ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Dimethoate induced changes in antioxidant parameters of female albino rats

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Manuscript Info

Manuscript History:

Received: 13 March 2015
Final Accepted: 18 April 2015
Published Online: May 2015

Key words:

Antioxidant enzymes, Plasma, Oxidative stress, Reactive Oxygen Species, Dimethoate

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Abstract

Dimethaote is one of the most important Organophosphate pesticides, is frequently used in agriculture against a wide range of insects and mites as both a systemic and a contact pesticides. It is also used for indoor control of houseflies. Dimethoate intoxication causes cellular injury and oxidative stress (OS) which leads to lipid peroxidation and free radical production. Present study was undertaken to investigate effects of dimethoate treatments at dose levels i.e. $1/20^{th}$, $1/40^{th}$ and $1/80^{th}$ 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. Dimethoate 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 Dimethoate 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 Dimethoate treated female albino rats. The results suggest that the exposure of female albino rats to Dimethote may induce OS at dose dependent manner.

INTRODUCTION

Pesticides have been used in agriculture to enhance food production by eradicating unwanted insects and controlling diseases vectors (Prakasam *et al.,* 2004). The use of pesticides causes severe environmental and health hazards to organisms (Abdollahi *et al.,* 2004, Tuzmen *et al.,* 2008). Organophosphate compounds are widely used and include some of the most toxic chemical agents. Organophosphorous (OP) insecticides are used throughout the world for control of agricultural and domestic insect pests. OP insecticides are employed in medicine and industry, because of their relatively low persistence due to biodegradability. (Uzun *et al.,* 2009).

Dimethoate(DM)[O,OdimethylS(Nmethylcarbomethyl)phosphorodithioate] which is one of the most important Organophosphate pesticides, is frequently used in agriculture against a wide range of insects and mites as both a systemic and a contact pesticides. It is also used for indoor control of houseflies. Dimethoate intoxication causes cellular injury and oxidative stress which leads to lipid peroxidation and free radical production (Maiti *et al.,* 1996, Maiti and Kar 1997, Singh *et al.,* 2004, 2006, Sharma *et al.,* 2005). Recent studies have shown that acute and subchronic exposure to Dimethoate alters the antioxidant status and the histology of liver, brain and testes of rats and human erythrocytes (Gargouri *et al.,* 2011).Moreover females are more vulnerable than males suggesting, a better antioxidative stress defense response in males(Al-Rejaie *et al.,* 2012). So in present investingation ,the toxicity effects of dimethoate at $1/20^{th}$,$1/40^{th}$ and $1/80^{th}$ of LD_{50} (i.e 310mg/kg of body weight) sub- chornic 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 SDFCL (SD Fine-Chem Ltd). SRL (Sissco Research Laboratories Pvt Ltd). All chemical used were either of analytical grade or the highest purity commercially avaible. Standard rat feed was purchased from Ashirwad Industries, Mohali, India.

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. IAEC/2014/125-53 dated 13/08/2014.

Experimental design

Female albino rats were acclimatized for ten days in laboratory conditions and were divided into four groups with six 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, Dimethoate (30% EC) dissolved in olive oil was given at a dose level of $1/20^{th}$, $1/40^{th}$ and $1/80^{th}$ of LD_{50} i.e. 310 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 as per CPCSEA guidelines 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

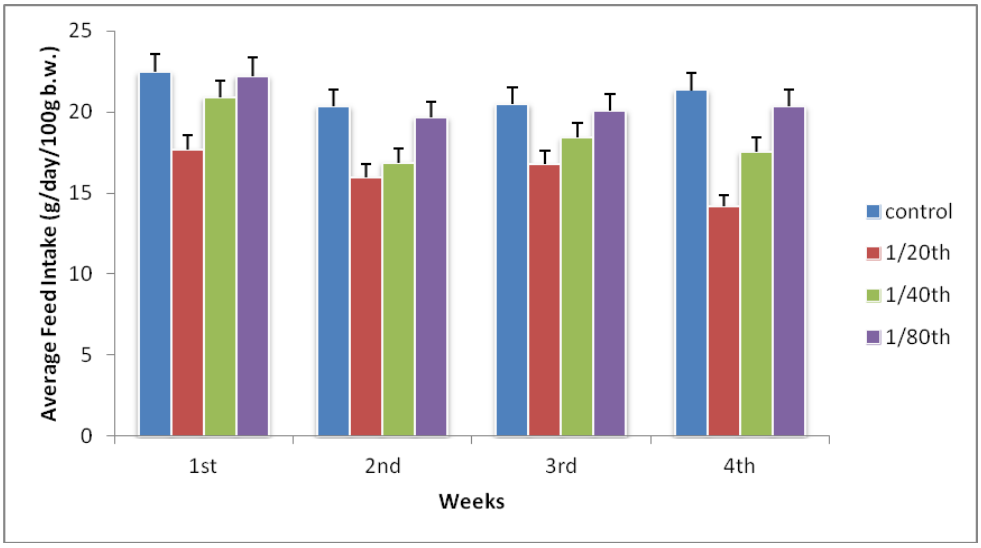
The experimental results are expressed as mean ± standard error of the mean (SEM) for n=6. Statistical analysis of data was performed on a computer by using CPCS1. One-way ANOVA was done to check any significance and the criterion for statistical significance was set at $P < 0.05$.

Results

Feed And Water Intake and Body Weight

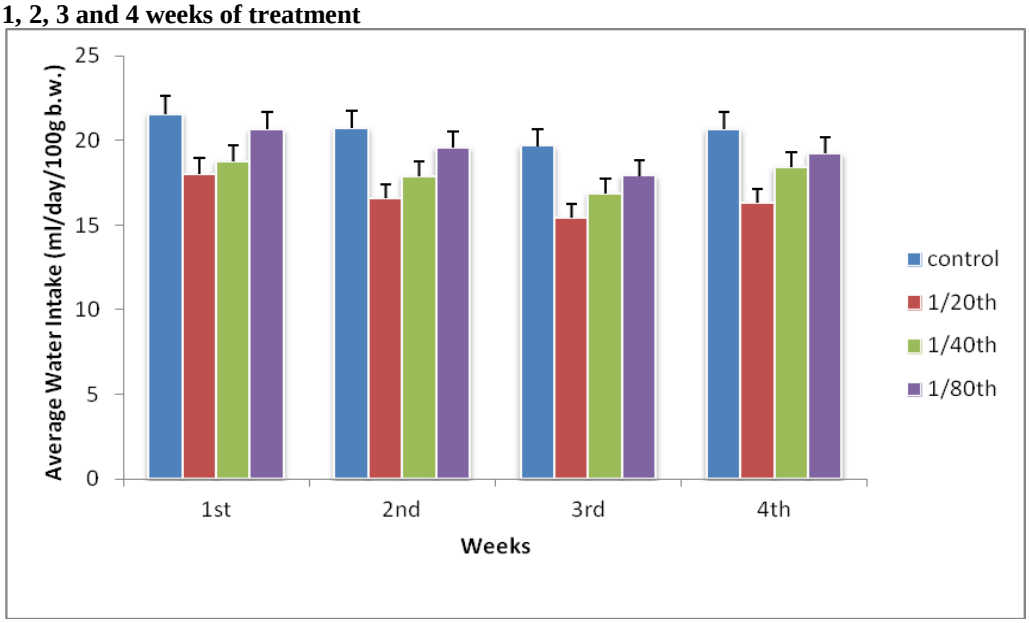
Daily feed intake (Figure 1) and water intake (Figure 2) during 30 days of treatment was non significant in all the treatment groups as compared to control female albino rat group. Average daily feed intake and water intake was low in $1/20^{th}$ and $1/40^{th}$ of LD_{50} Dimethoate treated rats, while at $1/80^{th}$ of LD_{50} Dimethoate 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 Dimethoate treated rats as compared to control female rats but was not significant ($P<0.05$) (Table 1). During 30 days of dimethoate treatment hyperirritability and loose feacal pellets were observed in $1/20^{th}$, $1/40^{th}$ and $1/80^{th}$ of LD_{50} treated rats, while excessive salivation, hair loss were reported in $1/20^{th}$ and $1/40^{th}$ female rats

Figure 1: Effect of Dimethoate 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=6).
*Significant difference (P ≤ 0.05) as compared to control

Figure 2: Effect of Dimethoate 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=6).
*Significant difference (P ≤ 0.05) as compared to control

Table 1: Effect of Dimethoate 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	0day	1st week	2nd week	3rd week	4th week
Control	Weight (g)	131.50 ± 9.43	142.50 ± 9.92	136.25 ±6.40	138.75 ± 6.64	150.00 ±7.50
	Growth rate (g/day/100g b.w.)	-- --	1.42 ± .10	-.05 ± .29	.29 ± .29	1.28 ±.26
1/20th	Weight (g)	134.16 ±5.45	135.00 ±5.51	139.16 ±5.09	137.50 ±4.46	140.00 ±4.18
	Growth rate	--	.687	.582	-.0241	.470

	(g/day/100g b.w.)	--	±.22	±.35	± .29	±.38
1/40th	Weight (g)	146.00 ±11.5	144.00 ±7.57	142.50 ±8.73	145.83 ±7.0	146.66 ±6.19
	Growth rate (g/day/100g b.w.)	-- --	1.734 ±.75	.086 ±.58	.419 ±.34	.427 ±.46
1/80th	Weight (g)	163.33 ±6.18	165.00 ±5.70	162.5 ±4.46	155.83 ±3.25	159.00 ±4.97
	Growth rate (g/day/100g b.w.)	-- --	4.475 ±1.87	.122 ±.58	-.362 ±.49	.489 ±.38

Values expressed as Mean ± SE (n=6)

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

Organs Weight

Dimethoate 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 and kidney was comparable in control and dimethoate treated female rats. Slight non-significant increase in heart and lungs weight was observed in all the treatment groups as compared to control. The weight of thyroid decreased while stomach and liver was increased with $1/20^{th}$ and $1/40^{th}$ of LD_{50} dose of dimethoate as compared to control and $1/80^{th}$ of LD_{50} treated rats.

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

ORGANS	Control	1/20TH	1/40TH	1/80TH
Brain	1.101±.079	1.125±.079	1.255±.055	1.089±.048
Heart	0.309±.045	0.374±.015	0.364±.021	0.332±.012
Lungs	1.018±.164	1.024±.166	1.254±.300	1.070±.049
Stomach	1.348±.208	1.998±.168	1.609±.336	1.411±.137
Liver	3.008±.483	4.142±.147	3.964±.235	3.623±.194
Spleen	0.274±.012	0.275±.021	0.269±.019	0.237±.009
Kidney	0.376±.032	0.391±.012	0.378±.024	0.376±.018
Thyroid	0.129±.015	0.107±.008	0.115±.009	0.087±.008
Parathyroid	0.038±.005	0.027±.007	0.016±.005	0.019±.004
Adrenals	0.019±.003	0.014±.003	0.016±.001	0.015±.002

Values expressed as Mean ± SE (n=6).

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

Biochemical Observations

The amount of proteins did not differ significantly in plasma (Table 3) and hemolysate (Figure 3) of control and Dimethoate treated rats. Catalase activity was significantly increased in the dimethoate treated rats as compared to the control group ($P<0.05$) (Table 3). SOD activity decreased significantly in the plasma with the higher doses of dimethoate, while no significant difference in the SOD activity between $1/40^{th}$ of LD_{50} doses of dimethoate treated rats as compared to control rats (Table 3). Dimethoate treatment caused increase in GST activity as compared to control rats. The treatment of female rats with the higher doses of dimethoate i.e. $1/20^{th}$ and $1/40^{th}$ of LD_{50} dimethoate, resulted in significant increased activity of GR and there was no significant change in the activity of this enzyme at lowest dose i.e. $1/80^{th}$ of LD_{50} dimethoate (Table 3). The activity of GPx was significantly increased in all dimethoate treated rats. Dimethoate at highest dose i.e. $1/20^{th}$ of LD_{50} caused significant increase in the MDA levels as a result of lipid peroxidation (LPO) (Table 3). Lower doses of dimethoate i.e. $1/40^{th}$ and $1/80^{th}$ of LD_{50} showed increased value of MDA levels, but it was non significant as compared to control rats ($P<0.05$).

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

Parameters	Control	1/20th	1/40th	1/80th
Protein	6.034±0.210	5.96±0.187	5.060±0.171	5.128±0.172
CAT	15.319±0.637	18.010±0.957*	17.429±0.487*	15.143±0.851
SOD	8.173±0.232	4.813±0.346*	7.473±0.267*	6.234±0.315
GST	1.580±0.022	1.092±0.116	1.340±0.163	1.274±0.147

GPX	1.456±0.078	3.566±0.045*	3.367±0.165*	2.678±0.112*
LPO	2.987±0.389	5.203±0.475	4.304±0.506	3.129±0.338
GR	0.012±0.001	0.017±0.002*	0.011±0.001*	0.008±0.001

Values expressed as Mean ± SE (n=6).
*Significant difference ($P \leq 0.05$) as compared to control
Units: Proteins (gm/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 Effects of dimethoate doses 1/20th ,1/40th on different body parts of female albino rats

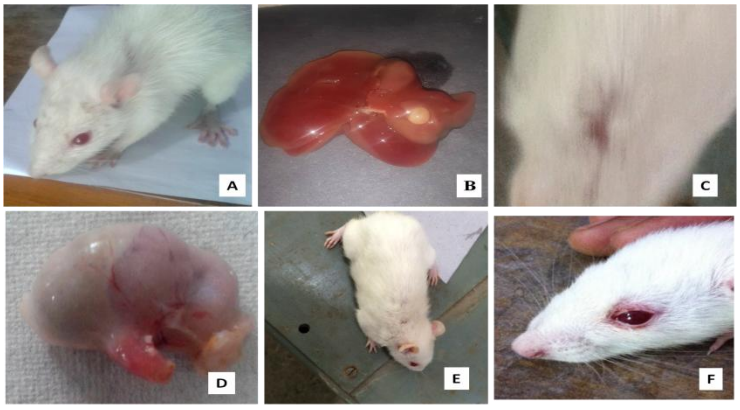
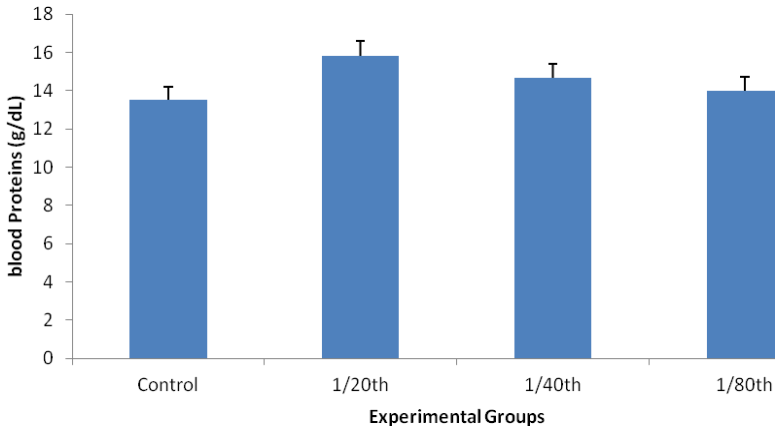


Figure 3: (A) Hair loss (B) cyst in liver (C) closing of eye (D) stomach problem (E) neural dysfunction (F) reddening of eye

Figure 4: Effect of Dimethoate on hemolysate total proteins (g/dL) in control and treated female albino rats



Values expressed as Mean ± SE (n=6).
*Significant difference ($P \leq 0.05$) as compared to control

4. 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).Dimethoate 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 and Various studies have investigated the toxic effects of cypermethrin in mammals, revealing increase in salivation, lack of coordination, muscle tremor and convulsions. (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 dimethoate on feed intake and water intake were statistically found non significant. No significant effect on feed and water intake in cypermethrin and triazophos treated female rats were observed as compared to control groups (Sangha *et al*., 2011 and Sharma *et al.*, 2014). Also Carbofuran at doses of 0.1 and 0.15 mg/kg b.w. also did not show any significant difference ($P<0.05$) on feed intake as compared to control (Alewud and Anukad, 2009). 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). 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 plasma of Dimethoate 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 Dimethoate treatment resulted in increased CAT activities in treated rats which may alter the other antioxidant enzymes. Increase in CAT activity in plasma is further supported by significantly elevated CAT activities reported in dimethoate treated rats as compared to control (Attia
and Nasr, 2009). SOD is the first and major line of defense against the action of $\bullet O_2^-$ and other ROS. SOD converts superoxide into H_2O_2 and O_2, and its decreased activity in the present study is suggestive of its excessive utilization for neutralizing superoxide (Yousef *et al*., 2006; Machlin *et al*., 1987; Kant *et al.*, 2009) . SOD activity was decreased significantly in $1/20^{th}$ and $1/40^{th}$ of LD_{50} of Dimethoate 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).Increased adrenals weight has also been obserbed in chlorpyrifos treated rats (Akhtar 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 Dimethoate 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 plasma after Dimethoate treatment of rats for 30 days with the $1/20^{th}$ and $1/40^{th}$ doses. Also at dose levels of $1/20^{th}$ and $1/40^{th}$ of LD_{50} of Dimethoate treated female rats, GPx activity levels were increased significantly. Similar trends in GR and GPx activities were also reported in plasma 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). Antioxidant capacity is an important factor for all physiological standards in animals (Prior and Gao, 1999).

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 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 Dimethoate 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 Dimethoate 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 Dimethoate on various organs physiology and induced pathology.

Acknowledgment

Authors are thankful to Department of Zoology, PAU Ludhiana, Punjab (India) for providing finical assistance and infrastructure to carry out the research.

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