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CYPERMETHRIN EXPOSURE INDUCED DETERIORATION OF ENZYMATIC AND NON-ENZYMATIC ANTIOXIDANTS IN HEPATIC AND RENAL TISSUES OF MICE

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ABSTRACT

Cypermethrin is an artificial pyrethroid insecticide which is broadly used in various applications such as public health protection, agriculture and household pests' control. However, exposure to cypermethrin may result in several harmful effects on non-target species. This study was designed to investigate the toxic impacts which are caused by exposure to sub-lethal dose of cypermethrin, on antioxidant defense system in liver and kidney. The study was conducted on forty adult albino mice which were randomly distributed into four groups with ten mice each. First group served as healthy control and the rest received cypermethrin for periods of 2, 4 and 8 weeks. Mice were sacrificed and followed by collection and preparation of blood and tissue samples for qualitative, quantitative and biochemical analysis. The findings of this investigation revealed that *in vivo* administration of cypermethrin lead to remarkable stimulation of oxidative damage in hepatic and renal tissues, which was evidenced by alterations of non-enzymatic antioxidants such as depletion of GSH content associated with increased level of MDA, LOOH and AOPP resulting in induction of lipid peroxidation and protein oxidation. In addition, cypermethrin treatment significantly inhibited the antioxidant enzymatic activity including SOD, CAT, GR and GPx, while enhanced the activity of GST in Liver and kidney tissues. Furthermore, cypermethrin administration stimulated the activity of liver marker enzymes such as ALT, AST, GGT and ALP. Therefore, the results of this study suggest that cypermethrin intoxication induced formation of free radicals leading to oxidative damage, hepatotoxicity and nephropathy in adult albino mice.

KEYWORDS: Cypermethrin, free radicals, oxidative stress, antioxidant, liver, kidney.

1. INTRODUCTION

Pesticides are broadly deemed as one of the most functional ways to control pests worldwide. However, their utilization has increased to alarming extents due to their various adverse impacts on non-target species.[1-3] Pyrethroids are a group of pesticides which are used commercially in several applications including agriculture, public health, veterinary, and household pests' control. However, their expanding reliance has intensified many negative effects on non-target organisms. Pyrethroids are organic compounds that are derived from the natural pyrethrins, which are formed by the flowers of pyrethrums.[4,5]

Cypermethrin is an artificial pyrethroid insecticide that is vastly used in many agriculture and household

applications. It effectively acts as neurotoxin for different kinds of pests.[6] However, exposure to cypermethrin may cause several toxic side effects such as deterioration of cell membrane structure due to its lipophilic characteristics leading to cellular enzyme leakage. In addition, cypermethrin can reach our bodies through inhalation, ingestion and absorption through skin causing various symptoms such as skin irritation, tingling, numbness, burning itchy eyes. convulsions, loss of bladder control, as well as death in serious cases.[7,8] Furthermore, cypermethrin can accumulate in several tissues including liver, kidneys, adipose tissue, brain, under skin, ovaries, and adrenal glands. In mammals, partial or total temporary impairment of the nervous system resulting from over-stimulation of central nervous system, and over induction of gamma-aminobutyric acid, as well as higher formation of free radicals.[9-11] Additionally, cypermethrin can be degraded by water and sunlight, though it can persist in soil and subsequently cause groundwater pollution.

Liver is an important organ that performs large number of vital processes such as xenobiotics detoxification, protein biosynthesis, and regulating several cellular activities. Disturbing hepatic homeostasis because of oxidative imbalance leads to impairment of many physiological functions in our bodies.[12] Xenobiotics metabolism primarily occurs in liver tissue. This process can occasionally produce toxic byproducts which sometimes are extra toxic than the initial substances causing hepatic impairment and liver disorders. The resulting products can contain oxidizing constituents which inflict serious damage to key cellular components such as lipids, proteins and nucleic acids, via oxidation.[13,14] Oxidative stress is pathophysiological disturbance in the balance between production of reactive oxygen species (ROS) and failure of cellular detoxifying systems through neutralization by antioxidants. In addition, overproduction and inadequate removal of free radicals may cause destructive and irreversible cell injury.[15,16] Therefore, the main aim of this work is to investigate the negative effects, that might result from cypermethrin exposure, on antioxidants defense system in hepatic and renal tissues of mice.

2. MATERIALS AND METHODS

2.1 Experimental animals and study design

The study was conducted on healthy adult white wool albino mice, *Mus musculus*, aged four months and weighing 80-100 g. Mice were kept under standardized healthy conditions in clean, ventilated metal cages in 12 hours of light and darkness at 18-24°C. Animals were acclimatized to laboratory environment 14 days before study commencement. All mice were handled humanely following the instructions of the National Institutes of Health for ethical treatment of laboratory animals, USA. The mice were distributed into 4 groups including 10 animals each. Animals in group I served as healthy control and received water orally at each period of the experiment. Groups II, III and IV received cypermethrin orally in a dose of 35 mg/kg. Measurements were recorded after 2, 4 and 8 weeks. Animals were fed with standard pellet diets which were got from LabDiet, Missouri, USA, and provided with free access to drinking water and food, *ad libitum*, throughout the investigation time.

2.2 Samples collection and preparation

Mice were anaesthetized and decapitated after being fasted for 12 hrs. The collected blood samples were centrifuged at 2000 rpm for 25 min using centrifuge 5418R (Eppendorf, Ontario, Canada). The resulting serum was utilized to measure serum enzymes activity. Liver and kidney were collected from animals directly, cleaned in ice cold saline and dried by filter papers. The obtained tissues were weighed and homogenized by Teflon glass homogenizer. The homogenate was prepared using ice cold phosphate buffer (50 mM, pH 7.4, 0.1% triton and 0.5 mM EDTA) prior to centrifugation for 15 min at 3000 g, 4°C by cooling centrifuge (type 3K-30, Sigma, Germany) to eliminate any cellular debris. The resulting supernatant was utilized for biochemical examination using auto-analyzer (Roche Diagnostics Corporation, Indianapolis, USA).

2.3 Evaluation of LPO and GSH levels

The quantification of lipid peroxidation (LPO) was performed by malondialdehyde (MDA) assay kit (Sigma-aldrich Ltd., UK) following manufacturer's instructions. In this method, LOP was analyzed by the reaction of MDA with thiobarbituric acid (TBA) to produce colorimetric products that are proportional to the MDA present. The MDA-TBA complex was formed by adding 600 mL of TBA solution to each sample, followed by incubation at 95°C for 60 min, prior to cooling to room temperature. The absorbance was measured at 532 nm. Glutathione (GSH) level was measured using GSH assay kit (Sigma). The biological sample is deproteinized with sulfosalicylic acid solution, centrifuged to eliminate any sediments, followed by glutathione check. This analysis is kinetic method in which catalytic amounts of GSH cause continuous reduction of 5-dithiobis nitrobenzoic acid (DTNB) to 5-thio nitrobenzoic acid (TNB) and the oxidized glutathione formed is recycled by glutathione reductase and nicotinamide adenine dinucleotide phosphate (NADPH). The reaction rate is proportional to the concentration of glutathione. TNB product was examined using spectrophotometer at 412 nm.

2.4 Assessment of enzymatic activities

The activity of catalase (CAT) was evaluated using catalase assay kit (Sigma). CAT decomposes hydrogen peroxide by catalytic pathway, in which two molecules of hydrogen peroxide are converted to water and oxygen, prior to terminating by sodium azide. This examination is based on estimation of hydrogen peroxide substrate remaining after the action of catalase. The absorbance was checked spectrophotometrically at 520 nm. In addition, Superoxide dismutase (SOD) activity was measured using SOD assay kit (Sigma) following the

manufacturer's guidelines. In this process, water soluble tetrazolium allows very convenient SOD assaying by using WST salt which forms water-soluble formazan dye with reduction by superoxide anion. The reduction rate with oxygen is consistently proportional to the activity of xanthine oxidase (XO) and is hindered by SOD. Consequently, SOD activity was estimated by measuring the decrease in color development at 440 nm which is proportional to the amount of superoxide anion.

The activity of glutathione reductase (GR) was analyzed using GR assay kit (Sigma). This method is based on the reduction of oxidized glutathione (GSSG) by NADPH and catalyzes by GR. In addition, dithiobis nitrobenzoic acid reacts with GSH formed. The first reaction was evaluated by the decrease in NADPH absorbance at 340 nm, and the second reaction was determined by elevation in thio-nitrobenzoic acid absorbance at 412 nm. Furthermore, glutathione peroxidase (GPx) activity was examined using GPx cellular activity assay kit (Sigma), following the manufacturer's guidelines. This reagent performs indirect estimation assay which is based on oxidation of GSH to GSSG catalyzes by GPx, that is coupled to recycling of GSSG back to GSH using GR and NADPH. Decline in NADPH absorbance, determined at 340 nm during its oxidation, which is an indicative of GPx activity. The analysis was conducted at 25°C and commenced by adding organic peroxide, *tert*-butyl hydroperoxide. This substrate is appropriate for the reaction because its spontaneous reaction with GSH is low, as well as not being metabolized by catalase. The reaction with *tert*-butyl hydroperoxide estimates GPx activity. Moreover, the activity of glutathione-S-transferase (GST) was quantified using GST assay kit (Sigma) which uses chloro-dinitrobenzene (CDNB), that is appropriate for large range of GST isozymes. Following conjugation of thiol group of glutathione to CDNB substrate, there was elevation in the absorbance at 340 nm.

To estimate the activity of alanine aminotransferase (ALT), buffered solution containing alanine and ketoglutarate was loaded to the serum, followed by incubation at 37°C for 30 min. DNPH and NaOH were added to the reaction mix afterward. The activity level was obtained by reading the absorbance at 500 nm. On the other hand, aspartic acid was utilized to examine the activity of aspartate aminotransferase (AST) in serum, in place of alanine, and the incubation time was 1 hr. In addition, γ-glutamyl transferase (GGT) activity was measured by adding substrate solution containing glycylglycine, magnesium chloride and γ-glutamyl-nitroanilide, to the serum. Afterward, the reaction mix was incubated at 37°C for 1 min, followed by measuring the absorbance at 405 nm within 1 min interval for 5 min. Moreover, Alkaline phosphatase (ALP) hydrolyzes colorless substrate containing disodium-phenyl phosphate into phenol and phosphate. The enzymatic reaction was terminated by amino-antipyrine and sodium arsenate. The liberated phenol was determined using colorimetric method which used potassium ferricyanide as a color developing reagent.

2.5 Statistical analysis

Data analysis was performed using the SPSS software for windows, version 23 (SPSS Institute Inc., USA). Results were represented as means ± standard error (SE) and analysed using analysis of variance (ANOVA) followed by Student's *t*-test at probability of less than 0.05 to evaluate the statistical differences between the experimental groups.

3. RESULTS

3.1 Effects on non-enzymatic antioxidants

The present work investigated the effects of cypermethrin exposure (35 mg/kg body weight) on hepatic and renal tissues of mice after 2, 4 and 8 weeks of treatment. To determine the influence of cypermethrin on antioxidants and oxidant balance in liver and kidney, the levels of MDA, lipid hydroperoxide (LOOH), GSH and advanced oxidized protein product (AOPP) were measured in tissues (table 1). The result showed that treatment with cypermethrin caused significant elevation in MDA and LOOH levels, which indicates increasing in lipid peroxidation (LPO) in the examined tissues. In addition, mice treated with cypermethrin showed remarkable reduction in GSH levels in liver and kidney tissues indicating tissue damage caused by accumulation of free radicals and ROS within cells with the increase of cypermethrin accumulation in tissues. Moreover, the levels of AOPP were also increased significantly in hepatic and renal tissues of mice which demonstrate increasing protein oxidation in cypermethrin-treated animals (table 1).

3.2 Effects on antioxidant enzymes

The results also revealed a considerable reduction in the activity of antioxidant enzymes including CAT, SOD, GPx and GR in liver and kidney tissues of cypermethrin treated mice after 2, 4, 8 weeks of cypermethrin administration. It's also observed that this significant decrease in enzymatic activity reached the lowest level after 8 weeks of treatment as shown in fig 1 and fig 2. In addition, the data also showed a remarkable increase in GST activity in animals treated with cypermethrin, which reached a peak following cypermethrin application for 8 weeks.

3.3 Alteration in liver marker enzymes

It has been observed from collected data that mice treated with cypermethrin showed a significant elevation in the activity of aminotransferases including AST, ALT and GGT (fig 3). Moreover, increasing in hepatic phosphatases (ALP) activity was also observed in liver tissues of all treated animals. In addition, the increase in liver biomarker enzymes recorded highest level following 8 weeks of cypermethrin exposure compared to those in the control, depending on accumulation of cypermethrin in tissues.

Table 1: The influence of cypermethrin exposure (35 mg/kg bd wt) on the level of LPO, LOOH, AOPP and GSH in liver and kidney tissues of mice.

Parameter	Control	Period		
		2 weeks	4 weeks	8 weeks
Liver tissue:				
MDA (nmol/g tissue)	54.67±1.85	59.98±1.61	75.92±2.42*	88.78±1.73*
LOOH (nmol/g tissue)	4.87±0.92	5.21±0.81*	7.38±0.70*	8.41±0.64*
AOPP (µmol/g tissue)	68.54±1.73	69.98±2.72	83.42±1.84*	99.53±2.79*
GSH (mg/g tissue)	98.89±2.71	87.57±1.65*	67.09±3.59*	57.58±2.83*
Kidney tissue:				
MDA (nmol/g tissue)	44.16±2.29	53.82±1.79*	59.49±1.63*	70.35±2.59*
LOOH (nmol/g tissue)	2.54±0.71	2.99±0.39	3.76±0.82*	4.20±0.78*
AOPP (µmol/g tissue)	59.29±2.62	64.25±1.83*	69.87±1.79*	84.93±2.66*
GSH (mg/g tissue)	86.53±1.82	80.09±3.49	69.53±2.76*	52.34±1.91*

Data are expressed as mean ± SE, n = 10, * P<0.05

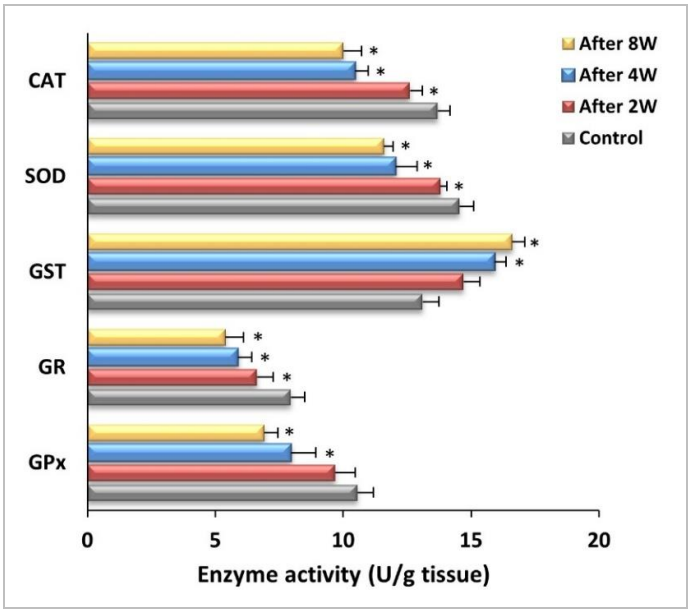

Fig 1: Changes in antioxidant enzymes in hepatic tissue of mice at different periods (2, 4, 8 weeks) following cypermethrin treatment (35 mg/kg bd wt). Values are represented as mean ± SE, n = 10, * P<0.05.

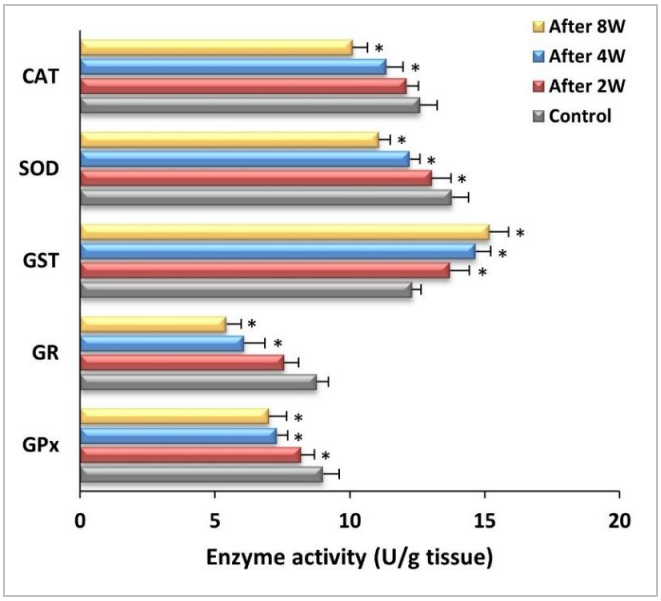

Fig 2: Effect of cypermethrin exposure on antioxidant enzymes in renal tissue of mice at different periods (2, 4, 8 weeks). Values are represented as mean ± SE, n = 10, * P<0.05.

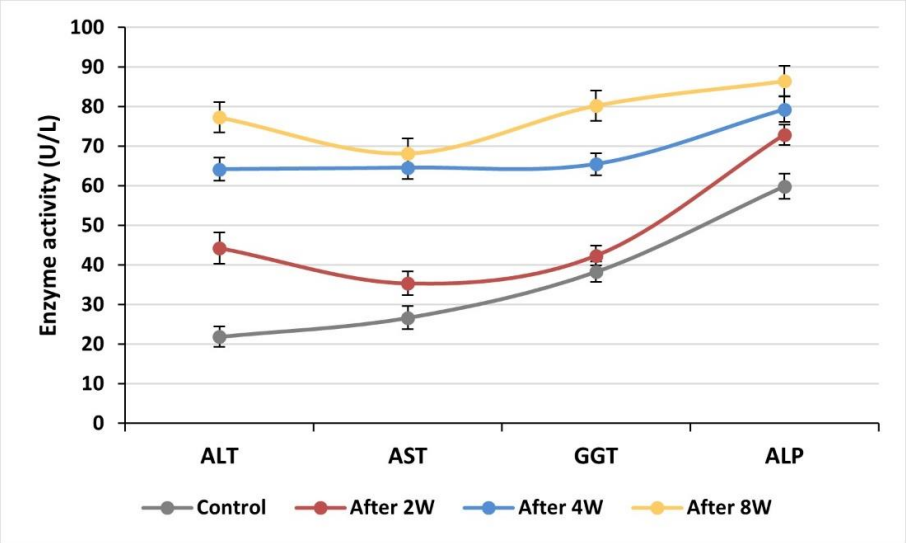

Fig 3: Effect of *in vivo* administration of cypermethrin on liver biomarker enzymes of cypermethrin-treated mice. Data are expressed as mean ± SE, n = 10, * P<0.05.

4. DISCUSSION

Accumulation of pesticides, such as cypermethrin, within cells induced excessive formation of ROS leading to cellular oxidative damage.[17,18] It has been observed that pyrethroids stimulate accumulation of peroxidation byproducts in tissues resulting in xenobiotic stress.[19-21] ROS are generated across oxidative metabolism of pyrethroids by cytochrome P450 in hepatocytes. By utilizing available mitochondrial electrons, oxidative stress transforms mitochondrial oxygen into more reactive superoxide.[22] The resulting superoxide anions are disassembled to hydrogen peroxide and water by SOD.[23] The resulting oxidative products of such reactions are widely used to assess oxidative damage that occurs through xenobiotic metabolism which causes alteration in antioxidant defense system.

The current work revealed significant increase in the level of MDA, LOOH and AOPP in hepatic and renal tissues following cypermethrin treatment, indicating LOP and protein oxidation leading to cell injury. Lipid peroxidation is an autocatalytic reaction that results in oxidative degradation of lipids causing destruction of cellular membranes and consequent cellular damage.[24] This process is mainly induced by the influence of various ROS including hydrogen peroxide, superoxide anions and hydroxyl radicals.[25] LPO is a chain reaction initiated by the abstraction of hydrogen atoms from the side chain of polyunsaturated fatty acids, eventually causing demolition of cellular membranes. Decomposition of these intermediates compounds results in formation of various secondary byproducts, especially MDA.[26] Accumulation of these products within cells decreases the fluidity of cell membrane which is essential for proper cell function. High level of MDA and LOOH found in the current work, which indicates LPO, suggests remarkable damage of cell membrane in liver and kidney following cypermethrin treatment. Due to cypermethrin lipophilic characteristics, it can easily pass the cell membrane leading to cell injury.[27] The increased level of AOPP indicates that cypermethrin induced cellular oxidation of protein. These observations concur with previous study reported that cypermethrin induced ROS production which causes oxidative damage in hepatic and renal tissue of rat.[28,29] It has been observed that cypermethrin had the ability to disrupt the antioxidant defense system.[30,31]

Pesticides exposure is commonly associated with deterioration of the antioxidant defense system, along with diminishing of non-enzymatic antioxidants such as GSH, which plays a crucial role in scavenging damaging free radicals and can function as a co-substrate for detoxification of peroxide by glutathione peroxidases.[18,32] In addition, GSH also catalyzes the reduction of hydrogen peroxide to water, as well as GSH non-enzymatically reacts with superoxide, hydroxyl radicals and singlet oxygen.[33-35] Therefore, ROS are quenched by interaction with GSH before they initiate their chain reaction damaging effects.[36] Depletion of cellular glutathione content may be one of the reasons for the increase in cell vulnerability to oxidative stress.[37,38] Moreover, diminished level of GSH in liver and renal tissues following cypermethrin treatment is associated with inhibition of GSH production, or perhaps due to an increased utilization of GSH to detoxify toxicants which stimulate higher production of free radicals.[39] Therefore, this suggests an imbalance in non-enzymatic defense molecules in hepatic and renal tissues induced by cypermethrin exposure.

Within cells, antioxidant enzymes play crucial roles in cellular defense mechanisms by minimizing the adverse effect of oxidant molecules and protecting cells against oxidative damage through scavenging free radicals. However, any perversion in physiological concentrations of these enzymes might decline their efficiency to remove ROS, resulting in excessive oxidative damage to

lipids, proteins, and DNA.[40,41] In the current work, the activities of antioxidant enzymes SOD, CAT, GPx and GR were significantly reduced in cypermethrin intoxicated animals. Declined activities of such enzymes as well as reduced level of GSH may refer to the damaging effect of free radicals produced following cypermethrin exposure. SOD is a main enzyme in the antioxidant defense system which catalyzes the transformation of endogenous cytotoxic superoxide radicals into hydrogen peroxide (H_2O_2) and ordinary molecular oxygen, thereby inhibiting oxidative cellular damage.[42] Depletion of SOD in liver and kidney, following cypermethrin intake, referred to inability of cells to control the excessive production of free radicals[22], as well as the ROS formed by pyrethroid.[43] The reduction of GSH content and SOD activity indicates that cypermethrin exposure may lead to higher formation of free radicals which may attack the thiol-group of cysteine residues and polyunsaturated fatty acids of cellular membranes.[44] Accumulation of free radicals within tissues induced oxidative stress and lipid peroxidation which cause degradation of biological membranes.[45]

In addition, CAT is an important antioxidant enzyme that promotes cellular ability to convert hydrogen peroxide to water and molecular oxygen.[46-48] Insufficient activity of CAT to decompose hydrogen peroxide, leading to more production of toxic hydroxyl radicals that might contribute to oxidative stress[49] following cypermethrin treatment. CAT can be found in two forms including soluble and membrane-bound enzyme, that could be affected by higher production of free radicals, which attack cell membrane and subsequently leading to alteration in membrane fluidity, as well as inhibition of membrane-bound enzymes.[50,51]

Furthermore, the activity of GPx was also inhibited in liver and kidney of cypermethrin treated animals. GPx plays a crucial role in the reductive detoxification of peroxides inside cells to protect them from oxidative damage by converting harmful peroxides into less toxic compounds by utilizing GSH molecules which serve as hydrogen donors. GPx is involved in decomposition of peroxides and glutathione to produce oxidized glutathione and water.[52,53] Thereby, the decreased activity of GPx might be attributed to excessive formation of free radicals which participate in oxidative stress.[54] Moreover, this reduction might be referred to the depletion of GSH through its utilization in scavenging free radicals, as GPx involved in glutathione-dependent removal of hydroperoxides in liver and kidney cells. This concurs with other investigations showed a decline in GSH which is associated with subsequent inhibition of glutathione-dependent enzymes activity following pyrethroid treatment.[55-58]

GR is an essential antioxidant cellular enzyme which plays a vital role in the maintenance of GSH in liver cells by catalyzing the transformation of oxidized glutathione (GSSG), commonly referred to glutathione disulfide, to GSH which conducts a crucial function in scavenging free radicals. Therefore, the declined activity of GR may indicate a deficit in production of GSSG back from GSH.[59] In addition, GST represents a group of detoxification enzymes that promotes the combination of reduced glutathione to electrophiles and are involved in the detoxification of xenobiotics and signaling cascades, to preserve cellular structures from oxidative damage.[60,61] The increased activity of GST observed in the current investigation might be a tissue response to oxidative stress stimulated by cypermethrin intoxication to protect cells from oxidative damage. This concurs with other studies reported an increase in GST activity in liver tissue of rats exposed to cypermethrin[62,63], and in *Drosophila melanogaster* exposed to insecticides[64], as well as in a pyrethroid insecticide resistant strain of insect called *Nilaparvata lugens.*[65]

Moreover, the current investigation also suggested that cypermethrin exposure may cause liver damage which was marked by higher serum levels of liver biomarker enzymes including ALT, AST, ALP and GGT. The elevated serum levels of these enzymes observed perhaps result from cypermethrin intoxication, which is previously reported to cause changes in oxidant/antioxidant balance and surface charge density followed by cellular leakage of AST and ALT.[62,63] ALP is a membrane associated enzyme which plays a role in the process of dephosphorylation. Increment in its activities can be used as an indicator of liver injury.[66] GGT is a microsomal enzyme present in liver tissue which catalyses metabolizing of extracellular GSH allowing for precursor amino acids to be assimilated and reutilized for synthesis of intracellular GSH. An elevation of serum GGT can be considered as a defence mechanism reflecting the induction of cellular GGT in the case of oxidative stress.[67]

5. CONCLUSION

To conclude, the current work demonstrated that *in vivo* administration of sub-lethal dose of cypermethrin can induce oxidative stress in hepatic and renal tissues, leading to elevation of LPO, depleting of GSH and induction of protein oxidation. This is evident by elevated level of MDA, LOOH and AOPP, as well as negative alterations in the activity of antioxidant defense enzymes and liver marker enzymes. Thus, this suggests that ROS might be involved in the toxic impacts of cypermethrin exposure on liver and kidney tissues. However, further investigations are required to evaluate the toxicity of cypermethrin on molecular level.

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