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Original Article

Toxicological effects of arsenic trioxide on blood, serum biochemical constituents and hormonal profile of rabbits and their amelioration with olive oil

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Abstract

Arsenic is considered one of the major environmental toxic metals causing male infertility. The objective of the present study was to evaluate the toxic effects of arsenic trioxide on the body weight, serum biochemical constituents, hematological parameters, and hormonal profile of male rabbits. To ameliorate the toxicity of this metal, olive oil was used. For this purpose, sixteen adult male rabbits were randomly divided into four groups for this experiment. Group A was kept as control, group B (arsenic trioxide 5 mg/kg body weight), C (arsenic trioxide as in group B + olive oil 5 ml/kg body weight), and Group D (olive oil 5 ml/kg BW) were used in this experiment. The blood samples from these animals were collected every two weeks to determine the hematological values. Serum was also separated to analyze the hormonal profile and serum biochemical constituents. Obtained data of this experiment were subjected to two-way analysis factorial. Following the oral administration of arsenic trioxide, body weight significantly reduces in group B as compared to groups A, C and D. Similarly, level white blood cells, red blood cells, packed cell volume, and hemoglobin was reduced in group B as compared to other three groups. The endocrine profile indicated that the level of testosterone, follicle-stimulating hormone, luteinizing hormone reduced in the arsenic trioxide group as compared to the control group. Arsenic trioxide in group B negatively influences the serum biochemical parameters as compared to the other three groups. Supplementation of olive oil alleviated the toxic effects on of parameters. It is concluded that arsenic trioxide causes major male reproductive toxicity, whereas olive oil has an ameliorating effect to reduce toxicity.

Keywords: Arsenic trioxide, Olive oil, Toxicological effects, Hormonal level

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Introduction

The pollution of heavy metals has been increasing due to the rise of anthropogenic activities (Gouva et al., 2020). These metals rise is considered as an important source of contamination of the environment and potential to human health (Sharaf et al., 2020). Arsenic is a metal that is considered human carcinogenic. It is continuously produced from insecticides and pesticides. It contaminates the water and fodder for livestock in developing countries. Agriculture soil and water are continuously contaminating due to their natural products from the crust. Exposure to arsenic can occur through different routes and inhalation and skin contact are also important. Food and water are two major sources of the exposure of arsenic to humans (Tahir et al., 2017).

Hematological exposure to arsenic resulted in major adverse effects in the form of decreased hemoglobin, packed cell volume, red blood cells, and lymphocytes (Simonato et al., 2008). Arsenic is known as carcinogenic metal especially in visceral organs and skin (Zhao et al., 1997). The liver and kidney are considered the most susceptible organs for arsenic toxicity (Mashkoor et al., 2013). Feeding of arsenic to White Leghorn Cockerels resulted in the reduction of body weight and degenerative changes in the histology of the liver and kidney (Ghaffar et al., 2017). Exposure of this metal leads to moderate changes in the tissues of rabbits and rats (Kannan et al., 2001; Gora et al., 2014).

Arsenite induces reproductive toxicity in the male reproductive system when given through water or by intraperitoneal injections (Pant et al., 2004; Sarkar et al., 2003). Arsenic trioxide causes interference in the process of spermatogenesis and inhibits the activities of testicular enzymes (Chinoy et al., 2004). The reduction of body weights, serum level of luteinizing hormone, follicle-stimulating, and testosterone are caused by feeding sodium arsenite to rats (Morakinyo et al., 2010). Sodium arsenite caused changes in the blood of goats (Islam et al., 2011).

Natural treatments with fruits and vegetables have been used due to their no side effects (Sindu et al., 2019). Olive oil is known as the main fat in human food and has many useful effects on the health of humans (Waterman and Lockwood, 2007). Olive oil has a rich quantity of phenolic compounds which gives its proper taste and antioxidants properties (Caruso et al., 2001). Antioxidant property may be due to its strong anti-inflammatory, antioxidant, and vasodilator effects (Covas, 2007). Olive oil has been famous for its antioxidants properties in hypotension, hypoglycemia, and liver protection (Bitler et al., 2005). The use of olive oil in feed containing a higher concentration of cholesterol improves the lipid metabolism and antioxidants status in rats (Gorinstein et al., 2002). The use of cooking oil in food has the ability to the reduction of malignant tumors in the stomach, ovary, and colon (Rodriguez-Rodriguez et al., 2006). The use of olive oil in the feed also improves the semen parameters in goat bucks (Farooq et al., 2019).

Therefore, the objectives of the present study were to determine the toxic effects of arsenic trioxide on body weight, blood parameters, and serum biochemical constituents, hormonal profile and their protection with olive oil in rabbits.

Material and Methods

Experimental animals and treatments

A total of sixteen adult rabbits weighing 1300-1500 g, were purchased from the market and kept in cages. These animals were kept for 15 days to acclimatize the environment and all the procedure of this experiment was approved from the animal ethical committee of University. The experiment was conducted at the Department of Veterinary Clinical Sciences, University of Poonch Rawalakot Azad Kashmir. The animals were randomly divided into four groups. Each group contains four rabbits. These animals were given carrots and spinach for feeding. All the rabbits were given an acclimatization period of 28 days. The Rabbits of group A were kept in control. Rabbits of group B were fed Arsenic trioxide orally (5mg/day). Rabbits of group C were fed with Arsenic trioxide (5mg/day) and olive oil (2ml). Rabbits of group D were given olive oil (2ml) only. All the above treatments were continued for 28 days.

Bodyweight of rabbits

The body weights of these animals were recorded before the start of the experiment. Animals were placed individually on the electric weighing balance and body weights on days 0 and 28 of the experiment were recorded.

Evaluation of blood parameters

Blood samples of 3ml were collected from the jugular vein at days 0 and 28 for the blood analysis. One ml was used to determine the blood parameters

and the rest serum was separated after centrifugation at 1200 g for 15 minutes and the serum was kept at (-20°C) until analysis. All parameters of blood were measured by a blood analyzer kept in the laboratory of Physiology, Faculty of Veterinary Sciences. The blood parameters include red blood cells, white blood cells, packed cell volume, hemoglobin.

Evaluation of endocrine profile

Serum concentrations of Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), and Testosterone (T4) were determined using commercially available ELISA kits on 0 and 28 days of the experiment. The concentration of Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), and testosterone were determined by Solid-phase ELISA which is based on the principle that competitive binding between testosterone in the sample and testosterone-HRP conjugated for a constant amount of rabbit anti-testosterone by using commercial ELISA based kits Monobind Inc. USA.

Evaluation of blood biochemical constituents

The blood sample (3ml) was collected from the jugular vein on days 0 and 28 of the experiment. Serum biochemical constituents like blood glucose, blood urea, serum creatinine, SGPT, serum cholesterol, serum triglycerides, SGOT, total protein, serum albumin, and serum globulin were determined using commercially available kits (Sigma Co. (USA; Cat. no. 14018 and no. 14002) on Chemistry Analyze (BTS-330, Biosystems, Spain.

This analyzer was used to measure the absorbance of standards and samples. The concentration of each sample was measured by dividing it with standard as well as by multiplication with a concentration of standard.

Statistical analysis

The data were subjected to two factors CRD for analysis. Data were expressed as mean ± SEM. Data were analyzed by using Statistical Software (SPSS; version 20.0, IBM Corp. Armonk, NY) and a *P*-value ≤ of 0.05 was considered significant.

Results

Effect on body weight

In the current study, oral administration of Arsenic trioxide (group B) significantly (P<0.05) reduces the body weight as compared to day 0. However, oral administration of olive oil reduces the negative effect of Arsenic trioxide administration, as there is a non-significant (P>0.05) difference in Group C. Similarly, body weight remains the same (P>0.05) as compared to day 0 in groups A and D (Table 1).

Table 1: Mean values (±SEM) of Body weight, Red Blood Cells (RBCs), White Blood Cells (WBCs), Hemoglobin (Hb), and Packed Cell Volume (PCV) at day 0 and 28 of the experiment

Parameters/Groups	Days	
	0	28
Body weight (g)		
A	1350 ± 64.5^{a}	1400 ± 40.8^{a}
B	1400 ± 40.8^{a}	1100 ± 40.8^{b}
C	1475 ± 47.8^{a}	1300.0 ± 40.8^{ab}
D	1450 ± 28.8^{a}	1550 ± 64.5^{a}
RBCs		
A	5.7 ± 0.2^{a}	5.9 ± 0.2^{a}
B	6.1±0.4^{b}	3.3 ± 0.2^{c}
C	6.1±0.3^{b}	3.8±0.7^{bc}
D	5.2±0.4^{a}	5.5±0.6^{ab}
WBCs		
A	7.7±0.4^{a}	6.7±0.3^{ab}
B	7.7±0.4^{a}	3.5±0.3^{c}
C	7.6±0.8^{a}	4.7±0.2^{bc}
D	7.3±0.5^{a}	7.0±0.1^{a}
Hb		
A	14.7±0.9^{a}	13.5±0.6^{ab}
B	14.9±0.7^{a}	6.5±0.6^{c}
C	14.0±0.7^{ab}	10.5±0.6^{b}
D	13.7±1.1^{ab}	10.5±0.6^{b}
PCV		
A	64.5±2.5 ^{a}	62.0±1.9^{a}
B	63.5±1.8 ^{a}	42.0±1.2^{b}
C	63.0±2.7 ^{a}	55.5±2.2^{a}
D	59.0±2.0 ^{a}	61.7±1.5^{a}

Group A = Control group; Group B = Arsenic trioxide group; Group C = Arsenic trioxide + olive oil group; Group D = Olive oil group: Different superscript within column and row show significant difference (P<0.05)

Effect on blood parameters

In the current experiment, there was a significant (P<0.05) reduction in the level of RBCs as compared to day 0 (Group B). However, olive oil reduces the negative impact of arsenic trioxide as a level of RBCs remains the same (P>0.05; Group C). Similarly, the level of RBCs remains the same (P>0.05) in, A and D

as compared to day 0 (Table 1).

Oral administration of arsenic trioxide significantly (P<0.05) reduces the level of WBCs in group B as compared to day 0. However, the level of WBCs remains the same (P>0.05) in group C that indicates the ameliorating effect of olive oil. Similarly, the level of WBCs remains the same in groups A and D (Table 1).

Data indicate the negative impact of arsenic trioxide on blood parameters, as the level of Hb reduces (P<0.05) as compared to day 0 in group B. However, there was limited (P>0.05) impact of arsenic trioxide on Hb due to ameliorating effects of olive oil group C. Similarly, Hb level remain the same in groups A and D during the experiment (Table 1).

Similarly, the level of PCV remains the same (P>0.05) at days 0 and 28 in groups A, C and D. However, oral administration of arsenic trioxide reduces (P<0.05) the level of PCV in group B as compared to day 0 (Table 1).

Table 2: Mean ± SEM of FSH, LH and testosterone at 0 and 28 days of experiments

Parameters/ Groups	Days	
	0	28
FSH (mIU/ml)		
A	10.1 ± 0.4^{a}	10.2 ± 0.4^{bc}
B	11.3 ± 0.4^{b}	5.5 ± 0.2^{d}
C	10.3 ± 0.6^{a}	8.9 ± 0.5^{c}
D	11.3 ± 0.4^{b}	13.1 ± 0.3^{a}
LH (mIU/ml)		
A	0.45 ± 0.1^{a}	0.42 ± 0.1^{a}
B	0.47 ± 0.1^{a}	0.12 ± 0.03^{b}
C	0.52 ± 0.1^{a}	0.35 ± 0.1^{ab}
D	0.45 ± 0.1^{a}	0.55 ± 0.1^{a}
T4 (ng/ml)		
A	0.85 ± 0.1^{ab}	1.02 ± 0.1^{a}
B	0.92 ± 0.04^{a}	0.5 ± 0.1^{b}
C	0.92 ± 0.05^{a}	0.75 ± 0.1^{ab}
D	0.82 ± 0.1^{ab}	1.07 ± 0.1^{a}

Group A = Control group; Group B = Arsenic trioxide group; Group C = Arsenic trioxide + olive oil group; Group D = Olive oil group: Different superscript within column and row show significant difference (P<0.05)

Endocrine profile

In the current study, the level of FSH decreases (P<0.05) as compared to day 0 in group B. However, group C olive oil, mimic the negative effect of arsenic trioxide as the level of FSH remain the same (P>0.05) during the experiment. Similarly, the level remains the same (P>0.05) in groups A and D (Table 2).

LH concentration also decreases (P<0.05) following the oral administration of Arsenic trioxide as compared to day 0 in group B. However, LH concentration remains the same (P>0.05) in group C that indicates the ameliorating effects of Olive oil. Similarly, LH concentration remains the same in groups A and D (Table 2).

Level of testosterone decreases (P<0.05) following the oral administration of arsenic trioxide in group B as compared to day 0. However, in group C olive oil limit the negative impact of arsenic trioxide on the endocrine profile as concentration remain the same (P>0.05) as compared to day 0. Similarly, the T4 level remains the same in groups A and D during the experiment (Table 2).

Biochemical constituents

Level of albumin decreases (P<0.05) as compared to day 0 following the oral administration of arsenic trioxide (group B). However, olive oil limits the negative impact of arsenic trioxide in group C as the level of albumin remains the same (P>0.05) as compared to day 0. Similarly, in groups, A and D levels of albumin remain the same (P>0.050 during the experiment (Table 3).

Cholesterol level increases (P<0.05) following the oral administration of arsenic trioxide as compared to day 0 in group B. However levels remain the same (P>0.05) in groups A, C, and D during the experiment (Table 3).

Similarly, creatinine level increases (P<0.05) as compared to day 0 in group B, following the oral administration of arsenic trioxide. In group, C the level remains the same due to the ameliorating effect of olive oil. Similarly, in groups, A and D levels remains the same during the experiment (Table 3).

Contrary wise, level of globulin decrease (P<0.05) after the oral administration of arsenic trioxide in group B. However, oil olive reduces the negative impact of arsenic trioxide on globulin as level remain same (P>0.05) as compared to day 0 in group C. Similarly, level remains same in group A and D during the experiment (Table 3).

Level of glucose increases (P<0.05) following the oral administration of arsenic trioxide in group B.

However, the level remains the same in groups A, C, and D during the experiment (Table 3).

Table-3: Mean Level of Serum Biochemical Constituents

Parameters/Groups	Days	
Albumin	0	28
A	3.1 ± 0.05^{a}	3.15 ± 0.06^{a}
B	3.1 ± 0.1^{a}	2.2 ± 0.1^{b}
C	3.1 ± 0.04^{a}	2.9 ± 0.05^{a}
D	3.0 ± 0.04^{a}	3.1 ± 0.04^{a}
Cholesterol		
A	14.7 ± 1.3^{a}	15.2 ± 0.7^{a}
B	14.5 ± 1.3^{a}	33.2 ± 1.1^{b}
C	13.7 ± 0.8^{a}	19 ± 2.0^{a}
D	14.2 ± 1.3^{a}	15 ± 1.2^{a}
Serum Critine (mg/dl)		
A	0.95 ±0.03^{a}	0.97 ± 0.08^{ab}
B	1.07 ± 0.08^{a}	2.07 ± 0.08^{c}
C	0.97 ± 0.1^{ab}	1.15 ± 0.1^{b}
D	1.07 ± 0.04^{ab}	1.05 ± 0.05^{b}
Globulin		
A	2.2 ± 0.08^{a}	2.1 ± 0.08^{a}
B	2.1 ± 0.09^{a}	0.6 ± 0.2^{b}
C	2.2 ± 0.08^{a}	1.5 ± 0.1^{a}
D	2.15 ± 0.06^{a}	2.15 ± 0.06^{a}
Glucose (mg/dl)		
A	115 ± 1.1^{a}	114 ± 1.8^{a}
B	114.2 ± 0.8^{b}	146.7 ± 9.0^{c}
C	114.7 ± 1.3^{b}	121.7 ± 1.4^{bc}
D	114.7 ± 1.7^{c}	118.2 ± 1.0^{ab}
Total protein		
A	5.5 ± 0.1^{a}	5.3 ± 0.02^{a}
B	5.6 ± 0.1^{a}	2.9 ± 0.06^{b}
C	5.6 ± 0.1^{a}	4.4 ± 0.2^{a}
D	5.4 ± 0.06^{a}	5.3 ± 0.1^{a}
AST (SGOT)		
A	12 ± 0.8^{a}	11.5 ± 0.6^{a}
B	11.5 ± 0.6^{a}	38 ± 1.0^{b}
C	11 ± 0.9^{a}	19.5 ± 0.64^{a}
D	12 ± 0.4^{a}	11.7 ± 0.7^{a}
ALT (SGPT)		
A	34 ± 0.57^{a}	31.5 ± 0.6^{a}
B	33.2 ± 1.6^{a}	53.2 ± 1.2^{b}
C	32 ± 0.9^{a}	38.7 ± 0.7^{a}
D	33.2 ± 1.3^{a}	32.7 ±1.0^{a}

Group A = Control group; Group B = Arsenic trioxide group; Group C = Arsenic trioxide + olive oil group; Group D = Olive oil group: Different superscript within column show significant difference ($P<0.05$).

Data indicated that the level of total protein decreases ($P<0.05$) following the administration of arsenic trioxide in group B as compared to day 0. Ameliorating effects were found in olive oil as the level of the total protein remains the same ($P>0.05$) in group C. Similarly, there were no differences ($P>0.05$) in group A and D during the experiment (Table 3).

In group B, levels of SGOT and SGPT increase ($P<0.05$) as compared to day 0 following the oral administration of arsenic trioxide. Oil olive administration decreases the negative impact of arsenic trioxide as the level remains the same ($P>0.05$) during the experiment in group C. Also level remains the same in groups A and D (Table 3).

Discussion

Arsenic trioxide is considered the notorious poison derived from many anthropogenic as well as natural sources. The incidence of contamination of arsenic in groundwater as well fodder is injurious for humans as well as animals. This contamination is going the source of threat for wildlife as well. This toxicity is manifested in the form of reduction in feed intake, body weight, and death in acute cases. There was a loss of body weight after feeding arsenic trioxide as compared to the control group. A similar type of findings has been reported in goats and mice (Akter et al., 2010). This reduction in body weight may be the production of free reactive oxygen species. Feeding of olive oil along arsenic trioxide restored the volume in group C. As many plants contain (Lobitaña et al., 2020) the antioxidant and this amelioration may be due to antioxidant properties.

Similarly, there was a 9.4% loss of body weight of goats which was the result of feeding sodium arsenite of 8mg/ kg per day for eighteen days (Halim, 2007). Severe toxicities in dogs with superior doses of arsenic have been reported, it has been documented that sodium arsenite with a dose of 4 or 8mg/kg as per body weight for eight months had decreased the weight in dogs (Neiger and Osweiler, 1992). Arsenic is considered the main cause of expression of clinical signs. The feeding of olive oil in this study ameliorated the toxic effects on bodyweight which may be due to the antioxidant properties of olive oil.

In the current study, there was a significant deficiency in the blood values following the feeding of arsenic as compared to the control group. Hematological values are considered in the first line of defense against toxicity in humans and animals (Saxena et al., 2011; Ohaeri and Eluwa, 2011). Exposure to arsenic for 30 days caused the reduction

in erythrocytes to count and hemoglobin concentration in humans and mice ((Biswas et al., 2008; Ferzand et al., 2008). Red blood cells are considered as the major targets for arsenic toxicity most important in hemolysis and anemia (Bollini et al., 2010). Reduction in hemoglobin may be due to inactivation of the δ-aminolevulinic acid dehydrates enzyme which plays a significant function in the production of hemoglobin (Li and Sun, 2015; Bhattacharya and Haldar, 2012). This reduction in hemoglobin may be due to the apoptosis of plasma cells due to arsenic (Ferzand et al., 2008). There were scavenging effects present in group C due to olive oil. These effects may be due to bioactive compounds like hydrocarbon and triterpenes. These compounds act as antioxidants against arsenic toxicity.

In the current study, reproductive hormones FSH, LH, and T4 decreased following the oral administration of arsenic trioxide in group B. The findings were comparable to the previous studies in rats (Sarkar et al., 2003; Morakinyo et al., 2010). Reduction in the level of testosterone in arsenic toxicity may be attributed to a reduction in the weight of testes as well as sex organs weight which play an important role in the synthesis of testosterone (Ahmed et al., 2019). Reduction of LH and FSH may be since arsenic toxicity increases the level of cortisol that ultimately reduces the level of male hormone (Biswas et al., 1995). An increase in the level of these hormones in the olive oil group is close with Farooq et al. (2019) and this rise may be due to the activation of GnRH impulses from the hypothalamus by ingesting the polyunsaturated fatty acids present in this oil (Attia et al., 2012).

Alterations in serum biochemical constituents are considered important indicators of arsenic toxicity in animals (Ohaeri and Eluwa, 2011). In the present study, serum liver enzymes (AST and ALT) were elevated significantly and these findings were in close harmony with previous findings (Sayed et al., 2015; Ahmed et al., 2019). This rise of liver enzymes cab is due to cellular damages or an increase in the permeability of the cell membrane (Sayed et al., 2015).

Moreover, there was also a rise in cholesterol, glucose, and creatinine and similar kind of findings were present in the studies of Amer et al. (2016) and Zhang et al. (2014). In our study, there was a significant reduction in the level of albumin, globulin, and total protein and these findings are consistent with previous findings of Charles, (2014) and Mohammed et al. (2014). Feeding of olive oil along arsenic trioxide has restored these serum biochemical constituents and similar kinds of findings were reported by Rashid et al., 2005 and Mohammed et al. (2014). Olive oil contains a large amount of leuropein and tyrosol and this restoration may be due to inhibiting effects of reactive oxygen species (Feng et al., 2008).

Conclusion

In conclusion, arsenic trioxide adversely affects body weights, serum biochemical properties, endocrine profile, and hematological parameters of rabbits. However, ameliorative effects were present in olive oil as it limits the negative impact of arsenic trioxide. Further studies are required to find out the mechanism of arsenic trioxide in the form of oxidative stress and molecular characteristics.

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Contribution of Authors

Zubair M, Shafique S, Shahbaz M & Husain AM: Designed the experiment, collected data and wrote manuscript.
Khalique MA, Saleemi MK, Khan MI & Hameed N: Performed data analysis and manuscript editing.