate hypertrophy of sinusoids.
H & E × 400

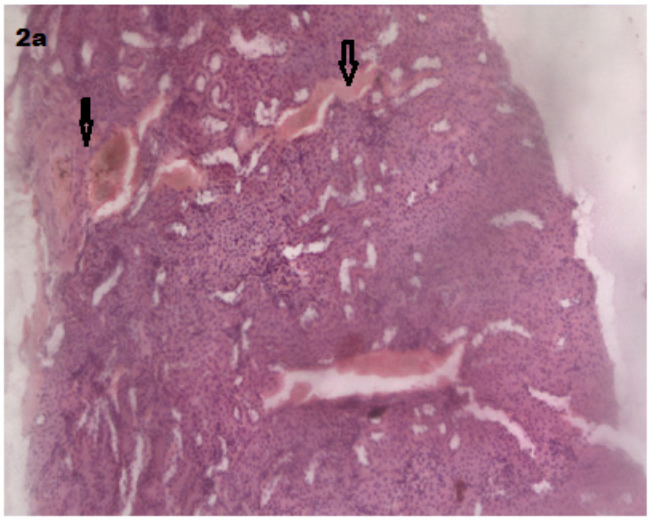

Fig. 2a: Photomicrograph of kidney of mice challenged with arsenic trioxide showing tubular hypertrophy and hyperplasia. Note extensive haemorrhage in the parenchyma
H & E × 100

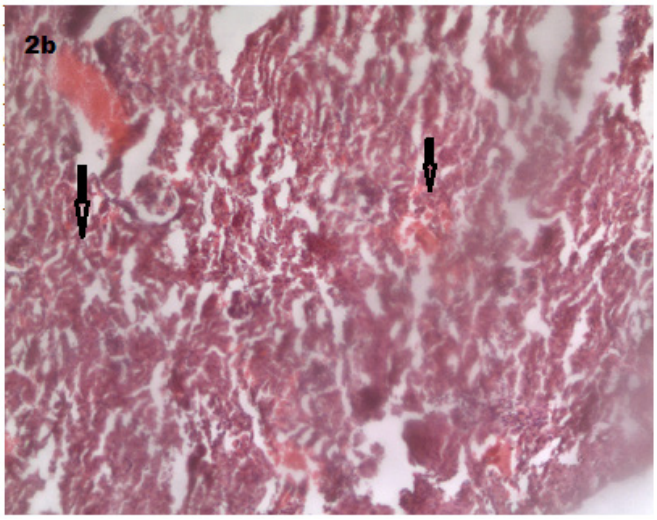

Fig.2b: Photomicrograph of kidney of mice treated with morin @50 mg/kg b.wt. and arsenic trioxide @ 3 mg/kg b.wt showing tubular necrosis and haemorrhage in the parenchyma
H & E × 100

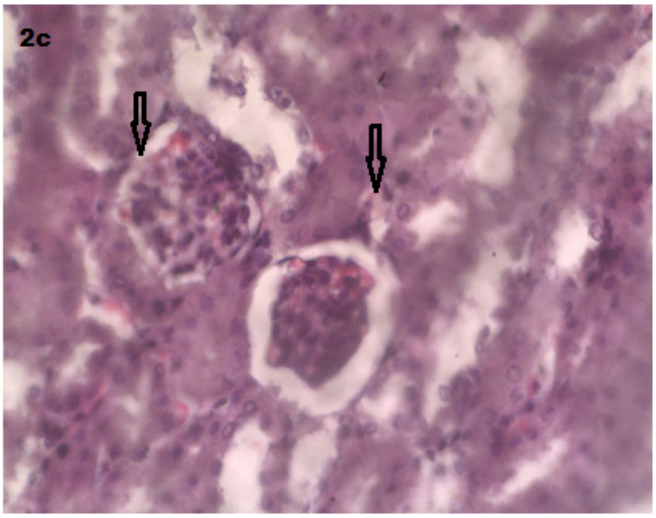

Fig. 2c: Photomicrograph of kidney of mice treated with morin @100 mg/kg b.wt. and arsenic trioxide @ 3 mg/kg b.wt showing the normal architecture of the renal parenchyma with mild oedema and hypertrophy of renal tubules
H & E × 400

severe hypertrophy with distinct fatty changes in their cytoplasm (Fig. 1b). In arsenic-intoxicated mice pre-treated with morin @100 mg/kg p.o (Gr IV), hepatocytes appeared normal with moderate hypertrophied sinusoid (Fig. 1c).

The histoarchitecture of kidney of the arsenic-intoxicated group (Gr II) revealed glomerular hypertrophy, necrosis of the tubular cells, and hemorrhage in the parenchyma with mild proliferation (Fig 2a). This is justified by recently observed hyperplasia in the bladder epithelium in mice treated with sodium arsenite (Suzuki *et al*., 2008). The renal tissue damage observed during this study may be interlinked to a higher level of creatinine and urea detected in animals administered with arsenic trioxide (Noman *et al*., 2015). In Gr III, the renal parenchyma revealed mild congestion and a moderate degree of tubular hypertrophy. There was a remarkable proliferation of the capillaries in the parenchyma, including hemorrhage (Fig. 2b). In Gr IV, the histomorphology of the renal parenchyma was apparently normal with typical glomeruli and glomerular cells. The renal tubules revealed mild to moderate degree of hypertrophy (Fig. 2c).

Conclusion

The toxicity of arsenic and the ameliorative effect of morin was evaluated based on hemato - biochemical and histopathological changes. The study reveals that morin @ 100 mg/kg p.o co-administration can ameliorate the toxicity developed by arsenic.

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