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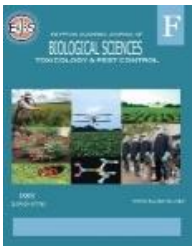

Protective Efficacy of Combined Administration of Vitamins C and Curcumin on Cypermethrin - Induced Oxidative Stress in Male Albino Rats.

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ABSTRACT

Back Ground: Cypermethrin (CPM) is non-systematic type II synthetic pyrethroid, commonly used for pest control in livestock, forestry, horticulture, household, public and animal health services, private homes, and animal husbandry. By scavenging free radicals and modulating antioxidant protection mechanism, plant phytochemicals (vitamin C and Curcumin) are known to exert their protective impact,

Aim: The current research aimed to examine the ameliorative effect of combining curcumin with prevention of vitamin C against the toxic effects of cypermethrin.

Method: Four groups of ten male rats each, –ve control, +ve control group (200 mg curcumin and 100 mg vit. C/ kg bw), cypermethrin alone (200 mg / Kg bw), and cypermethrin supplemented with the protective antioxidants orally intubated for 28 - days.

Result: Oral cypermethrin induced a significant increase in MDA and PC in serum, liver and brain as the oxidant biomarkers. While the antioxidant biomarkers (CAT, GSH or SH protein) were significantly decreases in serum and brain tissues. The phase II biotransformation GST was increased significantly in brain and liver tissues. ATPase activity declined significantly in brain tissue only.

Conclusion: we can deduce that, cypermethrin induce oxidative stress in serum and organs tissues of male rats and the protective role curcumin and vit. C was more evident on serum, brain than liver.

INTRODUCTION

Due to high effectiveness against a wide range of insects, rapid biodegradation, low mammalian toxicity and target oriented - mechanism of action, pyrethroids (PYP) insecticides are widely used in crop protection and public health (Sharma, *et. al.*, 2014). Cypermethrin is non-systematic pesticide used in large-scale, Type II pyrethroids, which have cyano-group (Mueller, *et. al.*, 2006, Debbab, *et. al.*, 2014). Cypermethrin used for ecto-parasite infestations in animals as chemotherapy (Wang, 2009). Nervous and muscular systems are the mostly affected cypermethrin and other synthetic pyrethroids during exposure to these insecticides. Cypermethrin also, have many health impacts such

as neurotoxicity, reproductive toxicity, and molecular toxicity and so on, due to the severe increase in Cypermethrin usage in daily life (Aman, *et. al.,* 2018).

Cellular protection mechanisms that restrict the damaging effect of oxidative stress on organisms and defend against detrimental cell injury are part of antioxidant enzymes. Differences in their physiological concentrations can impair their ability to eliminate reactive oxygen species as a result of increased oxidative damage to cellular lipids, proteins, and DNA (Afolabi, *et. al.,* 2019) Cell's Protection is an important role of Antioxidants against the oxidative damage induced by contaminants (Bouayed and Bohn, 2010) delaying and neutralization of ROS, reducing the oxidative damage and induction of diseases state (Majeed, *et. al.,* 2016). Vitamin C is well known powerful antioxidant that can protect the body against damage caused by free radicals during normal metabolism and exposure to toxins and carcinogens (Banerjee, *et. al.,* 2009). Vitamin C is the most important free radical scavengers in extracellular fluids that quenches the aqueous phase of free radicals and protects bio-membranes from per-oxidative damage (Sulak, *et. al.,* 2005).

Curcumin (CMN) has been shown to have a wide variety of anti-neoplastic, anti-mutagenic, anti-inflammatory antiseptic, analgesic, antimalarial, anti-carcinogenic and antioxidant phytochemical activities (Voja, *et. al.,* 2019). Curcumin is an antioxidants natural compound against many free radicals containing polyphenolic compound derived from turmeric (Curcuma longa). (Pattanayak, *et. al.,* 2016). CMN has protective effects against oxidative damage and has antioxidant and anticonvulsant properties that exert strong ROS scavenging effects and increased concentration of intracellular glutathione thus protecting against LPO (Abdul-Hamid, *et. al.,* 2017). Curcumin, being a lipid soluble substance, is an important trapper of peroxyl radicals, thus, likes vit. E; curcumin is also known an antioxidant breaking chain (Kunwar, *et. al.,* 2011).

The role of reactive oxygen (ROS) species has been documented in the toxicity of contaminants. One of the really predominant environmental pollutants is CPM. Recently, authors try to investigate the consequences of exposure to CPM and the activation of oxidative stress. There isn't enough evidence to safeguard toward CPM toxicity. Therefore, this research was intended to investigate: oxidative stress induction possibility by CPM and the alleviation the toxic effects of CPM using the curcumin and vitamin C.

MATERIALS AND METHODS

Tested Materials:

a) Insecticide:

Cypermethrin was supplied as (Cyper® 50 % EC) formulation by the Mammalian and Aquatic Toxicology Department, Central Agricultural of Pesticides Laboratory (CAPL), Agricultural Research Centre (ARC), Dokki, Giza, Egypt.

b) Ascorbic Acid (Vitamin C):

A pure form of ascorbic acid was supplied as pure crystals (Sigma code: AX 1776 - 1) by E. Merck Science, a division of EM industries Inc., Darmstadt, West Germany. A freshly prepared aqueous solution of ascorbic acid was orally administered to the treated rats throughout the experiments, at a dose level of 100 mg/kg b.w. (Rana, and Ahmed, 2012).

C) Extraction of *Curcuma longa* (Curcumin):

The plant material was obtained from the local market of spices in Egypt ground into powder and curcumin was obtained and used in a dose of 200 mg/kg bw. according to Elhalwagy, *et. al.* (2015).

Animals and Treatments Schedule:

Forty adult male Wistar albino rats weighing between 160 - 180 g (12 weeks' age), were used. Animals were supplied by the breeding unit of the National Organization for Drug Control and Research (NODCAR), Egypt. The animals were held in 23 ± 2 °C dark/light cycles in plastic cages. Before beginning the experiment, the rats were fed and water *ad libitum* and acclimatized for two weeks. All animals were treated according to the guidelines repeated dose oral toxicity study in rodents (OCED, 2008, No. 407).

Rats were randomly divided into 4 equal groups (10 rats each) and treated orally by gavage (5 days/week) for 28 days as follows:

Group (Cont.): treated with distilled water, as (-ve control).

Group (+cont.): treated with aqueous extract of *Curcuma longa* (200 mg / Kg bw) and vitamin C (100 mg / Kg bw) as (+ve control)

Group (CPM): treated with cypermethrin at a dose level 200 mg / Kg bw (1 / 25 LD_{50}).

Group (Protective + CPM): treated with cypermethrin (200mg/kg bw) and supplemented with Antioxidants (Curcumin and vitamin C) at a dose of 200 mg / Kg bw and 100 mg / Kg bw for Curcumin and vitamin C respectively.

Biochemical Assay:

Rats fasted overnight at the end of the experiment and blood samples were obtained from the retro-orbital plexus vein into non - heparinized tubes. In order to acquire serum, blood samples were centrifuged at 2000 g for 15 min to obtain serum. Serum was separated and kept in a deep-freezer at - 20 ºC till the assays were carried out.

At the end of the experiment (28 days), the liver and brain were removed from rats under ether anesthesia and washed with cold saline buffer. Washed tissues were immediately stored at - 80 ºC. Tissues were homogenized in ice-cold 50 mM sodium phosphate buffer (pH: 7) containing 0.1 mM ethylendiaminetetraacetic acid (EDTA) yielding 10 % (W / V) homogenate for determination of enzymatic activities. At 4 ºC, the homogenates were centrifuged for 30 min at 12000 g. The supernatant was used to investigate enzyme activities.

Oxidative stress biomarkers were assessed in serum, liver, and brain. Lipid peroxidation was estimated as the concentration of thiobarbituric acid reactive products (malondialdehyde, MDA) (Ohkawa, *et al.*, 1979). Protein carbonyl content was assayed using the mentioned method Yan, *et al.* (1995), Total thiol proteins (SH - Protein) were determined in serum by the method of Hu and Dillard (1994). Superoxide dismutase (SOD), catalase (CAT), and glutathione - s - transferees (GST) activity was measured by the methods of (Marklund and Marklund, 1994; Aebi, *et. al.*, 1984; Habig, *et. al.*, 1973). Total adenosine triphosphates (ATPase) activity was determined (Samson and Quinn, 1967). Total glutathione content was measured in liver and brain tissues (Beutler, *et. al.*, 1963).

Ethical Statement:

This study was conducted in accordance with ethical procedures and policies approved by the Institutional Animal Care and Use Committee of Zagazig University (No.ZU-IACUC/ 2 / F / 43 / 2019).

Statistical Analysis:

The data obtained from the biochemical analysis of various groups are represented as Mean ± Standard error (M ± SE) in tables. The significance of the difference between the groups was calculated by one - way analysis of variance (ANOVA) followed by Duncan's test at $P \leq 0.05$ using the SPSS - PC computer software package version 25. Letters a, b and c are significant differences versus control, CMN + Vit. C, and CPM groups at $p \leq 0.05$ respectively.

RESULTS

Oxidative Stress Biomarkers in Brain:

The effect of CPM exposure during subacute toxicity period (28 days) on brain oxidative stress markers is tabulated in Table (1). The results revealed a drastic increase in MDA and PC level compared with control group. The increase in MDA and PC reached 41.5% and 26.37%, respectively. The increase in oxidant biomarkers (MDA and PC) was connected with a significant decline in GSH (69.18%) which responsible for the viability of cell. Also, the results pointed out that, the antioxidant enzymes (CAT and SOD) of brain rats exposed to CPM were significantly changed where; CAT activity was declined (38.55%). While SOD activity was increased (19.82%). The increase in MDA and PC (oxidant biomarkers) was connected with the significant increase in GST (22.36%) activity (Phase II biotransformation). The mode of action of pyrethroids insecticides is depending on inhibition of ATPases which, noticed in this study. The inhibition of ATPases reached 9.37%. Treatment of rats exposed to CPM with CMN and vit C ameliorated the effect of insecticide on the studied biomarkers (PC, CAT, SOD, GSH and GST).

Table 1: Effect of Co-administration with curcumin + Vit. C on oxidative stress biomarkers in brain tissues of rats intoxicated orally with cypermethrin for 28-days.

Biomarker & Treatments	**ATPase** (µmol/min/mg pt.)	**MDA** (mmol/ml)	**PC** (mmol/ml)	**GSH** (µmol/dl)	**CAT** (U/mg pt.)	**SOD** (U/mg pt.)	**GST** (mmol/min/mg pt.)
CPM	42.95 ±1.087^{a} *-9.37%*	20.18 ±0.9507^{a} *41.5%*	27.40 ±0.5868^{ab} *26.37%*	2.62 ±0.0986^{ab} *-69.18%*	3.06 ±0.1834^{ab} *-38.55%*	4.098 ±0.1637^{a} *19.82%*	20.34 ±0.3002^{ab} *22.36%*
CPM & (CMN+Vit.C)	46.142 ±0.6052^{bc} *-2.63%*	24.75 ±0.9015^{a} *73.5%*	23.22 ±1.538^{c} *7.11%*	7.962 ±0.2166^{bc} *-6.35%*	4.24 ±0.1724^{ac} *-14.86%*	4.002 ±0.1211^{a} *17.02%*	17.35 ±0.3907^{bc} *4.39%*
CMN+Vit.C	42.62 ±0.6360^{a} *-10.07%*	21.48 ±0.7810^{a} *50.6%*	21.41 ±0.5505 *-1.24%*	5.79 ±0.0493^{a} *-31.9%*	4.668 ±0.1327 *-6.27%*	3.918 ±0.1817^{a} *14.56%*	23.91 ±0.9047^{a} *43.85%*
Control	47.39 ±1.171	14.26 ±1.025	21.68 ±0.4174	8.502 ±0.4949	4.98 ±0.0601	3.42 ±0.1005	16.62 ±1.160

All data are expressed as means ± SE . %: changes from control.
a, b and c: are significant differences versus control, CMN + Vit, C and CPM groups at $p \leq 0.05$ respectively.

Oxidative Stress Biomarkers in Liver:

The alterations in Liver oxidative stress biomarkers in rats exposed to CPM only or CPM concomitant with CMN and Vit. C is shown below in Table (1). The obtained data refer that, a significant increase in the liver MDA and PC was noticed in CPM group which were administered the CPM comparing with control group. The increase in MDA and PC was 51.8 % and 11.43%, respectively. The data depicted in the same table (2) showed that GST activity and GSH level significantly declined to 28.53 % and 50.95% in both CPM implemented rats compared to control group (Table 2). The antioxidant enzymes (SOD and CAT) insignificantly changed in insecticide exposed group compared with control group. The same trend of insignificantly change was noticed in live ATPase. The treatment of rats with CMN + Vit.C concomitant with CPM exhibited a slightly ameliorative effect in liver tissues.

Table 2: Effect of Co-administration with curcumin +Vit. C on oxidative stress biomarkers in liver tissues of rats intoxicated orally with cypermethrin for 28-days**.**

Biomarker & Treatments	ATPase (µmol/min/mg pt.)	MDA (mmol/ml)	PC (mmol/ml)	GSH (µmol/dl)	CAT (U/mg pt.)	SOD (U/mg pt.)	GST (mmol/min/mg pt.)
CPM	57.49 ±0.9185^{b} *0.34%*	46.36 ±1.843^{ab} *51.8%*	114.4 ±0.4601^{ab} *11.43%*	7.058 ±0.2577^{ab} *-50.95%*	84.57 ±0.8703^{b} *3.87%*	15.18 ±0.2764^{b} *2.90%*	15.042 ±0.3412^{ab} *-28.53%*
CPM & (CMN + Vit.C)	67.30 ±0.4758^{abc} *17.46%*	43.63 ±1.100^{ab} *42.9%*	114.4 ±4.705^{ab} *11.49%*	11.20 ±0.2817^{abc} *-22.16%*	79.16 ±2.363^{bc} *-2.78%*	14.55 ±0.0952^{c} *-1.36%*	19.07 ±0.5664^{bc} *-9.41%*
CMN + Vit.C	70.21 ±1.416^{a} *22.54%*	32.67 ±0.8402 *6.98%*	101.7 ±4.713 *-0.88%*	14.12 ±1.075 *-1.89%*	69.66 ±2.035^{a} *-14.44%*	14.15 ±0.1405^{a} *-4.09%*	23.72 ±0.6240^{a} *12.70%*
Control	57.30 ±0.6316	30.54 ±0.8087	102.6 ±3.148	14.39 ±0.4799	81.42 ±1.234	14.75 ±0.0574	21.05 ±1.129

All data are expressed as means ± SE. %: changes from control.
a, b and c: are significant differences versus control, CMN + Vit, C and CPM groups at $p \leq 0.05$ respectively.

Oxidative Stress Biomarker Changes in Serum:

Regarding, the biomarkers of oxidative stress in rat serum intoxicated with CPM orally for 28-days (Table, 3). Data recorded significant elevations in serum MDA (15.1%) and PC (33.06%) in comparison with control group. Meanwhile, remarkable significant decrease in SH-protein, CAT and SOD was observed in orally intoxicated group (80.49%, 32.94% and 5.69 %respectively) comparing with control. On the other hand, GST activity (4.92%) was significantly increased in serum compared with control. No significant reduction in ATPase activity (21.35%) was recorded in CPM intoxicated group.

Table 3: Effect of Co-administration with curcumin + Vit.C on oxidative stress biomarkers in serum samples of rats intoxicated orally with cypermethrin for 28-days.

Biomarker & Treatments	ATPase (µmol/min/mg pt.)	MDA (mmol/ml)	PC (mmol/ml)	SH-Pt. (µmol/dl)	CAT (U/mg pt.)	SOD (U/mg pt.)	GST (mmol/min/mg pt.)
CPM	84.11 ±0.1932 *-7.08%*	122.5 ±2.140^{ab} *15.1%*	143.2 ±3.795^{ab} *33.06%*	78.76 ±2.709^{ab} *-80.49%*	4.406 ±0.2388^{ab} *-32.94%*	12.14 ±0.1742^{ab} *-5.69%*	88.60 ±0.8491^{b} *4.92%*
CPM & (CMN+Vit.C	86.16 ±1.764 -4.82%	110.3 ±1.356^{bc} *3.59%*	127.4 ±1.179^{ac} *18.44%*	255.2 ±8.673^{abc} *-36.77%*	6.348 ±0.1286^{c} *-3.38%*	12.56 ±0.1652 *-2.42%*	76.84 ±2.225^{abc} *-9.01%*
CMN+Vit.C	89.42 ±0.6937 *-1.22%*	94.05 ±1.455^{a} *-11.6%*	121.6 ±5.704^{a} *13.01%*	329.9 ±6.599^{a} *-18.26%*	6.80 ±0.3194 *3.50%*	12.73 ±0.1450 *-1.09%*	95.41 ±2.294^{a} *12.98%*
Control	90.52 ±1.656	106.4 ±2.948	107.58 ±0.9965	403.6 ±22.06	6.57 ±0.2136	12.87 ±0.1875	84.45 ±1.983

All data are expressed as means ± SE. %: changes from control.
a, b and c: are significant differences versus control, CMN + Vit, C and CPM groups at $p \leq 0.05$ respectively.

DISCUSSION

In developing countries CPM is used as an insecticide to control many insect species. Human exposure to CPM has been reported to occur primarily during application or from pyrethroids residues such as, those detected in fruits, vegetables, cow's milk and bread (Sankar, *et. al.,* 2010). The halogen containing pyrethroids are much more

photostable. This allows them to persist on the surface of plants much longer than the earlier pyrethroids. They are also highly lipophilic, which promotes higher bioavailability in mammals (Nunomura, *et. al.*, 2007)

Lipophilic characteristic of CPM makes its bioaccumulation in cell membranes and stimulate oxidative stress that disrupt vital components of cell leading to membrane structure and functions disruption (Elblehi, *et. al.*, 2015).

There is a relation between pesticides exposure and environmental contaminants and the metabolic disorders or human diseases including parkin disease (Bastias-Candia, *et. al.*, 2019). CPM's mechanism of action can be assumed to have two ways: it can induce Oxidative stress that causes oxidative stress, but it could also begin building in the cell membrane and destroy the cell membranes due to hydrophobic structure (Abdul-Hamid, *et. al.*, 2017).

The observed dramatic increases in MDA levels in treated group with CPM. This impact may be clarified by the fact that the raise in the production of lipid peroxidation in CPM-intoxicated animals behaved as a warning for potent antioxidant enzymes to improve the detoxification process for CPM. Malondialdhyde (MDA) becomes one of the most often used as a redox state marker and recognized as the late oxidative stress biomarker end product (López, *et. al.*, 2007). MDA has a higher reactivity toward nucleophiles (MDA adduct) such as amino acids or protein. Where, these reactions have secondary deleterious reactions by induction of biomolecular interaction leading to biochemical properties alterations (Ayala, *et. al.*, 2014). Modified or oxidized protein aggregation trigger releasing of ROS in brain and mitochondrial dysfunction which tightly linked with neurodegenerative diseases (Liu, *et. al.*, 2017).

The homeostasis of equivalents intracellular oxidation and reduction is mediated by a fine balance of antioxidants system (vital functions of cells) to preserve the cellular functions activity and cell viability. Redox homeostasis and pH balance is the main processes for life. Whereas, redox balance governs all processes of life such as metabolism and bioenergetics (Laforgia, *et. al.*, 2018)

Many biomolecules are oxidized and/or nitrated by peroxynitrite-derived radicals, including amino acids (such tyrosine, tryptophan residues), DNA, and fatty acids. These biological mechanisms, as well as protein aggregation, suppress (and rarely activate) enzymes, receptors, transporters, and membrane channels. (Aoyama and Toshio, 2015)

Oxidation triggers permanent protein thiol oxidation in the intracellular redox state and further changes protein functions as enzymes, receptors and transporters during oxidative damage conditions. In order to prevent oxidative damage, GSH may preferentially create mixed disulfide bonds between protein thiols (S-glutathionylation). The thiol redox status of cell depends on the reduced and oxidized form of glutathione ratio. Changes in the thiol redox status toward the oxidized form affect the cell biochemical processes such as cell proliferation and cell death. Thiol protein is vital in many biochemical reactions for cell so, cell maintain the thiol protein in reduced form by conjugation with GSH (Aoyama and Toshio, 2015).

It has been identified that, biotransformation of xenobiotic can be occurred in other organs and tissues although; the major organ of metabolic disposition is liver. If it takes place at the site of action, even small metabolic pathways of xenobiotic metabolism may cause major effects. (Pai, *et. al.*, 2002). Decline of pyrethroids metabolism may be found in lipid tissues although, pyrethroids metabolism quickly happened in plasma and liver. As, brain have lower P450 activity than liver, metabolism of chemicals in brain decreased than liver and active metabolites can be occurred in brain at a significant quantity. The enhancing liver detoxification by curcumin is connected with its ability to increase the GST activity (conjugates glutathione with a wide variety of toxic materials).

Whereas, curcumin ameliorate the oxidative damage induced by cypermethrin in liver, kidney and brain of treated rats (Madkour, 2012). In the adipose tissue of rodents, pyrethroids such as deltamethrin and cypermethrin exist after oral route Its high log octanol/water that makes these insecticides distributes to adipose tissue and accumulates to levels higher than observed in other organs or tissues. Persistence of pyrethroids in adipose tissues is longer than other organs as lipases have no enzymatic activity toward these insecticides. Redistribution into the systemic circulation facilitate its hydrolysis by serum esterase or liver oxidation (Hughes, *et. al.*, 2015)

Inactivation of oxidants (ROS) rapidly is the responsibility of antioxidant battery which considers the endogenous defense's mechanism (Rambabu, *et. al.*, 2020). The good biomarkers of antioxidant status are the CAT enzyme responsible for elimination of H_2O_2. The pronounced decline in CAT activity may have been attributable to production of H_2O_2 induced by oxidative stress of CYP (Abdelhafidh, *et. al.*, 2018). Such results observed in the study of (Sankar, *et. al.*, 2012).

The protection of curcumin in male rat organs (liver, testis, brain, kidneys and lungs) from oxidative injury induced by sodium-arsenite may be attributed to increasing the activities of GSH S-transferase, superoxide dismutase and catalase (Alrawaiq and Abdullah, 2014). Interestingly, curcumin not only exhibits antioxidative and free radical scavenging properties, but also enhances the activity of other antioxidants, such as superoxide dismutase, catalase, and glutathione peroxidase (Reddy and Lokesh, 1994). Curcumin may have antioxidant properties either directly as natural antioxidants because its ability to scrounge oxygen radicals or via amplifying cellular defenses which have protective capacity themselves (Azab and Mohamed, 2018).

CONCLUSION:

Our results could be concluded that cypermethrin insecticide induced elevation oxidative stress parameters (MDA and PC) in all tissues of treated rats. On the other hand, GSH (brain and liver) and SH-Protein (serum) activities as defense systems were depletion. based influence of antioxidant enzymes (SOD, CAT, and GST) by cypermethrin exposure was different according to tissue. Finally, the effect of subacute to sub - exposure - lethal doses of cypermethrin cause oxidative stress in treated rats on the brain, serum then liver was severe and the protective effects of the two natural products (curcumin and vitamin C) on insecticide cypermethrin's oxidative stress were more evident on serum, the brain then liver.

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