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Evaluation of an Antioxidant Containing Drug Action against Pyrethroid Toxicity

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ABSTRACT

Oxidative stress may be caused by reactive oxygen intermediates which are involved in development of many diseases. This study was designed to determine whether antioxidant containing drug (antox) which contain antioxidant vitamins (A, C, E and seleninium) can ameliorate toxic effect of prallethrin insecticide. Four equal groups of adult albino male rats were used in this study which namely, control group, pyrethroid (prallethrin) group, antioxidant containing drug (antox) treated group and test treated group with antox in a dose of (21.15 mg /Kg.b.w.) and prallethrin in a dose of 1/10 LD_{50} (4480 mg /Kg.b.w.). The test drug as well as prallethrin were given to the test animal for 10 days. Blood samples were withdrawal after ten days and were subjected to biochemical assays including malonaldehyde (MDA), reduced glutathione (GSH) activity, nitric oxide (NO) concentration, alanine and aspartate aminotransferase (ALT & AST) activities, total protein, albumin and cholesterol contents.Treatment with prallethrin alone resulted in a significant increase ($P<0.05$) in ALT, AST activities, MDA, cholesterol and nitric oxide (NO) levels. The activity of reduced (GSH) Total protein and albumin were significantly decreased in prallethrin treated group compared to control. Treatment for ten days with antox after prallethrin significantly decrease ALT, AST activities compared to prallethrin alone. In addition the activity of GSH, total protein and albumin increased significantly after treatment with antox (in prallethrin + antox group) compared to prallethrin treated group. In conclusion treatment of antox after prallethrin induced an improvement in AST, ALT activities and could restore GSH, cholesterol and albumin to their normal values.

Key words: Prallethrin insecticide, pyrethroid, Antox, Malonaldehyde, Glutathione, Nitric Oxide, Total protein, albumin.

Introduction

Pyrethroids are synthetic insecticides derived from pyrethrins (Casida, 1980). Pyrethroids are increasingly used in a wide array of pesticide applications, including veterinary, agriculture, and home pest control (Amweg *et al*., 2005). Pesticides may cause reproductive toxicity through several mechanisms; direct damage to structure of cells, interference with biochemical processes necessary for normal cell function and biotransformations resulting in toxic metabolites (Agarwal and Sharma, 2010). Allethrin and prallethrin are type-I pyrethroids commonly used for domestic and agricultural purposes to get protection from mosquitoes and other insects. Use of these pyrethroids for longer durations and for prolonged periods in the form of coils and mats, results in biochemical and biophysical changes in erythrocyte biomembrane has been established (Narendra *et al*., 2014).

An antioxidant is a substance capable of preventing or slowing the oxidation of other molecules. Generally, an antioxidant can protect against metal toxicity by trapping free radicals thus terminating the chain reaction, by chelating metal ion and preventing the reaction with reactive oxygen species or by chelating metal and maintaining it in a redox state leading to its incompetency to reduce molecular oxygen. Substances which protect biomolecules from free radical-mediated damage both in vivo and in vitro fall under this category (Swaran, 2009). The antioxidant system such as antioxidant vitamins (A, C, and E) protects the cell against lipid peroxidation, which is the base of many pathologic processes (Ikeda *et al.*, 2004). Antioxidant vitamins are the most important free radical scavengers in extracellular fluids, trapping radicals in the aqueous phase and protect biomembranes from peroxidative damage (Yavuz *et al*., 2004 and Sulak *et al*., 2005).

Antioxidant containing drug (Antox) inhibits free radical generation in small intestine which acts as a contributing factor to the rejection process (Daoud *et al*., 2000). Vitamins are ideal antioxidants to increase tissue protection from oxidative stress due to their effective and safe dietary administration in a wide range of concentrations without harmful side effects (Cadenas and Cadenas, 2002). β-carotene is the best-known carotenoid due to its importance as a vitamin A (retinol) precursor. β -carotene possesses antioxidant activity somewhat analogous to that of vitamin E .Early studies showed that within 24 hr. after the clinical event, acute ischemic stroke patients had lowered levels of carotenoids and vitamin E as compared with matched controls.

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Vitamin C is a powerful electron donor, reacting with both O-2 and OH. It plays an important role in the defense against oxidative damage especially in leukocytes. The main role of vitamin C in the organism is linked to its function as a reductor, but it also participates in the modulation of complex biochemical pathways which are an essential part of the normal metabolism of immune cells (Zaki *et al*., 2007). Moreover, vitamin E has been shown to have several additional biologically important effects apart from its role as an antioxidant. These include the inhibition of arachidonic acid oxidative metabolism and the inhibition of protein kinase C (PKC) activity (Victor *et al.*, 2006).

Furthermore, selenium (Se) is an essential trace element for mammalian cells. It has regulatory functions in cell growth, cellular death and modulates signals transduction in various cells (Park *et al*., 2000). Se regulates immune function; it may provide important health benefits to people whose oxidative stress loads are high, such as those with inflammatory or infectious diseases (Ryan-Harshman and Aldoori, 2005). Selenium as an essential constituent of Glutathione -peroxidase enzyme (GSH-Px) plays an important role in scavenging reactive oxygen species (ROS). It is known that ROS and GSH are closely involved in Se metabolism and bioactivity of various cells (Kim *et al*., 2004).

Antioxidants such as vitamin E, coenzyme Q, vitamin C, glutathione (GSH) and selenium may act synergically, preventing lipid peroxidation and cell destruction (Lass and Sohal, 2000). Moreover, in vitro studies have shown that antioxidative vitamins (C& E) and selenium protected DNA damage against oxidative challenge (Fabiani *et al.*, 2001).

Aim of the work: The objective of this study is to indicate the value of antox to overcome and avoid pyrethroid (Raid) toxicity.

Materials and Methods

Animals:

Twenty four adult male albino rats, each weighing 180-200g were supplied from animal house of National Organization for Drug Control and Research (NODCAR). They were housed in wire cages with natural ventilation, illumination and allowed free water and standard diet for acclimatization in two weeks before being used for the experiment. Before and during the experiment the rats were housed under controlled environmental conditions of temperature (22 ± 2 ^{0}C) and a 12 hour light and dark cycle.

Insecticide:

Prallethrin in the formulated form with trade name Raid 1.25% (2-Methyl-4-oxo-3-(prop-2-ynyl) cyclopent-2-en-1-yl-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclo propanecarboxylate was purchased from Jonson wax Company.

Drug:

Antox drug was purchased from local pharmacy and is produced by Arab Company for pharmaceutical & medical plant Mepaco-Egypt. Each tablet contains: Selenium (55.7 mcg), Ascorbic acid (90 mg), Vitamin E (15 mg) and Vitamin A (2036.46 IU). The administrated dose for rat was (21.15mg/Kg b.w) calculated according to Paget and Barens (1964).

Experimental design:

Rats were classified into four equal main groups; each group consists of six rats as follows:

Group (1): Rats served as control and were received daily (corn oil) for 10 days.

Group (2): Rats were orally treated with 1/10LD_{50} (4480 mg/Kg b.w) prallethrin daily for 10 days.

Group (3): Rats were orally treated with (21.15 mg/Kg b.w) antox daily for 10 days 1hour after administration of 1/10 LD_{50} (4.48 mg/Kg b.w) prallethrin.

Group (4): Rats were orally treated with (21.15 mg/Kg b.w) antox consecutively given daily for 10 day and severed as positive control.

Sampling:

At the end of 10 days experiment, animals were sacrificed and blood samples collected. GSH content was determined immediately in fresh blood samples according to Beutler *et al*. (1963). Blood samples were centrifuged at 4000 rpm for 5 minutes, plasma stored at -20 ^{o}C. Plasma were used for determination of MDA, according to Sharma and Wadhwa (1983), nitric oxide according Montgomery and Dymock (1961), (ALT & AST) activities were estimated according to Reitman and Frankel (1957). Total protein was estimated according to Biuret reaction as described by Gornall *et al*. (1949) and Tietz (1994). Albumin was determined with bromocresol green as described by Doumas *et al*. (1997). Cholesterol was estimated according to method of Ellefson and Caraway (1974). All of the above mentioned parameters were determined using the corresponding diagnostic kits of Spectrum Company.

Statistical Analysis:

All the data of control and treated groups express as mean value ± standard error. The results were calculated statically by one-way analysis of variance (ANOVA test). Subsequent multiple comparisons between the different groups were analyzed by Duncan's multiple comparison tests. Data were statistically analyzed using the statistical package for social science (SPSS 11.0 software) values at $P < 0.05$ were considered significant (Armitage and Berry, 1987).

Results

The present study shows that MDA and NO recorded a significant increase in the rats treated with prallethrin with a percentage of change (16% & 53%) respectively as compared to the control group (Fig 1& 2). Prallethrin induced significant decrease in GSH level (53%) as compared to the control group (Fig 3) .There is no change observed in the level of MDA when antox administered after prallethrin treatment while there is a decrease in NO level and significant increase in GSH level as compared to the prallethrin group. Antox treated group recorded significant reduction in MDA level by (16%) and significant increase in GSH level by (26%) as compared to the control group as shown in figures(1&3)respectively.

As shown in figures (4 & 5), ALT & AST activity recorded a significant increase by 139% and 54% respectively when compared with control group. Antox treatment after prallethrin induces significant decrease in ALT & AST activity versus to the prallethrin treated group

Prallethrin induces a significant decrease in total protein and albumin levels 30 % & 17% respectively (Fig 6 &7) and a significant increase in cholesterol level (10%) as compared to the control group (Fig 8). Administrations of antox after prallethrin caused significant increase in total protein and albumin levels (Fig 6 &7) and a significant decrease in cholesterol level versus to prallethrin group (Fig 8).

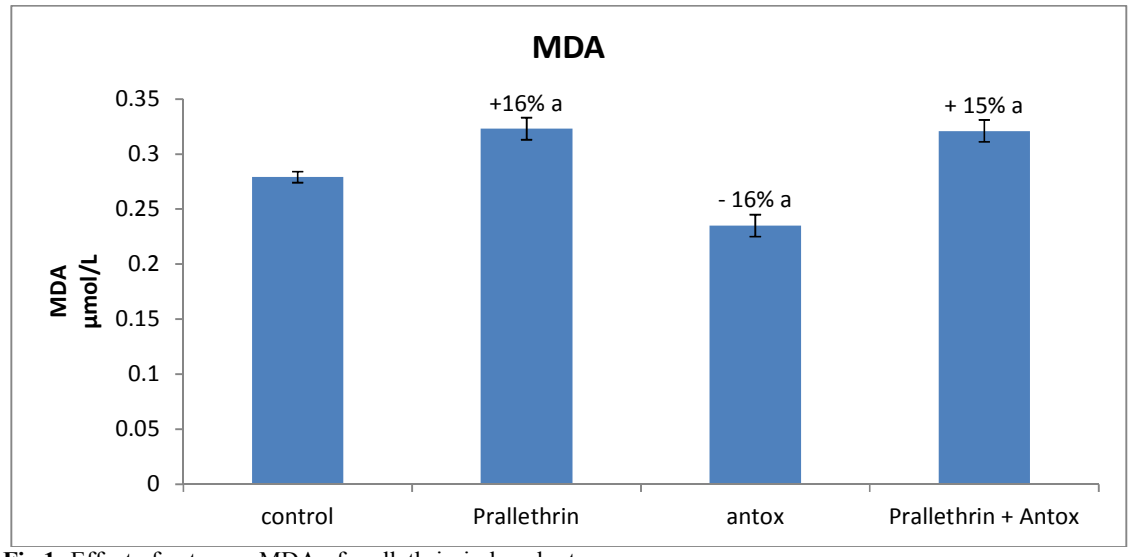

Fig 1: Effect of antox on MDA of prallethrin-induced rats.

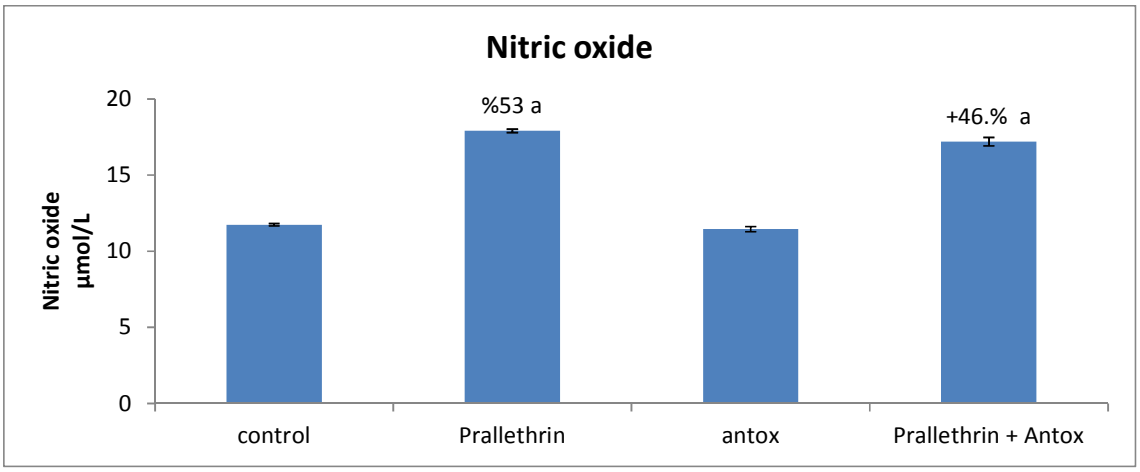

Fig 2: Effect of antox on nitric oxide of prallethrin-induced rats. Bars are expressed as mean± S.E. per group. % percentage of change, [a] Significant different from Control group at $P < 0.05$ [b] Significant different from prallethrin -treated group at $P < 0.05$.

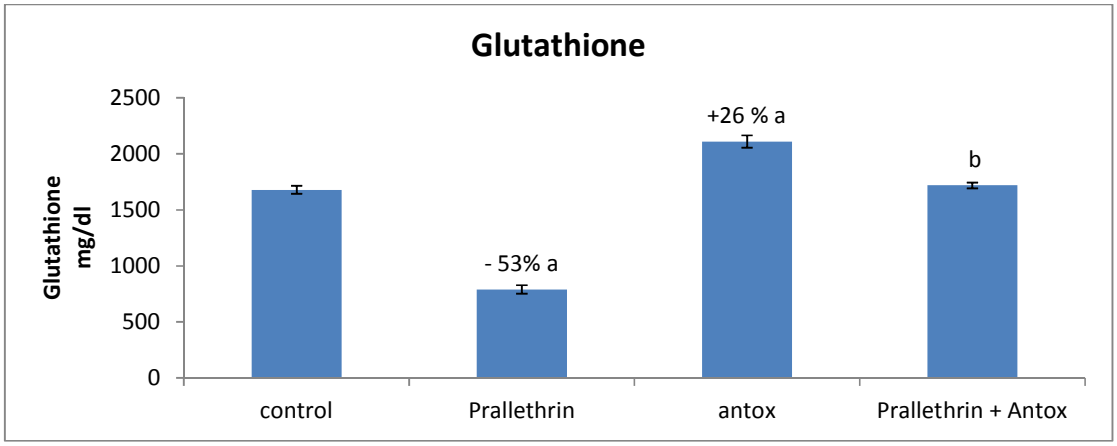

Fig 3: Effect of antox on glutathione of prallethrin -induced rats. Bars are expressed as mean± S.E. % percentage of change from control, [a] Significant different from Control group at $P < 0.05$ [b] Significant different from prallethrin -treated group at $P < 0.05$.

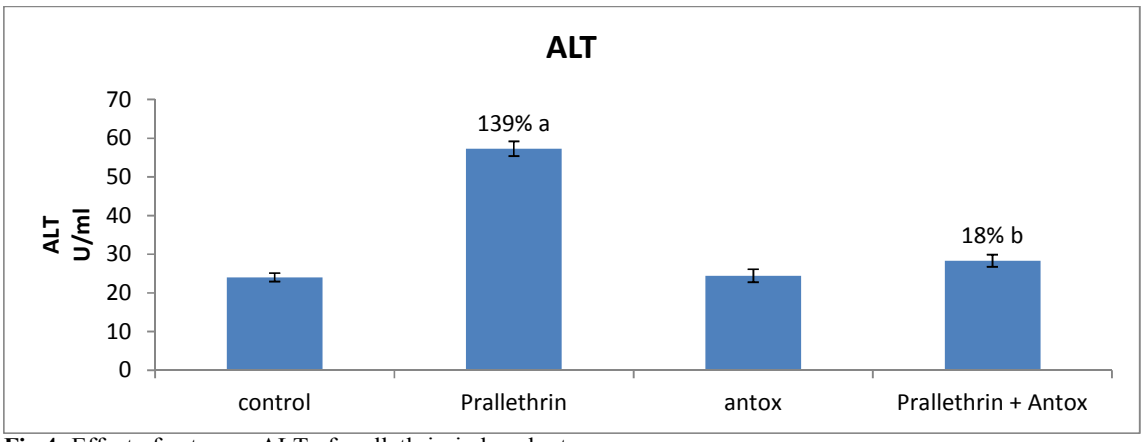

Fig 4: Effect of antox on ALT of prallethrin-induced rats.

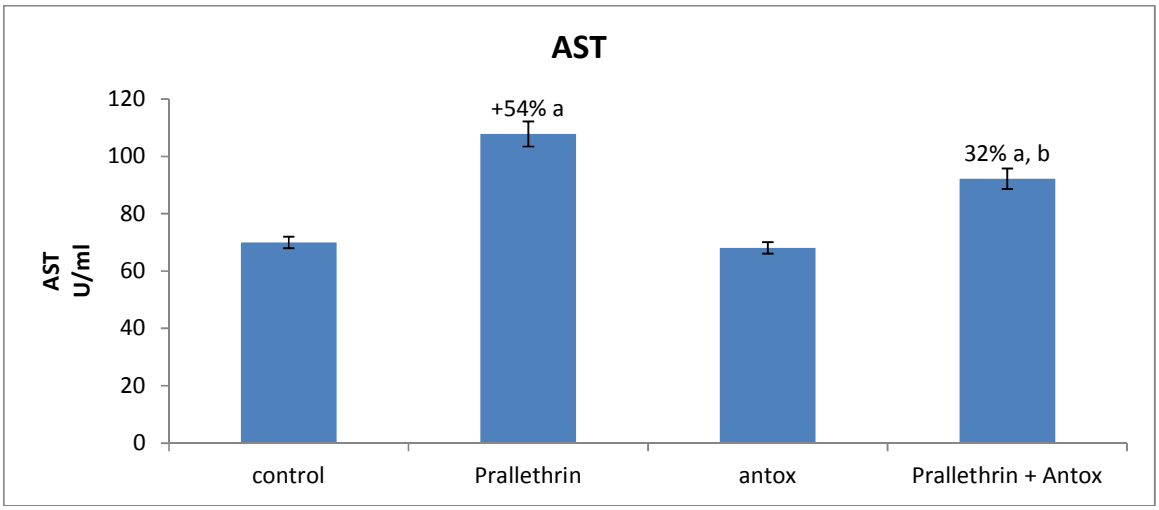

Fig 5: Effect of antox on AST of prallethrin-induced rats. Bars are expressed as mean± S.E. percentage of change from control, [a] Significant different from Control group at $P < 0.05$, [b] Significant different from prallethrin -treated group at $P < 0.05$.

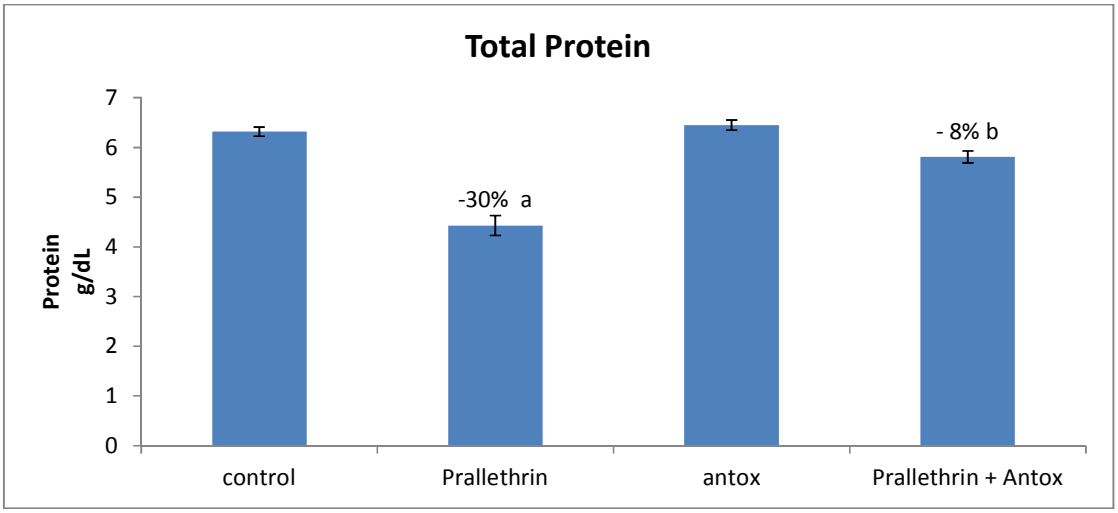

Fig 6: Effect of antox on total protein of prallethrin-induced rats

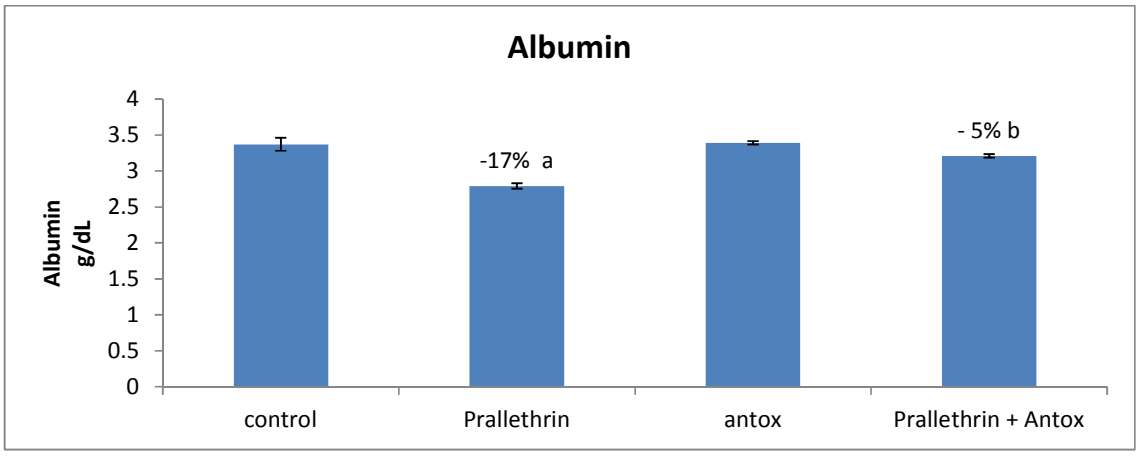

Fig 7: Effect of antox on albuminof prallethrin-induced rats

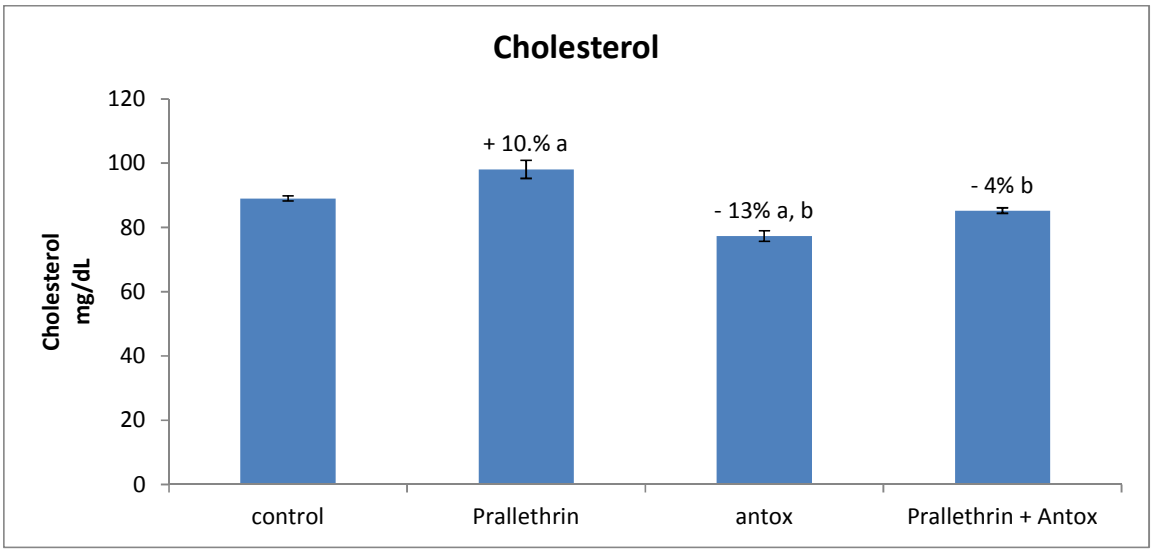

Fig 8: Effect of antox on cholesterol of prallethrin-induced rats. Bars are expressed as mean± S.E. per group. % percentage of change from control, [a] Significant different from Control group at $P < 0.05$, [b] Significant different from prallethrin -treated group at $P < 0.05$.

Discussion

Pyrethroids are axonic excitoxins, the toxic effects of which are mediated through preventing the closure of the voltage-gated sodium channels in the axonal membranes. The sodium channel is a membrane protein with a hydrophilic interior. This interior is a tiny hole which is shaped precisely to strip away the partially charged water molecules from a sodium ion and create a favorable way for sodium ions to pass through the membrane, enter the axon, and propagate an action potential. When the toxin keeps the channels in their open state, the nerves cannot repolarize, leaving the axonal membrane permanently depolarized, thereby paralyzing the organism (Soderlund *et al*. 2002).

Pyrethroids act primarily on the nervous system (Narahashi, 2000). These pyrethroids, which are widely used insecticides, induce oxidative stress through the generation of free oxygen radicals .Abnormal production of free radicals leads to damage of some macromolecules including proteins, lipids, and nucleic acids, and this is believed to be involved in the etiology of many chemicals and diseases (Parvez and Raisuddin, 2006; Rehman *et al*., 2006 and Huang *et al*., 2007).

Erythrocytes are particularly sensitive to oxidative damage due to presence of high poly unsaturated fatty acids content in their membranes and high cellular concentration of oxygen and hemoglobin (Muthuviveganandavel *et al*., 2011).

Production of oxygen radicals was parallel by an augmented lipid peroxidative index as evidenced by the significant increase in malonaldehyde detected in plasma of rats intoxicated with prallethrin in this study. These results run parallel with that previously reported by Kale *et al*., 1999 who mentioned that lipid peroxidation in erythrocytes increased within 3 days of pyrethroid treatment. Prasanta and Anand (1998) recorded an elevation in lipid peroxidation level in mice following administration of (120 mg/ Kg b.w.) of pyrethroid insecticide fenvalerate for a period of 15 days. In addition, results in this study coincide with those of (Wielgomas and Krechniak, 2007; Manna *et al*., 2004; Omotuyll *et al*., 2006 and Raina *et al*., 2009).

Malondialdehyde (MDA) level in Lambadacyhalothrin treatment was significantly higher than that in control. These indirectly suggest an increased production of oxygen free radicals in rats. Highly reactive oxygen metabolites, especially hydroxyl radicals, act on unsaturated fatty acids of phospholipid components of membranes to produce malondialdehyde, a lipid peroxidation product, where the accumulation of excess free radicals may be responsible for the increased lipid peroxidation (Abbassy *et al*., 2014).

Reduced glutathione (GSH) plays an important role in antioxidantion of reactive oxygen species and free radicals, increasing oxidative stress accompanied by decline in GSH level (Bray and Taylor, 1993). In the present study, there is a significant reduce in the reduced glutathione level. This reduction in GSH level is may be due to either the inhibition of GSH synthesis or increased utilization of GSH for detoxification of toxicant induced free radicals. The decrease in blood GSH and GSH-Px suggests that the dermal exposure of cypermethrin may lead to excessive free radical generation. These free radicals might be attacking the thiol group of cysteine residues and polyunsaturated fatty acids of biological membranes (Raina *et al*., 2009).These findings run parallel with that previously reported by Omotuyll *et al*., 2006 who recorded a significant decrease in the reduced glutathione level after oral administration of cyfuthrin (Pyrethroid) for 15 weeks. Also, Raina *et*

al. (2009) recorded a significantly decline in blood glutathione after 30 days of cypermethrin (Pyrethroid) dermal application. Kale *et al*. (1999) recorded an increase in reduced glutathione (GSH) content in erythrocyte after oral administration of a single dose of cypermethrin and or fenvalerate (Pyrethroid) to rats. This increase may be an initial adaptive response to increase oxidative stress in pyrethroid intoxicated rats. Sharma *et al*. (2014) showed that cypermethrin treated group (at the dose of 3.83mg/ Kg b.w. for 7 days) showed elevation in lipid peroxidation and inhibition in glutathione in wister rat brain. In addition, Abbassy *et al*. (2014) observed significant decrease in GSH after treatment of rats with lambadacyhalothrin in a dose equal 2.6 mg/kg b.w, for 6 weeks (3 doses/week).

Increase in nitric oxide and lipid peroxidation levels in plasma due to the role of NO in regulation of glucose metabolism in insulin insensitive tissue where it could function in parallel to insulin to keep glucose concentration in normal range (Cremer and Seville, 1982 and Cremer *et al*., 1983). Nitric oxide appears to protect membrane integration and function by blocking lipid derived radicals and thereby antagonizing oxidative and photo oxidative stress which affect glucose homeostasis (Burg, 1995; Hotta, 1997 and Ramana *et al*., 2003). The present study shows an elevation in NO level after pralletrin administration. This finding parallel with Wang *et al*. (2009) who mentioned that 35 days administration of either moderate or high doses of Beta-cypermethrin (pyrethroid) induced an increase in testes nitric oxide level of male mice. Kanbur *et al*. (2008) demonstrated that the administration of two doses (5 and 10 mg/Kg) of cypermethrin (pyrethroid) to mice for a period of 60 days produce oxidative stress. The degree of oxidative stress was found to be related to the dose administered and the duration of exposure. In addition, Narendra *et al*. (2008) showed less significant increase in the level of nitrite and nitrate when human volunteers exposed to commercially available mosquito repellent pyrethroids, allethrin and prallethrin. Increased production and bioavailability of nitric oxide that might have rendered tolerance against haemolysis by the free radical scavenging effect and indirectly by other possible protective mechanisms of nitric oxide (Narendra *et al*., 2008 and Oekonomaki *et al*., 2004)

A significant increase in ALT and AST activities recorded in the present study is in harmony with that previously obtained by Manna *et al*. (2004); Narendra *et al*., 2008; Bhushan *et al*., (2013) and Ibiang *et al*., (2013) . Increased aminotransferase (ALT, AST) activity in serum reflects hepatocellular damage under cypermethrin stress, leading to leakage of this enzymes into general circulation (Manna *et al*., 2004; Bhushan *et al*., 2013 and Ibiang *et al*., (2013). Increase in the activity of plasma ALT in allethrin indicated liver damage, probably by the direct effects of allethrin on membrane of hepatocytes, via interdigitation of pyrethroid between phospholipids, and/or indirect effects caused by products derived from pyrethroid metabolism (Narendra *et al*., 2008). Amaravathi *et al*. (2010) reported that treating rats with fenvalerate caused degenerative changes in the liver, haemorrhages, mild fatty changes, infiltration of mono nuclear cells and proliferation of bile duct.

GSH and MAD levels in the liver reflect the oxidative status and the serum enzymes like AST and ALT represent the functional status of the liver. Chemical-induced cellular alteration varies from simple increase of metabolism to death of cell. The increase or decrease of enzyme activity is related to the intensity of cellular damage. Increased MAD level in the liver as well as increased serum AST, ALT and ALP levels suggest that Cyfluthrin causes hepatic damage which may be through free radicals (Omotuyl *et al*., 2006). The present study recorded a significant decrease in total protein after prallethrin administration, this result in agreement with previous studies demonstrating (Omotuyl *et al*. (2006) who mentioned that total protein showed a significant decrease in the test groups of rats which subjected to continuous oral administration of cyflthrin (pyrethroid) for 15 week., Narendra *et al*. (2008) and Muthuviveganandavel *et al*. (2011). Stress conditions cause release of adrdreno-corticotropic hormone, triggering consequent secretion of cortisol by the adrenal cortex which reduces cellular protein stores in liver (Hayes and Laws, 1991). The result in this study recorded a significant decrease in albumin due to administration of prallethrin and this result agree with (Saxena and Saxena, 2010) and Aldana *et al*. (1998) which reported that stress due to exposure to a pesticide cypermethrin may influence albumin synthesis. The changing levels of serum albumin, thus, provide valuable indices of severity progress and prognosis in hepatic disease. Decreased albumin in serum indicated hepatocellular origin of liver diseases (Sood, 2006).

Pesticides can cause changes in blood cholesterol level by alternating the permeability of hepatic cells and distribution lipid metabolism (Yousef *et al*., 2003) and this can be indicated by elevated cholesterol level in the serum (Ibiang *et al*., 2013). A Significant increase in cholesterol level was observed in this study agree with (Kalender *et al*., 2005; Muthuviveganandavel *et al*., 2011 and Bhushan *et al*., 2013). Cypermethrin has effect on serum lipids include cholesterol, triglycride, phospholipids and free fatty acids (Tortora and Graboski, 2003). Any increase in level of these forms will lead to an increase of total lipid concentration in serum. One of the causes of increased total lipid concentration appears to be disturbance of carbohydrate metabolism, due to probable cytotoxic effect of cypermethrin on cells of the pancreas leading to relative deficiency of insulin (Kalender *et al*., 2005). In such conditions, carbohydrates are not available to body tissues as insulin is not available to facilitate glucose transport in cells. In insulin deficiency, carbohydrates are not used to meet energy demands of body and most of the energy is derived from fats. The fat stored in adipose tissue is then hydrolyzed

and then the amount of free acids in blood is increased resulting in increased serum total lipid concentration (Gyton and Hall, 2001 and Rezg *et al.,* 2007).

Oxidative stress may induce a rapid alteration in the antioxidant systems by inducing protein that participate in these systems and/ or depleting cellular stores of endogenous antioxidants such as GSH and Vitamin E (Hsu *et al* ., 2004).

Antox contains three main antioxidants (A, C and E) and selenium. Vitamin C is an important dietary antioxidant; it significantly decrease the adverse effect of reactive species such as reactive oxygen and nitrogen species that can cause oxidative damage to macromolecules such as lipid, DNA and proteins, which implicated in chronic diseases (Halliwell and Gutteridge, 1989). It has been reported that, vitamin A and C either invaluably or in combination are reported to act as an effective antioxidant of major importance for protection against diseases and degenerative processes caused oxidative stress (Olas and Wachowicz, 2002 and Kanter *et al*., 2005).

Vitamin E is a potential antioxidant and a liposoluble antioxidant present in biological membranes and inhibits free radical formation in biological system (Mukai *et al*., 1993). Vitamin E, as an antioxidant, has protective against deltamethrin adverse effects by scavenging free radicals generated following pesticides exposure and supplementation of E is might be beneficial to deltamethrin exposed population vitamin (El-Maghraby and Taha, 2012).

Vitamin C is well known as an antioxidant; which act as an electron donor to protect the body from radicals and pollutants ((Igbal, K. *et al*., 2004). Vitamin C is also known to act as free radical trap and as cofactor in the synthesis of biologically antioxidant materials such as glutathione glutathione (Tppel, 1968 and Khedr *et al*., 1999). Vitamin E and Vitamin C caused a reduction in the production of free radicals and a decrease in the activities in ALT and AST (Yousef *et al*., 2003).

According to the present data, combined supplementation of antox after prallethrin induced significant reduction in NO level and ALT, AST activities. Hassan *et al*. (2006) who reported that treatment for seven days with either antioxidants alpha lipoic acid (ALA) or Antox prior to or after LPS challenge significantly ($P<0.05$) decrease ALT, AST, MDA and NO levels when compared to LPS alone that was reflect the role of Antox to overcome the oxidative stress and liver injury induced by LPS challenge. This result is accompanied by improvement in the content of GSH when compared with prallethrin treated group. This result in parallel with (Hamooda *et al*., 2003) who reported that antox succeeded in minimize cadmium induced toxicity in albino rats and increase the activity of endogenous antioxidants including glutathione. The present study has demonstrated no sign of therapeutic effect of antox supplementation on MAD after prallethrin administration, this result agree with El-Zayat *et al*. (2008)

Also the total protein and albumin showed a significant improvement and we found that Hassanin *et al*. (2010) obtained the same result when treated male rats with antox along with arsenic.

This result accompanied by improvement in the content of GSH and albumin when compared with prallethrin treated group. Also the total protein showed a significant increase. Antox alone improve MDA, GSH levels, activity and induce a decrease in AST activity, NO level as compared to the control group. These results agree with the results obtained by Daoud *et al*. (2000) and EL-Gohary *et al*. (2003) who reported that antox inhibited free radical generation in small intestine. Antioxidants like vitamin E had played a protective role against the pyrethroid induced oxidative stress (Kale *et al*., 1999a & 1999 b ; Aldana *et al*., 2001and Parvez and Raisuddin, 2006).The results obtained by Pieneli-Saavedra (2003) and Das *et al*. (2004) postulated that vitamin E improved the immune system by unknown ways in addition to its antioxidant properties, it may also exhibit immune-modulator effect. Moreover, Jones (1995) and El-Maghraby and Taha (2012) suggested that, the protective effect of vitamin E may be due to its lipophilic antioxidant property which may induce reduction of membrane lipid peroxidation and lipid peroxide formation. Raina *et al.* (2009) reported that α- Trocopherol supplementation plays a protective role in cypermethrin induced oxidative stress in rats. Selenium is an essential component of GSH-Px, which is an important enzyme for process that protects lipid in polyunsaturated membrane from oxidative degradation (Barceloux, 1999). Selenium stimulates Na, K-ATPase activity and inhibits lipid peroxidation. Since Na, K-ATPase activity is known to be inhibited by oxygen free radicals likely formed by deltamethrin (pyrethroid), selenium supplementation appears to exert its beneficial effect on Na, K-ATPase activity preventing free radical-induced damage (Siegel *et al*., 1999).

Conclusion

The present study indicates that administration of antox has the ability to reduce effects of prallethrin intoxication under experimental conditions. These signs of therapeutic effects might be correlated with the scavenging effect of selenium either individually or in presence of other antioxidant like (vitamins C and E in antox) and or the enhancing ability for the antioxidant defense system.

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