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ALPHA CYPERMETHRIN INDUCED OXIDATIVE STRESS AND ITS AMELIORATION BY RESVERATROL IN LIVER OF MICE

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ABSTRACT

Present study was undertaken to study the ameliorative potential of resveratrol on alpha cypermethrin induced oxidative stress in liver of mice. The insecticide was administered orally at 7 mg/kg body weight to female mice for period of thirty days. In another sets of experiment animals were treated with three different doses (50 mg/kg body weight, 100mg/kg body weight and 150mg/kg body weight) of resveratrol along with 7 mg/kg body weight alpha cypermethrin. Besides these, there were untreated control, vehicle control and resveratrol (antidote) control groups. For evaluating oxidative stress in liver of mice, enzymes of oxidative stress like Superoxide dismutase, Catalase, Glutathione peroxidase, Glutathione reducatse and Glutathione-S-tansferase were assayed in all experimental groups. Result revealed that alpha cypermethrin reduced all these enzymes level significantly $p<0.05$compared to alpha cypermethrin alone group. It is concluded that resveratrol ameliorates alpha cypermethrin induced oxidative stress in liver of mice.

KEY WORDS

Resveratrol, Alpha Cypermethrin, Catalase, Glutathione peroxidase, Glutathione reductase, Glutathione-S-transferase

INTRODUCTION

Pesticides are need of present time to get rid of pests on the crop fields. However, besides killing the pests these harmful chemicals enter our food chain. Human is off course, a non-target species of these pesticides. However, we do get accumulate them in our body through food chain or through occupational exposure or during handling them. Alpha cypermethrin is a synthetic pyrethroid insecticides used wildly over the crop field as its relatively safer compare to contemporary organochlorine and organophosphate pesticides. [01] Human chronically or sub chronically gets exposed to it which in turn leads to unwanted morbid changes. In many toxicological studies its toxicological potential has been evaluated. Alpha cypermethrin is a neurotoxin; its chronic exposure to lab animal had caused morbid changes in brain, liver, kidney, testis and immune system.[2] Its exposure leads to lipid peroxidation[3], depletion in protein level in liver[4], accumulation of lipid in liver[5] and generation of reactive oxygen species (ROS).[6] These ROS generate oxidative stress in various organs which leads to morbid changes in level of bio constituents and oxidative stress enzymes like catalase, superoxide dismutase (SOD) etc. [7], In present study its toxicological potential, in terms of its effect on oxidative stress enzymes like glutathione reductase(GR), glutathione peroxidase (GSH-Px), glutathione S transferase and catalase were evaluated in liver of mice after chronic exposure. On other hand resveratrol was used as an antidote to combat these toxicological alterations. Resveratrol is a stillbene a kind of polyphenol present in red grapes, peanut skin, red wine, itadori tea and root of *Polygonum caspadutum8*.It has been used since ages in Chines and Japanese traditional medicines [8]. It's an anti aging, anti-inflammatory and anti-carcinogenic [9] and the ayurvedic formula

'drakshashw' contain abundant amount of it[10]. It's a potent antioxidant and has also been found to boost antioxidant defense mechanisms of the body, in various studies. Hence in present studies impact of resveratrol co treatment along with high does alpha cypermethrin treatment was evaluated.

MATERIAL AND METHOD

In present study, female strain Swiss albino mice (*Mus musculus*) were selected as the test animal. Animals were kept at Animal House of Department of Zoology, Gujarat University, Ahmedabad. These animals were procured from Cadila Research Centre, Dholka, Ahmedabad. Entire work was carried out in the research laboratory of the zoology department, Gujarat University. Animal were kept in an animal house room with 12 hrs of light and dark period. Animal were kept at 25C $\pm$ 2 C° temperature with relative humidity 50-55% and provided standard mice pellet diet prepared by Amrut Feeds, Pranav Industries Ltd., Pune. All chemicals were of analytical grade and had purity of 99% and purchased from Himedia Ltd. And Sigma-aldrich limited. Alpha cypermethrin 99.5% was gifted from local pesticide manufacturing company. Animals were fed both alpha cypermethrin and resveratrol diluted in corn oil through oral feeding gauge. The experimental groups were prepared as follows with each group bear ten female Swiss albino mice.

Table1: Experimental groups and dose

Groups	Treatment	No.of Animal	Duration of treatment	Day of Autopsy
I	Untreated control	10	30 days	31st
II	Corn oil control (0.2 ml/animal/day)	10	30 days	31st
III	Resveratrol control High dose resveratrol (150 mg/ kg b.w./day)	10	30 days	31st
IV.	High dose alpha cypermethrin (7mg/kg body weight (b.w) /day)	10	30 days	31st
V.	High dose alpha cypermethrin (7mg/kg b.w./day) + Low dose resveratrol (50mg/kg b.w./day)	10	30 days	31st
VI.	High dose alpha cypermethrin (7mg/kg b.w./day) + Mid dose resveratrol (100mg/ kg b.w./ day)	10	30 days	31st
VII.	High dose alpha cypermethrin (7mg/kg b.w/day) + High dose resveratrol (150 mg/ kg b.w./day)	10	30 days	31st

On 31st day mice were autopsied by cervical dislocation and liver tissues were cut in to pieces of 100 mg for the estimation of Catalase, Superoxide dismutase (SOD), Glutathione reductase (GR), Glutathione peroxidase (GSH-Px) and Glutathione-S-Transferase (GST) in all experimental groups.

Catalase (EC.1.11.1.6) activity: The catalase activity was estimated by luck,1939's [11] method. A known amount of liver tissue was homogenized in a known volume of 0.01 % chilled digitonin and centrifuged at 3,000 g for 30 mm at 4°C. The supernatant was used as an aliquot. The estimation mixture contained 50 milimolar phosphate buffer with pH 7.0, 1 ml aliqot and 10 milimolar H2O2 was added to begin reaction. The decrease in absorbance was noted at interval of 5 seconds at 240 nm. The enzymatic activity was expressed as µ moles H_2O_2 consumed/mg protein/min.

Superoxide dismutase (EC.1.15.1.1) activity: Kakkar et, al. 1984[12], method was used to estimate the superoxide dismutase activity with slight modification.

The method is based on the NADPH-phenazine methosulfate-nitroblue tetrazolium formazon inhibition. The formazon formed at the end of the reaction was extracted into butanol layer after stopping the reaction by adding acetic acid. Prior to this, hypotonic KCl was used to extract enzyme. The activity was expressed as units/mg protein.

Glutathione reductase (E.C.1.6.4.2) activity: The glutathione reductase (GR) activity in liver was assayed by the method of Mavis and Stellwagen (1968) [13]. The enzyme catalyzes the conversion of oxidized glutathione (GSSG) to reduced glutathione (GSH). The decrease in absorbance was recorded for 5 min at 340 nm. The enzyme activity was calculated as nmoles NADPH consumed/mg protein/min.

Glutathione peroxidase (EC.1.11.1.9) activity: The glutathione peroxidase (GSH-Px) activity in the liver was assayed by the modified method of Pagila and Valentine (1967) [14]. The enzyme activity was expressed as units/mg protein/min, where 1 unit of GSH-Px equals to nmoles of NADPH consumed/mg protein/min.

Glutathione-S-transferase (EC 2.5.1.18) activity: The glutathione-S-transferase (GST) activity was assayed by the method of Habig et al. (1974) [15]. The increase in absorbance was noted at 340 nm using 1-chloro-2,4-dinitrobenzene (CDNB). The enzyme activity was calculated as µmoles CDNB conjugates formed/mg protein/min. To evaluate result scientifically, Mean and standard error were determined for all the parameters, and the results were expressed as a mean ± standard error of the mean (SEM). This was calculated through Microsoft Excel, 2007 software. The data were analyzed by employing analysis of variance (ANOVA) following TUKY'S test to determine significance difference among groups at $p<0.05$, using SPSS:16 software.

Results: Detail results are depicted in table-2.

Table-2: Showing effect of alpha cypermethrin on oxidative stress enzymes in liver of mice and its amelioration by resveratrol

Oxidative stress Parameter	EXPERIENTAL GROUPS						
	I	II	III	IV	V	VI	VII
	Untreated Control	Vehicle control	Resveratrol control	HD ACP	HD ACP + LD RES	HD ACP + MD RES	HD ACP + HD RES
CAT (µmoles H_2O_2 consumed/ mg protein/min)	10.44 ±0.08	10.45 ±0.08	10.68± 0.2	3.97 ± 0.32^{acde} *(62.01)*	5.25± 0.05^{abde} **(19.78)**	7.2± 0.02^{abce} **(49.92)**	9.24± 0.04^{abcd} **(81.45)**
SOD (units/mg protein)	4.31 ± 0.06	4.40 ± 0.07	4.27± 0.05	1.30 ±0.05^{acde} *(70.45)*	2.36± 0.06^{abde} **(35.22)**	3.41± 0.09^{abce} **(70.1)**	4.19± 0.03^{abcd} **(96.01)**
GR (nmoles NADPH consumed/mg protein/min)	4.43 ± 0.02	4.44 ± 0.04	4.44± 0.04	1.27 ± 0.02^{acde} *(71.40)*	2.19± 0.04^{abde} **(29.11)**	3.17± 0.09^{abce} **(60.12)**	4.24± 0.05^{abcd} **(93.99)**
GSH-Px (nmoles NADPH consumed/mg protein/min)	4.35 ± 0.06	4.32 ± 0.04	4.65± 0.07	0.99 ±0.02^{acde} *(77.08)*	1.81± 0.01^{abde} **(24.40)**	2.94± 0.04^{abce} **(58.04)**	3.97± 0.07^{abcd} **(88.69)**
GST (µmoles of CDNB conjugate formed/mg protein/min)	5.49 ± 0.05	5.54 ± 0.05	5.62± 0.06	1.46 ±0.06^{acde} *(67.84)*	2.37± 0.03^{abde} **(22.58)**	2.94± 0.04^{abce} **(36.72)**	4.13± 0.05^{abcd} **(66.25)**

Abbreviations: LD=Low dose, MD=Mid dose, HD=High dose,
ACP: alpha cypermethrin, RES=Resveratrol
'a' represents significant difference ($p<0.05$) when compared to vehicle contol, i.e group II
'b' represents significant difference ($p< 0.05$) when compared to Group IV
'c' represents significant difference ($p<0.05$) when compared to Group V
'd' represents significant difference ($p<0.05$) when compared to Group VI
'e' represents significant difference ($p<0.05$) when compared to Group VII
Values in Italics within parenthesis indicate percentage change from control value,
Values in Bold within parenthesis indicates hepatoprotective index based on Group IV values

Results indicate that there is no any significant difference among control groups of each parameter. In alpha cypermethrin treated group catalase level depletes 62.01 percent level which gets restored to all resveratrol co treatment groups. Highest Hepatoprotective index 81.45 in terms of catalase level restoration, is obtained in group VII, followed by 49.92 in group VI and 19.78 in group V. SOD level depletes significantly in alpha cypermethrin treated group (IV) with percentage change of 70.45 percent from vehicle control group (II). Resveratrol co treatment increase SOD level in each group V, VI and VII. In terms of Hepatoprotective index for SOD, 96.01 is obtained in group VII followed by 70.01 and 35.22 in VI and V respectively. In alpha cypermethrin treated group GR level depletes 71.40 percent level which gets restored to all resveratrol co treatment groups. Highest Hepatoprotective index 93.99 in terms of GR level restoration is obtained in group VII, followed by 60.12 in group VI and 29.11 in group V. GSH_PX and GST also show same pattern like other enzymes. High dose alpha cypermethrin treatment declined both enzymes level significantly ($p<0.05$) from vehicle control value. In term of percentage change, 77.08 and 67.84 percent change was observed in GSH-Px and GST level respectively among high dose alpha cypermethrin treated group. In terms of hepatoprotection, highest hepetoprotection (88.69) is observed in group VII followed by 58.04 and 24.4 in group VI and V respectively for GSH-Px. For GST highest hepatoprotective index was observed in group VII (66.25) followed by group VI (36.72) and group V (22.58).

DISCUSSION:

In present study alpha cypermethrin treatment has caused significant reduction in the oxidative stress enzymes parameters viz., CAT, SOD, GR, GSH-Px and GST from that of vehicle control. These enzymes keep cellular integrity and protect the cell from any oxidative damage. However, results depicted in table 2 clearly indicates that these enzymes level got hampered by the alpha cypermethrin treatment. In many studies it has been found that alpha cypermethrin treatment increases lipid peroxidation in various organs [16] [17] [18]. Lipid peroxidation along with oxidative stress enzymes depletion is the consequences of ROS leaded oxidative stress. Catalse is the enzyme that protects the cell from oxidative damage by reactive oxygen species (ROS). It converts hydrogen peroxide molecules to water [19] and thus protect the cell from oxidative damage. SOD catalyse the dismutation of superoxide radicles in to molecular oxygen or hydrogen peroxide. Catalase is an important enzyme to remove hydrogen peroxide generated by SOD. Depletion of SOD is suggestive of free radicles generation and utilization of SOD to combat it. Alpha cypermethrin metabolize in liver via oxidative and esoteric pathway through cytochrome p450 microsomal enzyme system and that causes production of reactive oxygen species which lead to decline in oxidative stress enzyme and production of reactive oxygen species [20] [21]. Cyanohydrin is a metabolic product of alpha cypermethrin which on further decomposition produce cyanides and aldehydes that can generate reactive oxygen species [22]. These finding confirms that alpha cypermethrin produces ROS. These ROS generate oxidative stress which lead to more and more utilization of these enzymes which lead to depletion of these enzymes level and that is evident from the result depicted in table 2. In a similar study by Khan et. al. (2005) [23] it was found that pesticide treatment caused increased in lipid peroxidation and decrease in GSH, GPx, GST,CAT and SOD level at $p<0.001$ level in liver of mice. GSH reductase is the enzyme that reduces glutathione. Glutathione is three amino acid peptides with thiol group which donates it hydrogen to free radicals and itself oxidized. Oxidized glutathione reacts with other oxidized glutathione molecule to form GSSG i.e. glutathione disulphide [24]. GSH can be regenerated from GSSG by GR [25]. Depletion of GR in present study may be attributed to its more utilization due to oxidative stress. GSH-Px is the enzyme that catalyzes the reduction of lipid hydroperoxide to corresponding alcohol and reduction of hydrogen peroxide to water. In a reaction two GSH molecules reacts with one hydrogen peroxide molecule to form one GSSG i.e glutathione disulphide and molecule of water [26] .As noted earlier GR regenerates GSH from GSSG. Along with GR here GSH-Px also depletes due to alpha cypermethrin treatment. This can be attributed to their more utilization during oxidative stress. GST binds to toxin and its metabolites which may have depleted its concentration due to alpha cypermethrin treatment. GST is the enzyme that has binding site for both xenobiotic or ROS as well as binding site for GSH; thus it mediates binding of GSH to its substrate and in addition it also activates GSH to neutralize ROS [27] [28]. Depleted level of GST under influence of the treatment of alpha

cypermethrin in present study is indication of its over utilization. The depletion of these enzymes may have other reasons besides their over utilization; all these enzymes are protein and it has been noted that alpha cypermethrin treatment damage DNA content [29]. which may to lead corresponding depletion in protein level too. In addition, ROS generated by alpha cypermethrin may altered the gene expression. Thus, it is possible that m-RNA content encoding for translation of these enzymes may have reduced.

On other hand resveratrol treatment has restored all these morbid changes in the dose dependent manner. In terms of protective index resveratrol treatment has restored oxidative enzymes level at more than 80 percent except GST (66.25) at the highest does. In a similar study, resveratrol ameliorated ethanol induced lipid peroxidation, SOD, GPX, Catalase and GR in liver of rat [30]. In a study where alloxan treatment had altered catalase, SOD, GSH-Px and GST in liver and kidney of mice, resveratrol cotreatment restored their level at significantly [31]. Resveratrol protects against methotrexate induced oxidative stress and maintains normal liver histophysiology [32]. All these studies corroborate our finding where resveratrol has significantly ameliorated alpha cypermethrin induced morbid changes in oxidative enzymes level significantly ($p<0.05$) in each resveratrol co treatment group along with alpha cypermethrin. The hepatoprotective effect of resveratrol is due to its immense antioxidant power. In an *in vitro* study, resveratrol scavenged reactive oxygen radicals [33].As noted earlier alpha cypermethrin treatment caused generation of free radicals, these radicals might had scavenged by resveratrol and thus liver's endogenous antioxidant system remain less affected and these enzymes had not used up and that leaded to their restoration with resveratrol co treatment along with alpha cypermethrin in present study. Resveratrol treatment also protects the cell from oxidative DNA damge [34], this might have leaded to protection of hepatocytes' DNA and subsequently m-RNA and proteins including all oxidative enzymes too from alpha cypermethrin induced changes which is also possible reason for the restoration of these antioxidant enzymes with resveratrol co treatment along with alpha cypermethrin.

CONCLUSIONS:

From present study it is evident that alpha cypermethrin causes significant alteration in liver oxidative stress enzymes like Catalase, Superoxide dismutase, Glutathione peroxidase, Glutathione reductase and Glutathione-S-transferase from vehicle control group. These changes can be considered as morbid changes and various researches supports these findings. On other hand resveratrol at three different doses had restored these oxidative stress enzymes significantly ($p<0.05$) from high dose alpha cypermethrin treated groups alone. Thus, it can be concluded that resveratrol has potential as antidote against chronic or sub chronic exposure to alpha cypermethrin in mice.

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