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ALPHA LIPOIC ACID AMELIORATE CHANGES OCCUR IN NEUROTRANSMITTERS AND ANTIOXIDANT ENZYMES THAT INFLUENCED BY PROFENOFOS INSECTICIDE

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ABSTRACT

This study was designed to determine whether alpha lipoic acid (ALA) which has been shown to have substantial antioxidant properties would ameliorate some of profenofos insecticide toxic effects. ALA administered (60mg/kg b.w.) to adult female rats for 14 days 1 hour after administration of 1/10 LD_{50} (45 mg/kg b.w.) & 1/20 LD_{50} (22.5 mg/kg b.w.) for profenofos insecticide which act as free radical inducer. Neurotransmitters [Dopamine (DA), Norepinephrin (NE), Serotonine (5-HT) and 5-Hydroxy indol acetic acid (5-HIAA)] were estimated in plasma. While malondialdehyde (MDA), reduced glutathione (GSH) level, glutathione-S-transferase (GST) and superoxide dismutase (SOD) activities were determined in liver, kidney and brain. The results revealed an increase in plasma serotonine (5-HT) levels in group of rats intoxicated with low dose of profenofos. A significant increase in MDA level (an indicator for lipid peroxidation) in liver of rats intoxicated with both doses of profenofos was recorded, concurrent with a significant reduction in GSH level and GST & SOD activities in most tested tissues of rats intoxicated with both doses of profenofos. Supplementation with alpha lipoic acid (60 mg/kg b.wt) 1 h after profenofos administration induced some but not complete improvement in all parameters whereas, it induced significant increase in plasma DA and 5-HT while it reduced lipid peroxidation in each of the examined tissues. These results accompanied with improvement in GSH level especially in liver, in addition to GST and SOD activities in some organs. Its effect differ from tissue to another. In conclusion ALA supplementation to profenofos intoxicated rats induced improvement in lipid peroxidation ,total glutathione level and glutathione-S- transferase activity.

Keywords: **Profenofos insecticide – Organophosphorus – Alpha lipoic acid – Oxidative stress – Neurotransmitters – Malondialdehyde – Glutathione-S-transferase – Total glutathione – Superoxide dismutase**

INTRODUCTION

Organophosphorus (OP) compounds are widely used in agriculture, medicines and industry. OP insecticides in addition to their intended effects like the control of insects or other pests are sometimes found to affect non-target organisms including humans (Chantelli-Forti *et al.*, 1993; Chaudhuri *et al.*, 1999). Exposure to OP is also a potential cause of longer term damage to the nervous system with respects of poor mental health and deficits in memory and concentration (Davis, 1991 and Mason, 2000). OP insecticides generally act through a common mechanism of toxicity initiated by inhibition of acetylcholinestrase (AchE) which could result in the accumulation of Ach and increase lymphocyte mobility and cytotoxicity. High concentrations have been associated with lymphocyte mortality due to the depletion of lymphocyte glutathion and compromised oxidative state of the cells (Banerjee *et al.*, 1999). Lin *et al.* (2003) suggests that profenofos can increase the activities of superoxide dismutase (SOD), catalase (CAT), glutathione-peroxidase (GSH-Px), which may be earlier diagnostic index in profenofos poisoning. With increasing evidence that shows the involvement of active oxygen and nitrogen species in a variety of disorders, cancer and aging, the role of antioxidant against oxidative stress has received attention (Noguchi & Niki, 2000). Alpha lipoic acid (ALA) was first discovered in 1951 as part of an enzyme complex within the cell which is responsible for energy production. It was later discovered that alpha lipoic acid also acted as an anti-oxidant. Because of its lipid and water solubility, lipoic acid can rapidly penetrate all portions of the cell, providing protection within the lipid cell membrane, as well as the aqueous compartment and the nucleus (Packer *et al.*, 1995). ALA has been identified as a powerful antioxidant found naturally in our diets but appears to have increased functional capacity when given as a supplement in the form

of a natural or synthetic isolate. ALA and its active reduced counterpart, dihydrolipoic acid (DHLA) have been shown to combat oxidative stress by quenching a variety of reactive oxygen species (ROS). Because this molecule is soluble in both aqueous and lipid portions of the cell, its biological functions are not limited solely to one environment. In addition to ROS scavenging, ALA has been shown to be involved in the recycling of other antioxidants in the body including vitamins C , E and glutathione (Wollin & Jones, 2003). ALA, a coenzyme of pyruvate and alpha-ketoglutarate dehydrogenase, has been used in Germany as an antioxidant and approved treatment for diabetic polyneuropathy for 40 years (Lyn Patrick, 2002). ALA has been shown to decrease lipid peroxidation in brain and sciatic nerve tissue (Nickander *et al.*, 1996) and when given orally to rats, decreased lipid peroxidation in brain tissue by 50 percent (Packer *et al.*, 1997). In diabetic neuropathy, free lipoic acid may prevent glucose-related oxidative damage by entering nerve tissue where it acts as both an antioxidant and heavy metal-binding agent (Queiroz et *al.*, 1998).

The aim of the present study was to investigate the ability of repeated dose of ALA in amelioration imbalance in the antioxidant enzyme system and neurotransmitters in adult female rats induced by repeated exposure to different doses of profenofos organophosphorus insecticide.

MATERIALS & METHODS

Animals:

Adult female albino rats each weighing 180-200 gm were used in the present study. The animals were housed in air conditioned room at 25ºC with 12 h light/dark cycle. The animals have been acclimatized for the experimental conditions two weeks prior the onset of the experiment. They were given a commercial pellet diet and free access to tap water.

Chemicals:

Pesticide:

Profenofos in the formulated form with trade name Coracron 72%; O-(4-bromo-2-chlorophenyl) o-ethyl S-propyl phosphorothiote-(p) was supplied by El-Helb Co. for the pesticide and agrochemical, Egypt.

Antioxidant:

Alpha lipoic acid supplemented as thiotic acid, supplied by EVA Pharma Co.

Experimental Design:

After the acclimatization period, the animals were divided into six equal groups (6 rats each) and treated as follows:

Group 1 (C): served as control.

Group 2 (HP): the rats were orally treated with 1/10 LD_{50} (45 mg/kg) profenofos consecutively given by gastric intubation daily for 14 days.

Group 3 (LP): the rats were orally treated with 1/20 LD_{50} (22.5 mg/kg) profenofos consecutively given by gastric intubation daily for 14 days.

Group 4 (ALA): the rats were orally treated with 60mg/kg alpha lipoic acid consecutively given by gastric intubation daily for 14 days and served as a positive control.

Group 5 (HP + ALA): the rats were orally treated with 60mg/kg alpha lipoic acid daily for 14 days 1h after administration of 1/10 LD_{50} (45 mg/kg) profenofos.

Group 6 (LP + ALA): the rats were orally treated with 60mg/kg alpha lipoic acid daily for 14 days 1h after administration of 1/20 LD_{50} (22.5 mg/kg) profenofos.

Sampling:

At the end of the experiment the animals were sacrificed and blood samples were collected in heparinized tubes and centrifuged at 3600 rpm. Plasma were separated and kept at -20ºC for estimation of DA, NE and 5-HT levels according to the fluorometric method described by Ciarlone (1978). 5-HIAA level was determined as described by Miller *et al.* (1970). The animals were dissected for liver, kidneys and brain, these organs were kept in liquid nitrogen (-196ºC) for further biochemical determinations. The tissues were homogenized in known volume of buffered solution for determination of lipid peroxidation active product malondialdehyed (MDA) according to Okhawa *et al.* (1979). Reduced glutathione (GSH) was determined according to Beulter *et al.* (1963); while glutathione-S-transferase (GST) was estimated by the method of Habig *et al.* (1974). Superoxide dismutase (SOD) was estimated according to Misra and Fridovich (1972). Moreover, protein content in tissues was determined according to Bradford (1976).

Statistical Analysis:

The data of control and treated animals were statistically done using analysis of variance (ANOVA) (Norman & Streiner, 1994) by means of SPSS statistical software.

RESULTS

Neurotransmitter levels in Plasma:

The data presented in table (1) reveal that profenofos intoxication with both doses induced insignificant changes in each of plasma Dopamine (DA), Norepinephrin (NE) and 5-hydroxyindol acetic acid (5-HIAA) whereas the high dose of profenofos induced the same effect on plasma serotonin (5-HT) but low dose profenofos induced significant increase (21.14 %) in 5-HT level as compared to the control. On the other hand, ALA supplementation to profenofos intoxicated

rats at both doses induced significant increase in plasma DA (22.82% & 28.74%) as compared to the respective non supplemented groups and 5-HT (19.96% & 22.33%) as compared to the control. It must be noted here that these recorded observation due to the effect of ALA per se on DA, NE as seen in Table (1), where, non significant increase in plasma NE (7.26%) in LP+ALA group confirmed this hypothesis.

Malondialdehyde level (MDA) in different tissues:

Table (2) indicate that (MDA) as the end product of lipid peroxidation recorded significant increase in liver of rats treated with high and low doses of profenofos. However, it recorded reduction in both kidney and brain tissues, this reduction was significant in kidney only (18.78% & 36.63 %) as compared to the control. ALA supplementated to profenofos intoxicated groups at the two levels of doses counteracts the level of MDA in liver as compared to the respective non supplemented groups to reach to the control level. In kidney, this combination resulted significant reduction in MDA level in LP+ALA group (38.76%) as compared to the control group. Meanwhile, significant reduction was recorded in brain of HP+ALA group (37.44%) as compared to the control and the respective non supplemented groups .

Reduced glutathione level (GSH) in different tissues:

As seen in table (3), the high dose of profenofos strongly decreased GSH level in all estimated organs. This decrease was 76%, 47% and 36.1% versus control in liver, kidney and brain respectively. Low dose caused a significant decrease (22.1% & 33.4%) only in kidney and brain respectively. Unexpectedly, the animals which received ALA exhibited a significant decrease in GSH level (27.8% & 60.9%) in both liver and kidney respectively. In contrast, treatment with ALA successfully restored liver GSH level near to the control level in high does supplemented group and kidney in low dose supplemented group. ALA supplementation failed to counteract the level of GSH in brain of rats treated with doses of profenofos as compared to the control group and the respective non supplemented groups.

Glutathione-S-transferas (GST) activity in tissues:

As shown in table (4) both doses of profenofos insecticide induced the same trend i.e. rats administrated high and low doses of profenfos exhibited reduction in the activity of (GST) in each of liver and brain tissues while the activity of GST increased significantly in kidney tissue (115%) in high dose treated group. On the other hand, supplementation with ALA to high dose intoxicated rats revealed significant increase in GST activity in liver & brain (13.8 % & 53.4%) respectively compared to the respective non supplemented group or the control group. Whereas, it restored the highly effect of profenofos in kidney tissue i.e. the significant increase in both supplemented groups were (40% & 55.7%) as compared to the respective non supplemented group and the control group respectivily.

Table (1): Neurotransmitter levels [Dopamin (DA), Norepinephrin (NE), Serotonin (5-HT)& 5-Hydroxy indol acetic acid (5-HIAA)] (µg/ml plasma) of rats treated with 1/10 LD_{50} (45mg/kg) & 1/20 LD_{50} (22.5mg/kg) for profenofos alone or supplement with alpha lipoic acid (60mg/kg) daily for 14 days.

Group	DA		NE		5-HT		5-HIAA	
	Mean ± S.E.	% change	Mean ± S.E.	% change	Mean ± S.E.	% change	Mean ± S.E.	% change
C	1.082 ± 0.039	—	0.275 ± 0.006	—	0.506 ± 0.030	—	0.089 ± 0.003	—
HP	0.964 ± 0.086	- 10.9	0.279 ± 0.011	1.45	0.542 ± 0.015	7.11	0.082 ± 0.006	- 7.86
LP	1.049 ± 0.017	- 3.04	0.265 ± 0.004	- 3.63	0.613 ± 0.027*	21.14	0.085 ± 0.004	- 4.49
ALA	1.657 ± 0.183*	53.14	0.362 ± 0.036*	31.63	0.352 ± 0.014*	-30.43	0.075 ± 0.007	- 15.73
HP+ALA	1.329 ± 0.067#	22.82	0.275 ± 0.007	0	0.607 ± 0.018*	19.96	0.08 ± 0.008	- 10.11
LP+ALA	1.393 ± 0.138#	28.74	0.295 ± 0.009	7.27	0.619 ± 0.032*	22.33	0.08 ± 0.005	- 4.49

* significant difference versus control group (P<0.05).

significant difference HP + ALA versus HP or LP + ALA versus LP group (P<0.05).

(C) = control.

(HP) = the rats were treated with 1/10 LD_{50} profenofos

(LP) = the rats were treated with 1/20 LD_{50} profenofos

(ALA) = the rats were treated with alpha lipoic acid

(HP + ALA) = the rats were treated with alpha lipoic acid after administration of 1/10 LD_{50} profenofos.

(LP + ALA) = the rats were treated with alpha lipoic acid after administration of 1/20 LD_{50} profenofos.

Table (2): Malondialdehyde (MDA) level (mmol/g tissue) in liver, kidney & Brain of rats treated with 1/10 LD_{50} (45mg/kg) & 1/20 LD_{50} (22.5mg/kg) for profenofos alone or supplement with alpha lipoic acid (60mg/kg) daily for 14days

Group	Liver		Kidney		Brain	
	Mean ± S.E.	% change	Mean ± S.E.	% change	Mean ± S.E.	% change
C	21.07 ± 0.62	—	19.05 ± 0.73	—	31.29 ± 2.29	—
HP	35.56 ± 1.07*	68.76	15.47± 1.07*	- 18.78	31.68 ± 0.96	1.25
LP	27.50 ± 0.63*	30.49	12.07± 0.99*	- 36.63	30.03 ± 1.79	- 4.01
ALA	18.44 ± 0.31	-12.49	7.59 ± 0.76*	- 60.14	24.73 ± 2.48*	- 20.96
HP+ALA	20.25 ± 1.03#	- 3.87	17.17 ± 1.31	- 9.90	19.57 ± 1.63*#	- 37.44
LP+ALA	21.23 ± 1.69#	0.76	11.67 ± 0.58*	- 38.76	29.28 ± 1.64	- 6.41

* significant difference versus control group (P<0.05).
# significant difference HP + ALA versus HP or LP + ALA versus LP group (P<0.05).
(C) = control.
(HP) = the rats were treated with 1/10 LD_{50} profenofos
(LP) = the rats were treated with 1/20 LD_{50} profenofos
(ALA) = the rats were treated with alpha lipoic acid
(HP + ALA) = the rats were treated with alpha lipoic acid after administration of 1/10 LD_{50} profenofos.
(LP + ALA) = the rats were treated with alpha lipoic acid after administration of 1/20 LD_{50} profenofos.

Table (3): Total glutathion (GSH) content (mg/tissue) in liver, kidney & Brain of rats treated with 1/10 LD_{50} (45mg/kg) & 1/20 LD_{50} (22.5mg/kg) for profenofos alone or supplement with alpha lipoic acid (60mg/kg) daily for 14 days.

Group	Liver		Kidney		Brain	
	Mean ± S.E.	% change	Mean ± S.E.	% change	Mean ± S.E.	% change
C	66 ± 7.19	—	93.05 ± 4.71	—	107.75 ± 6.89	—
HP	15.5 ± 0.91*	- 76	49.30 ± 1.99*	- 47	68.75 ± 2.68	- 36.1
LP	75.22 ± 5.13	13.9	72.46 ± 1.79*	- 22.1	71.66 ± 5.26	- 33.4
ALA	47.63 ± 4.36*	- 27.8	36.30 ± 3.79*	- 60.9	93.40 ± 8.44	- 13.3
HP+ALA	60.89 ± 5.53#	- 7.7	57.81 ± 5.83*	- 37.8	79.57 ± 3.00	- 26.15
LP+ALA	54.80 ± 5.34#	- 16.9	85.23 ± 1.69#	- 8.4	67.80 ± 4.89	- 37

* significant difference versus control group (P<0.05).
# significant difference HP + ALA versus HP or LP + ALA versus LP group (P<0.05).
(C) = control.
(HP) = the rats were treated with 1/10 LD_{50} profenofos
(LP) = the rats were treated with 1/20 LD_{50} profenofos
(ALA) = the rats were treated with alpha lipoic acid
(HP + ALA) = the rats were treated with alpha lipoic acid after administration of 1/10 LD_{50} profenofos.
(LP + ALA) = the rats were treated with alpha lipoic acid after administration of 1/20 LD_{50} profenofos.

Table (4): Glutathion-S-transferase (GST) activity (µmol/min/mg protein) in liver, kidney & Brain of rats treated with 1/10 LD_{50} (45mg/kg) & 1/20 LD_{50} (22.5mg/kg) for profenofos alone or supplement with alpha lipoic acid (60mg/kg) daily for 14 days.

Group	Liver		Kidney		Brain	
	Mean ± S.E.	% change	Mean ± S.E.	% change	Mean ± S.E.	% change
C	98.93 ± 6.64	---	8.90 ± 1.09	---	16.92 ± 1.57	---
HP	84.36 ± 4.86	- 14.7	19.19 ± 1.48*	115	13.60 ± 1.35	- 19.6
LP	85.11 ± 6.67	- 13.9	11.50 ± 0.79	29.2	12.90 ± 1.36	- 23.7
ALA	106.31 ± 6.32	7.4	16.75 ± 1.67*	88.2	15.14 ± 1.13	- 10.5
HP+ALA	112.62 ± 12.84#	13.8	12.46 ± 1.35#	40	25.96 ± 2.05*#	53.4
LP+ALA	78.93 ± 5.55	- 20.2	13.86 ± 1.29*	55.7	12.75 ± 0.42	- 24.64

* significant difference versus control group (P<0.05).
# significant difference HP + ALA versus HP or LP + ALA versus LP group (P<0.05).
(C) = control.
(HP) = the rats were treated with 1/10 LD_{50} profenofos
(LP) = the rats were treated with 1/20 LD_{50} profenofos
(ALA) = the rats were treated with alpha lipoic acid
(HP + ALA) = the rats were treated with alpha lipoic acid after administration of 1/10 LD_{50} profenofos.
(LP + ALA) = the rats were treated with alpha lipoic acid after administration of 1/20 LD_{50} profenofos.

Table (5): Superoxide dismutase (SOD) activity (U/gm tissue) in liver, kidney & Brain of rats treated with 1/10 LD_{50} (45mg/kg) & 1/20 LD_{50} (22.5mg/kg) for profenofos alone or supplement with alpha lipoic acid (60mg/kg) daily for 14 days.

Group	Liver		Kidney		Brain	
	Mean ± S.E.	% change	Mean ± S.E.	% change	Mean ± S.E.	% change
C	4.19 ± 0.07	—	1.46 ± 0.15	—	2.62 ± 0.16	—
HP	9.36 ± 0.27*	123.3	0.66 ± 0.22*	-54.79	1.68 ± 0.20*	-35.8
LP	9.24 ± 0.84*	120.5	1.21 ± 0.15	-17.22	2.51 ± 0.16	-4.1
ALA	6.02 ± 0.30*	43.6	1.31 ± 0.03	-10.27	0.83 ± 0.02*	-68.3
HP+ALA	1.76 ± 0.16*#	-57.9	0.88 ± 0.05	-39.73	1.73 ± 0.22*	-33.9
LP+ALA	3.97 ± 0.32#	-5.2	1.86 ± 0.39#	27.39	2.06 ± 0.09*	-21.3

* significant difference versus control group (P<0.05).
# significant difference HP + ALA versus HP or LP + ALA versus LP group (P<0.05).
(C) = control.
(HP) = the rats were treated with 1/10 LD_{50} profenofos
(LP) = the rats were treated with 1/20 LD_{50} profenofos
(ALA) = the rats were treated with alpha lipoic acid
(HP + ALA) = the rats were treated with alpha lipoic acid after administration of 1/10 LD_{50} profenofos.
(LP + ALA) = the rats were treated with alpha lipoic acid after administration of 1/20 LD_{50} profenofos.

Super oxide dismutase (SOD) activity in tissues:

Table (5) indicate that profenofos intoxicated rats at both dose levels induced significant increase in (SOD) activity in liver tissues compared to the control (123.3% & 120.5%). In contrast, reduction in SOD activity was recorded in kidney (54.79 & 17.22) and brain (35.8 & 4.1) tissues. This reduction was significant in high dose treated group as compared to the control group. On the other hand, supplementation with ALA to profenofos intoxicated groups at both doses counteracts the effect of profenofos on SOD activity in liver tissue. Significant reduction in SOD activity was recorded in brain in both doses as compared to the control. Low dose supplemented group revealed significant increase (27.39%) in kidney SOD compared to the respective non supplemented group.

DISCUSSION

Until recently, the toxic effects of organophosphorus (OP) were believed to be largely due to the hyperactivity of the cholinergic system as a result of the accumulation of Ach at the synaptic cleft. A few minutes after the exposure

to OP induced seizures, other neurotransmitter systems become progressively more disrupted, releasing initially catecholamines (Shih and McDonough, 1997). In the present study the rats intoxicated with both doses of profenofos (OP insecticide) have non significant changes in plasma catecholamine levels except serotonin (5-HT) where significant increase was observed in low level profenofos treated group. These results run parallel with that previously reported by Prioux-Guyonneau *et al.* (1982) who recorded an increase in 5-HT level during the first phase of soman (OP gas). Also, Rajendra *et al.* (1986) recorded an elevation in blood 5-HT levels in rats following oral administration of low doses of organophosphorus insecticide diazinon for a period of 7-28 weeks. Meanwhile, Fernando *et al.* (1984) mentioned that acute administration of the anticholinestrase agents diisopropyl flurophosphate, soman, sarin and tabun to rats in subconvulsive doses produced tremors and hind-limb abduction. Environmental toxicants that promote or interfere with neurotransmitter function evoke neurodevelopment abnormalities by disrupting the timing or intensity of neurotrophic actions (Slotkin, 2004). Production of oxygen radicals was parallel by an augmented lipid peroxidative index as evidenced by the significant increase in malondialdehyde detected in liver tissue of rats intoxicated with both doses of profenofose insecticide. These results coincide with those of Verma (2001), Irfan and Namik (2002), Ranjbar *et al.* (2002), Akhgari *et al.* (2003) and Yukti *et al.* (2005) but it is in the contrary to the results of MDA level in kidney and brain tissues present in this study. Reduced glutathione (GSH) plays an important role in the detoxification of xenobiotic compounds and in antioxidation of reactive oxygen species and free radicals, increasing oxidative stress accompanied by decline in GSH level (Bray and Taylor, 1993). Intoxication with different OP insecticides induced oxidative stress leading to generation of ROS and free radical, then convert GSH to oxidized form GSSG (Ahmed et *al.,* 2000 and Yukti *et al.,* 2005). These findings run parallel with our results where significant decrease in GSH level was recorded in liver, kidney and brain tissues in profenofos intoxicated groups. It must be declare here that depletion of tissue GSH is a prime factor which can impair the cell defense against the toxic action of ROS and may lead to peroxidative cell injury (Younes and siegers, 1981 & Deleve and Kaplowitz, 1990). Glutathione–S–transferase (GST) enzyme is one of the major enzyme systems responsible for the detoxification of xenobiotics (Chasseaud, 1979; Jakoby and Habig, 1980). The ability of the organism to survive from the oxidative stress adverse effects is determined by the GST efficiency. In the present study, non significant decrease in GST activity was observed in liver and brain after treatment with both doses of profenofos which was accompanied with elevation in MDA in liver. This decrease in GST activity could be attributed to the direct binding of insecticides with GST (Grant and Matsumura, 1988). A significant increase in GST activity in kidney tissues recorded in the present study is in harmony with that previously obtained by Ahmed *et al.* (2000) and Suna *et al.* (2003). In the present study, while a significant increase in SOD activity in liver was recorded a significant decrease in kidney and brain tissues were detected after treatment with both doses of profenofos, these results run partially parallel with that previously obtained by Ahmed *et al.* (2000), Akhgari et al. (2003), Lin *et al.* (2003) and Yukti *et al.* (2005) who reported that the increase in superoxide dismutase activity reflects the activation on the compensatory mechanism through the effect of pesticides on progenitor cells and its extent depends on the magnitude of the oxidative stress and hence dose of the pesticides, and the changes in the antioxidant status in different tissues seemed not to be significant as the induction can be said to be tissue dependant. ALA is a universal anti-oxidant; it works in both fatty and watery regions of cells to quench free radicals. Supplementation of antioxidant ALA alone or after treatment with profenofos induced significant increase in some but not all neurotransmitter levels i.e. it induced significant increase in dopamine, norepinephren and serotonin levels, it must be noted that it is the effect of ALA per se as demonstrated in table (1), these results confirmed by the results which previously recorded by Paker *et al.* (1997) and Pirlich *et al.* (2002) who reported that radical scavenging properties of ALA are effective in amelioration neurodegenerative disorders induced by ethanol. In the present study, combined supplementation of ALA and profenofos insecticide induced marked significant reduction in MDA level in almost all treated tissues that was reflect the role of ALA to overcome the oxidative stress induced by profenofos insecticide. These results accompanied by improvement in GSH level in all tested tissues in ALA supplementated groups as compared to the respective non supplemented one. These results agree with the previous results obtained by Nickandar *et al.* (1996), Sandhya and Varalakshmi, (1997) and Thirunavukkarasu and Anuradha, (2004) who recorded the role of ALA in reduction oxidative stress. Also, Pryor (1973) reported that thiols are thought to play a vital role in protecting cells against lipid peroxidation. ALA helps to overcome the oxidative stress by increasing the GSH status which in turn exhibits increased free radical scavenging property (Malarkodi *et al.,* 2003). Packer *et al.,* (1995) reported that ALA regenerate the glutathione pool by reduction of oxidized glutathione. On the other hand, supplementation of ALA per se or in combination with profenofos insecticide induced significant increase in GST activity these findings runs with that previously obtained by Malarkodi *et al.* (2003) who recorded improvement in GST activity as a result of ALA treatment . ALA has been reported to be effective in reducing the amount of OH. generated by fenton type reactions and also scavenger of peroxide and O_2 hence the role of ALA as a free radical scavenger has been highlighted and its role in maintaining the tissue antioxidant status. In conclusion ALA supplementation to profenofos intoxicated rats induced improvement in lipid peroxidation, total glutathione level and glutathione-S-transferase activity.

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