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RESEARCH ARTICLE

Triazophos induced oxidative stress in female albino rats

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Abstract

Triazophos (TZ), an organophosphate (OP), is widely used as non-systemic broad spectrum pesticide against insect pests. OPs, apart from neurotoxicity and neurobehavioral changes in animals, have been shown to induce oxidative stress (OS) by generating elevated levels of reactive oxygen species (ROS). Present study was undertaken to investigate effects of TZ treatments at dose levels *i.e.* $1/10^{th}$, $1/20^{th}$ and $1/40^{th}$ of LD_{50}, on feed and water intake and body weight in three group of female albino rats as compared to control receiving only olive oil during 30 days experiment. TZ induced OS biomarkers level viz; catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GR), glutathione peroxidase (GPx), glutathione-S-transferase (GST) and lipid peroxidation (LPO) were determined in blood. Results revealed non significant decrease in feed intake and water intake, while body weight and organs weight were comparable in TZ treated female rats ($p<0.05$). The value of total protein content was non-significant in lysate and plasma of blood while OS biomarkers such as CAT, SOD, GR, GPx and LPO were differentially modified in TZ treated female albino rats. Also the total antioxidant activity (AOA) was significantly decreased in plasma of the $1/10^{th}$ and $1/20^{th}$ of LD_{50} TZ treated rats. The results suggest that the exposure of female albino rats to TZ may induce OS at dose dependent manner.

Introduction

Pesticides intended for agricultural and other domestic practices not only produce adverse biological effects against the target species but also have the potential to affect the health of non-target species including human beings (Banerjee *et al.,* 1999; Etemadi-Aleagha *et al.,* 2002). Pesticides have been shown to induce the production of reactive oxygen species (ROS) which ultimately lead to a condition of oxidative stress (OS) (Abdollahi *et al.,* 2004). OS occurs when production of ROS overrides antioxidant capacity in target cells, resulting in the damage of macromolecules such as nucleic acids, lipids and proteins (Agrawal and Sharma, 2010). Organophosphorus pesticides (OPs) exposure is a major public health issue in terms of death, morbidity, health care and general safety from toxicity (Jaga and Dharmani, 2003) as OPs account for over 50% of all insecticides applied world-wide (Casida and Quistad, 2004).

Triazophos, O,O-diethyl-1-H-1,2,4-triazol-3-yl phosphorothioate, (TZ) a non-systemic broad spectrum OP is being extensively used against a wide range of pests and flies that damage agricultural, horticultural and forest crops. Though TZ can potentially affect during its formulation, transport and storage, but general population is exposed to TZ via different routes through food products, vegetables and drinking water (Rani *et al.,* 2001; Li *et al.,* 2008). The residual levels of triazophos in crops, vegetables and water may pose risks to the health of humans and other animals because the severity of TZ intoxication may vary with dose, route and extent of exposure.

OS has been evidenced in cells by the increased level of malondialdehyde (MDA) (end product of lipid peroxidation) and by differentially modified endogenous antioxidants like catalase (CAT), glutathione-S-transferase (GST), superoxide dismutase (SOD) and glutathione peroxidase (GPx), which can lead to development of moderate

to severe pathophysiological consequences (Bebe and Panemangalore, 2003; Mashali *et al.,* 2005). Few studies with laboratory animals regarding toxicokinetics and oxidative stress induction by TZ have been reported (Jain *et al.,* 2010; Jain *et al.,* 2011) which are limited to male albino rats, but no data is available regarding toxicokinetics of TZ in the female albino rats and its effects on blood oxidative stress biochemical parameters, having different physiology than males. Moreover females are more vulnerable than males suggesting a better antioxidative stress defense response in male's (Al-Rejaie *et al.,* 2012). So in present investigation, the toxicity effects of triazophos at $1/10^{th}$, $1/20^{th}$ and $1/40^{th}$ of LD_{50} (*i.e.* 8.2, 4.1 and 2.05 mg/kg of body weight (b.w.)) sub-chronic doses were carried out in terms of oxidative stress biomarkers in blood of female albino rats.

Material and Methods

Chemicals

All chemicals were purchased from Sigma-Aldrich, SDFCL (SD Fine-Chem Ltd), SRL (Sissco Research Laboratories Pvt. Ltd). All chemical used were either of analytical grade or the highest purity commercially available.

Animals

The female albino rats aging 8-10 weeks and weighing 100-150 grams were procured from the Department of Livestock Production and Management, GADVASU, Ludhiana and were maintained in Laboratory conditions with standard pelleted rat feed and water provided *ad libitum*. The animals were kept in a room in which the humidity and temperature were environmentally controlled. All methods and procedures of animal handling during research were conducted in accordance with the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India and experiments conducted in the present study were duly approved by Institutional Animal Ethics Committee (IAEC), Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana vide letter no. 3901-35 dated 06.08.2012.

Experimental design

Female albino rats were acclimatized for ten days in laboratory conditions and were divided into four groups with eight rats in each group. The first group of rats serving as control were given only olive oil and to the remaining three groups of rats, triazophos (40% EC) dissolved in olive oil was given at a dose level of $1/10^{th}$, $1/20^{th}$ and $1/40^{th}$ of LD_{50} *i.e.* 82 mg/kg of b.w. for 30 days by oral intubation. The rats were examined daily for feed intake, water intake and weekly for body weights. The signs of toxicity and mortality during dosing were also recorded.

Organs weight and Blood Hemolysate Preparation

After 30 days of treatment female rats were mildly anaesthetized using chloroform and blood sample from each rats was collected directly from heart in heparinised vials. Blood was centrifuged at 2300 r.p.m. for 15 minutes. Supernatant was obtained as plasma for biochemical analysis and pellet *i.e.* packed cell volume (PCV) was lysed in distilled water was used for preparation of 100% haemolysate as stock for biochemical parameters. After dissection vital organs viz: heart, lungs, brain, spleen, adrenals, thyroid and parathyroid were excised, cleared off the adhering tissue and weighed.

Biochemical Studies

Biochemical parameters of blood were assayed by standard methods. Total proteins was estimated in blood by Lowry *et al.,* (1951), CAT (catalase) by Aebi, (1983), SOD (Superoxide Dismutase) by Marklund and Marklund, (1974), GST (glutathione-S-transferase) by Habig *et al.,* (1974), GR (glutathione reductase) by Carlberg and Mannervik, (1985), GPx (glutathione peroxidase) by Hafeman *et al.,* (1984), LPO (Lipid peroxidation) by Stocks and Dormandy, (1971) and total antioxidant activity in plasma was assayed by Koracevic *et al.,* (2001).

Statistical Analysis

The experimental results are expressed as mean ± standard error of the mean (SEM) for n=6. Statistical analysis of data was performed on a computer by using CPCS1. One-way ANOVA was done to check any significance and the criterion for statistical significance was set at $P < 0.05$.

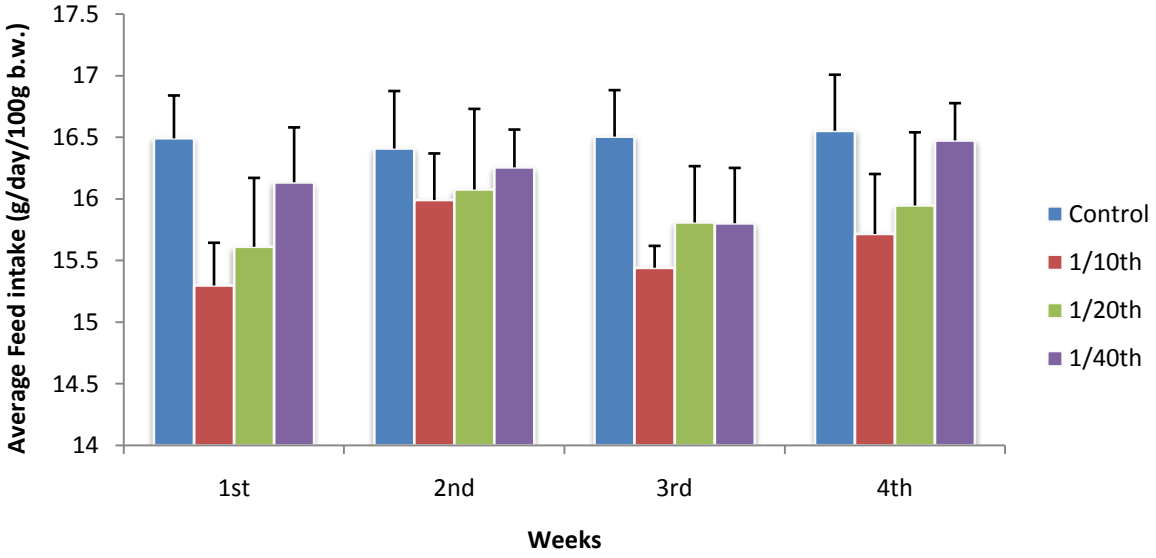
Results

Feed intake, Water intake and Body weight gain

Daily feed intake (Figure 1) and water intake (Figure 2) during 30 days of treatment was non significant in all the treatment groups as compared to control female albino rat group. Average daily feed intake and water intake was low in $1/10^{th}$ and $1/20^{th}$ of LD_{50} TZ treated rats, while at $1/40^{th}$ of LD_{50} TZ treated rats the average feed and water intake was comparable with the control female rats (Figure 1 and 2). Reduced body weight gain was observed in TZ treated rats as compared to control female rats but was not significant ($P<0.05$) (Table 1). During 30 days TZ

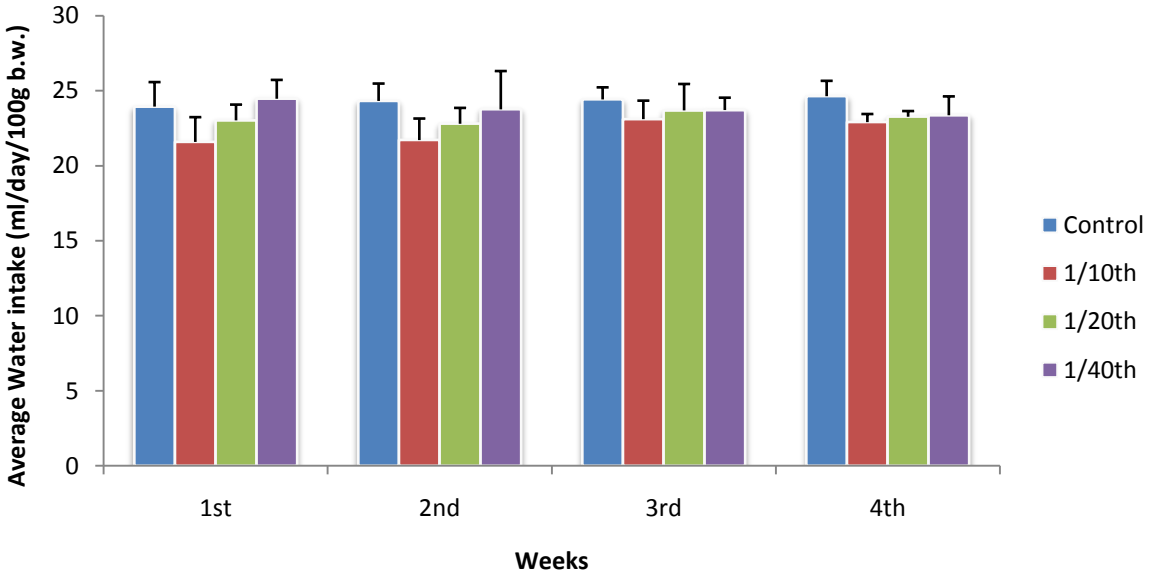
treatment slight hyperirritability and loose faecal pellets were observed in $1/10^{th}$ and $1/20^{th}$ of LD_{50} treated rats, while no excessive salivation were reported in any of the treated and control group rats.

Figure 1: Effect of Triazophos on Average feed intake (g/100g b.w.) in control and treated female albino rats after 1, 2, 3 and 4 weeks of treatment



Values expressed as Mean ± SE (n=8).
*Significant difference ($P \leq 0.05$) as compared to control

Figure 2: Effect of Triazophos on average water intake (ml/100g b.w.) in control and treated female albino rats after 1, 2, 3 and 4 weeks of treatment



Values expressed as Mean ± SE (n=8).
*Significant difference ($P \leq 0.05$) as compared to control

Table 1: Effect of Triazophos treatment on body weight (b.w.) of treated female albino rats as compared to control rats after 1, 2, 3 and 4 weeks of treatment

Treatment		0 day	1st week	2nd week	3rd week	4th week	b.w. gain (%)
Control	Weight (g)	130.71 ±9.15	135.00 ±9.25	149.29 ±10.88	155.71 ±10.32	159.29 ±10.55	21.85 ± 5.07
	Net b.w. gain (g/100g b.w.)	--	3.49 ± 1.58	10.46 ± 1.68	4.63 ± 1.11	2.38 ± 1.24	
	Growth rate (g/day/100g b.w.)	--	0.49 ± 0.23	1.49 ± 0.24	0.67 ± 0.16	0.34 ± 0.18	
I/10th	Weight (g)	134.28 ±7.59	135.71 ±6.31	155.00 ±5.45	155.00 ±6.17	157.14 ±5.21	17.02 ± 4.69
	Net b.w. gain (g/100g b.w.)	--	1.06 ± 0.62	14.69* ± 1.85	-0.09 ± 1.04	1.62 ± 1.39	
	Growth rate (g/day/100g b.w.)	--	0.29 ± 0.23	2.09 ± 0.26	-0.01 ± 0.14	0.23 ± 0.19	
1/20th	Weight (g)	132.28 ±6.12	136.00 ±5.77	145.71 ±5.71	150.00 ±3.93	155.29 ±5.33	17.39 ± 4.36
	Net b.w. gain (g/100g b.w.)	--	4.79 ± 1.51	12.26 ± 1.27	3.34 ± 2.35	3.43 ± 1.33	
	Growth rate (g/day/100g b.w.)	--	0.68 ± 0.21	1.75 ± 0.18	0.47 ± 0.34	0.49 ± 0.19	
1/40th	Weight (g)	131.42 ±9.62	138.14 ±7.71	152.86 ±8.51	156.00 ±8.89	158.57 ±8.41	20.65 ± 5.02
	Net b.w. gain (g/100g b.w.)	--	4.05 ± 1.53	9.47 ± 0.79	2.11 ± 1.30	1.87 ± 1.66	
	Growth rate (g/day/100g b.w.)	--	0.41 ± 0.21	1.07 ± 0.11	0.30 ± 0.18	0.27 ± 0.23	

Values expressed as Mean ± SE (n=8).
*Significant difference ($P \leq 0.05$) as compared to control

Organs Weight

TZ treated female albino rats did not show any significant changes in vital organs weight as compared to control female rats (Table 2). The weight of brain, heart, spleen, thyroid and parathyroid was comparable in control and triazophos treated female rats. Slight non-significant increase in lung and liver weight was observed in all the treatment groups as compared to control. The weight of stomach decreased while adrenals and kidney was increased with 1/10th and 1/20th of LD_{50} dose of TZ as compared to control and 1/40th of LD_{50} treated rats.

Table 2: Effect of Triazophos treatment on Organs Weight (g/100g b.w.) of treated female albino rats as compared to control

ORGANS	Control	1/10th	1/20th	1/40th
Brain	0.952±0.022	0.998±0.034	0.954±0.043	1.009±0.078
Heart	0.292±0.008	0.273±0.006	0.260±0.010	0.301±0.015
Lungs	0.499±0.083	0.532±0.057	0.522±0.022	0.527±0.115
Stomach	1.393±0.291	1.241±0.269	1.319±0.206	1.397±0.441
Liver	3.228±0.152	3.339±0.161	3.334±0.109	3.289±0.138
Spleen	0.239±0.010	0.246±0.003	0.242±0.010	0.242±0.013
Kidney	0.298±0.007	0.327±0.019	0.307±0.034	0.298±0.013
Thyroid	0.106±0.004	0.099±0.017	0.105±0.013	0.106±0.008
Parathyroid	0.046±0.002	0.045±0.005	0.044±0.002	0.045±0.003
Adrenals	0.014±0.002	0.016±0.004	0.016±0.001	0.014±0.001

Values expressed as Mean ± SE (n=8).
*Significant difference ($P \leq 0.05$) as compared to control

Biochemical Observations

The amount of proteins did not differ significantly in hemolysate (Table 3) and plasma (Figure 3) of control and triazophos treated rats. Catalase activity was significantly increased in the TZ treated rats as compared to the control group ($P<0.05$) (Table 3). SOD activity decreased significantly in the hemolysate with the higher doses of TZ, while no significant difference in the SOD activity between $1/40^{th}$ of LD_{50} doses of TZ treated rats as compared to control rats (Table 3). TZ treatment caused increase in GST activity as compare to control rats. The treatment of female rats with the higher doses of TZ *i.e.* $1/10^{th}$ and $1/20^{th}$ of LD_{50} TZ, resulted in significant increased activity of GR and there was no significant change in the activity of this enzyme at lowest dose *i.e.* $1/40^{th}$ of LD_{50} TZ (Table 3). The activity of GPx was significantly increased in all TZ treated rats. Triazophos at highest dose *i.e.* $1/10^{th}$ of LD_{50} caused significant increase in the MDA levels as a result of lipid peroxidation (LPO) (Table 3). Lower doses of TZ *i.e.* $1/20^{th}$ and $1/40^{th}$ of LD_{50} showed increased value of MDA levels, but it was non significant as compared to control rats ($P<0.05$). Significant increase ($P<0.05$) in total antioxidant activity (AOA) of plasma was also observed in all the TZ treated rats (Figure 4).

Table 3: Effect of Triazophos on Blood Biochemical parameters as compared to control

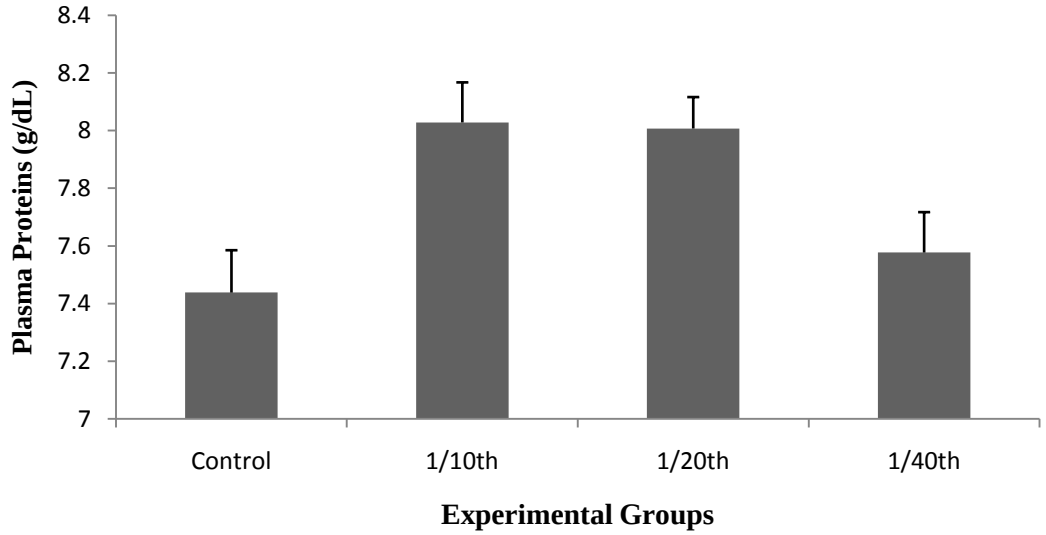
Parameters	Control	$1/10^{th}$	$1/20^{th}$	$1/40^{th}$
Protein	16.844±2.642	18.061±1.561	17.461±1.471	15.647±1.731
CAT	14.754±0.439	23.537±0.757*	19.567±0.629*	17.071±1.497
SOD	9.655±0.870	4.959±0.392*	5.345±0.471*	7.827±0.658
GST	0.012±0.003	0.016±0.002	0.015±0.003	0.016±0.004
GR	0.005±0.001	0.018±0.002*	0.013±0.001*	0.007±0.001
GPx	2.667±0.069	4.332±0.052*	4.004±0.175*	3.169±0.125*
LPO	2.753±0.397	4.474±0.546*	3.773±0.237	3.062±0.351

Values expressed as Mean ± SE (n=8).

*Significant difference ($P \leq 0.05$) as compared to control

Units: Proteins (g/dL sample), CAT (µmole of H_2O_2 decomposed/min/mg protein), SOD (U/mg protein), GST (µmoles of GSH-CDNB conjugate formed/ min/mg protein), GR (µmoles of NADPH oxidized/ min/mg protein), GPx (U/mg protein), LPO (nM MDA/ml sample).

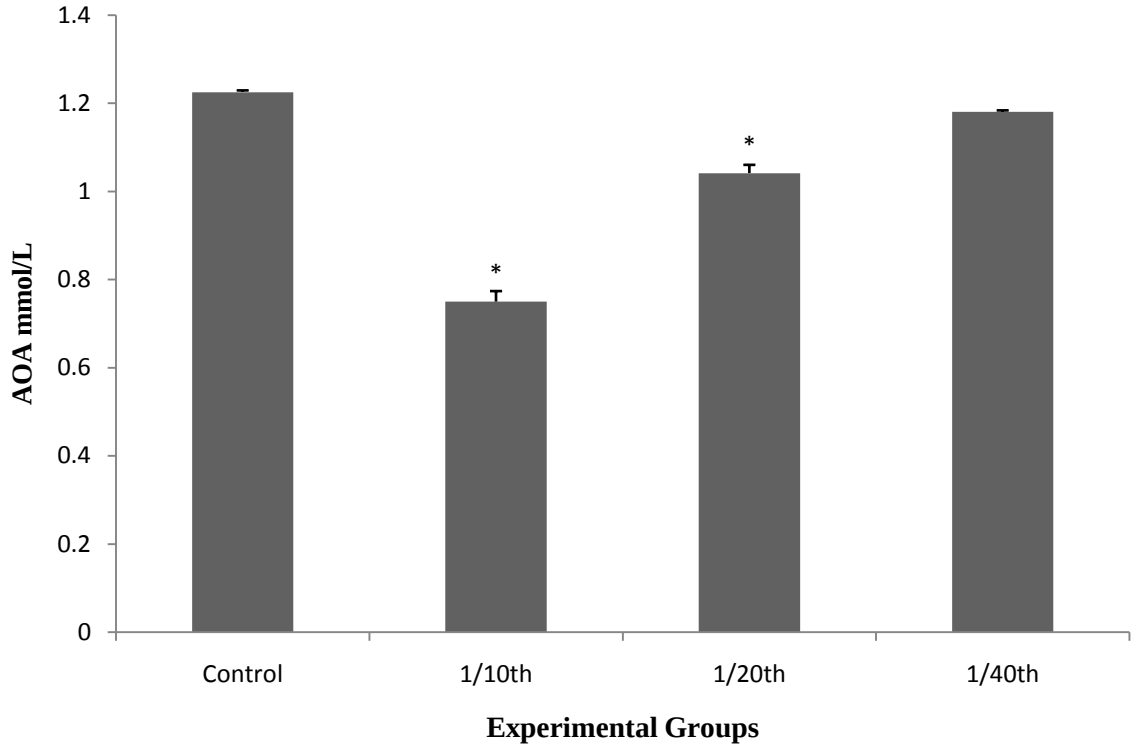
Figure 3: Effect of Triazophos on plasma total proteins (gm/dL) in control and treated female albino rats



Values expressed as Mean ± SE (n=8).

*Significant difference ($P \leq 0.05$) as compared to control

Figure 4: Effect of Triazophos on plasma AOA (mmol/L) in control and treated female albino rats



Values expressed as Mean ± SE (n=8).
*Significant difference ($P \leq 0.05$) as compared to control

Discussion

Organophosphates (OPs) due to their effectiveness, low cost and easy availability are the most widely used pesticides in agricultural practices and thus pose the greatest risk among all the pesticides to mammals, as they account for more than half of all the insecticides used in the world (Casida and Quistad, 2004; Uchendu *et al.*, 2012). Apart from cholinergic poisoning, OPs intoxication induces oxidative stress with increased generation of ROS (Soltaninejad and Abdollahi., 2009).

TZ treated rats showed hyperirrtability and aggressive behavior, observations are in agreement with the studies which have investigated the toxic effects of moderate toxicity in mammals, revealing neurotoxicity in terms of lack of coordination and aggression upon pesticides exposure (Manna *et al.*, 2005; Macan *et al.*, 2006). Dimethoate also didn't induce any distinctive clinical signs of toxicity or mortality (Attia and Nasr, 2009). The toxicological effects of TZ on feed intake and water intake were statistically found non significant. Carbofuran at doses of 0.1 and 0.15 mg/kg b.w. did not show any significant difference ($P<0.05$) on feed intake as compared to control (Alewud and Anukad, 2009). Also no significant effect on feed and water intake in cypermethrin treated female rats were observed as compared to control groups (Sangha *et al.*, 2011). Non significant changes in body weight and organs weight observed in present studies were comparable with literature where pesticides intoxication does not alter significantly body weight and organs weight of rats (Tuncmen and Tuzmen, 2007; Uzun and Kalender, 2011). Increased adrenals weight has also been obserbed in chlorpyrifos treated rats (Akhtar *et al.*, 2009) while the organophosphates had no influence on the relative organ weight, the increase of the absolute liver weight was recorded. Similar increase of the liver weight after diazinon administration in rats is also reported (Banerjee *et al.*, 1999; Baconi *et al.*, 2013).

In the present study the stimulation of non-enzymatic antioxidant systems as well as enzymes were demonstrated in the blood of TZ intoxicated rats. Total protein content was non significant for hemolysate and similar observations have been obtained in fenitrothion (FNT), an OP, treated rats (Budin *et al.*, 2013). Under normal physiological conditions, a delicate balance exists between the rate of formation of H_2O_2 via dismutation of O_2^- by SOD activity and the rate of removal of H_2O_2 by CAT and GPx. Any impairment in this pathway affects activities of other

enzymes in the cascade (Kono and Fridovich, 1982). The present study TZ treatment resulted in increased CAT activities in treated rats which may alter the other antioxidant enzymes. Increase in CAT activity in blood is further supported by significantly elevated CAT activities reported in dimethoate treated rats as compared to control (Attia and Nasr, 2009). SOD activity was decreased significantly in $1/10^{th}$ and $1/20^{th}$ of LD_{50} of TZ treated female rats. Significant decrease in erythrocytes SOD activity has also been reported in chlorpyrifos treated female rats as compared to control (Zama *et al.,* 2007). Also the antioxidant status parameter SOD of blood of grape garden sprayers was significantly decreased as compared to control group (Patil *et al.,* 2009).

GST is the major phase II detoxification enzyme and play important role in metabolism of xenobiotic substances. GST activity was non significant in all TZ treated rats in comparison to control rats. Similar non significant observations have been reported for GST activities in blood of ethion and monocroptophos treated rats as compared to control (Singh *et al.,* 2006). The reduced glutathione (GR) is a key cellular antioxidant that detoxifies ROSs and is predominant intracellularily in nearly all animal cells (Malmezat *et al.,* 2000) while glutathione (GSH) is very important in the protection of cells against toxic insults, because it participates in the detoxification of electrophilic metabolites of xenobiotic and is a very efficient free radicals scavenger (Parke and Piotrowski, 1996). Numerous enzymes participate in glutathione metabolism. The glutathione-dependent antioxidant system consists of glutathione and two enzymes: GPx and GR (Soplarics and Wu, 1997). The biological function of GPx is to reduce lipid hydroperoxides conversion to their corresponding alcohols and to reduce free hydrogen peroxide reaction (Verma *et al.,* 2007). Present study evidenced increased GR level in the blood after TZ treatment of rats for 30 days with the $1/10^{th}$ and $1/20^{th}$ doses. Also at dose levels of $1/10^{th}$ and $1/20^{th}$ of LD_{50} of TZ treated female rats, GPx activity levels were increased significantly. Similar trends in GR and GPx activities were also reported in blood of chlofenvinphos, an OP, treated rats (Lukaszewicz-Hussain and Moniuszko-Jakoniuk, 2003). Subchronic exposure of rats to dimethoate also caused a significant increase in the activity of GPx in erythrocytes (Barski and Spodniewska, 2012). The increase of GR and GPx activity might be a protective response against oxidative stress generated by sob-chronic doses of triazophos in blood (Singh *et al.,* 2006).

Antioxidant capacity is an important factor for all physiological standards in animals (Prior and Gao, 1999). Deccreased total antioxidant activity of plasma in TZ treated rats is also in agreement with number of studies where OPs exposure leads to decreased total antioxidant activity (Hundekari *et al.,* 2011; Aita *et al.,* 2012). OPs intoxication is associated with the generation of ROSs, and ROS are mainly responsible for LPO, thus leading to enhanced MDA levels in blood. MDA levels were high in the OPs treated rats as compared to control rats (Lukaszewicz-Hussain and Moniuszko-Jakoniuk, 2003; Budin *et al.,* 2013). Also intoxication with mixture of four OP insecticides have been observed with enhanced MDA levels in blood serum of all treated rats (Mossa *et al.,* 2011), further supports our findings.

Malondialdehyde (MDA) is an end product of lipid peroxidation including phospholipids in the cell membrane and the enhanced levels of MDA is an indicator of oxidative stress. The increased activity of CAT seen in the poisoning cases coupled with an increase in the lipid peroxidation level (MDA) suggests an insufficient antioxidant defense which could be due to both increase in pesticide-induced ROS formation and SOD inhibition (Gultekin, 2001). The increased levels of MDA and the decreased AOA along with reduced SOD activity may pose the survival threat to live cells, which may have the potential to affect various organs and their normal physiology leading to severe pathophysiological conditions.

Conclusion

In conclusion, it can be inferred that triazophos intoxication may induce oxidative stress, evidenced by the altered levels or activities of antioxidants such as CAT, GR, GPx, SOD and GST enzymes and lipid peroxidation. However, the effect of sub chronic exposure of TZ on female rats leading to oxidative stress still requires further evaluation at molecular level to elucidate and clarify the relative importance of acute and chronic exposure of TZ on various organs physiology and induced pathology.

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