Dichlorvos and lindane induced oxidative stress in rat brain: Protective effects of ginger

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ABSTRACT

Background: Dichlorvos and lindane pesticide causes toxicity in animals including humans. Ginger *(Zingiber officinale)* is widely used as a culinary medicine in the Ayurvedic system of medicine, possessing a number of pharmacological properties. **Objective:** This study was designed to assess ameliorating effects of ginger juice in dichlorvos and lindane induced neurotoxicity in wistar rats. **Materials and Methods:** Dichlorvos (8.8 mg/kg bw) and lindane (8.8 mg/kg bw) were orally administered alone as well as in combination to adult male and female wistar rats for 14 days followed by the post-treatment of ginger juice (100 mg/kg bw) for 14 days. Lipid peroxidation (LPO), reduced glutathione (GSH), and activities of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione S-transferase (GST), glutathione reductase (GR), quinine reductase (QR), and protein level were measured to evaluate the toxicity of these pesticides in brain. **Results:** Dichlorvos and lindane administration alone and in combination increased LPO and decreased the GSH level, SOD, CAT, GPx, GST, GR, QR activity, and protein. Oxidative stress due to abnormal production of reactive oxygen species (ROS) is believed to be involved in the toxicities induced by these pesticides. Post-treatment of ginger juice decreased LPO and increased the level of GSH, SOD, CAT, GPx, GST, GR, QR activity and protein in the brain of rats. **Conclusions:** The results indicated that dichlorovos and lindane induced tissue damage was ameliorated by ginger juice.

Key words: Dichlorvos, lindane, oxidative stress, reactive oxygen species, *Zingiber officinale*

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INTRODUCTION

Pesticides are chemicals used to control the insects/pests in agriculture, household, and public health programmes. Indiscriminate uses of pesticides have lead to a serious risk of toxicity in animals including humans. Dichlorvos is an organophosphate pesticide used to protect greenhouse plants, fruits and vegetables against mushroom flies, aphids, spider, mites, caterpillars, thrips, and white flies. It is also used to treat a variety of parasitic worm infections in livestock, dogs, and humans. Organophosphorus compounds are primarily recognized as neurotoxic in mammals as they inhibit acetylcholinestrase (AChE) activity.[1] Dichlorvos is reported to cause toxicity of reproductive system,[2] pancreas,[3] kidney and spleen,[4] brain,[5,6] and immune system.[7]

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Lindane is an organochlorine pesticide which had been earlier used for agricultural, domestic, and human applications. Lindane was an ingredient of shampoos used for removing head lice. Owing to its long half-life, lindane is persistent in the environment causing adverse effects to human health and the environment.[8] It enters in the animal system through the food chain and accumulates in brain tissues due to its lipophilic nature and slow rate of biotransformation.[9] Lindane is reported to induce oxidative stress in hepatic,[10] testicular,[11] and neuronal[12,13] tissues of rats.

Pesticides are believed to damage the lipoidal matrix in cell, generating reactive oxygen species (ROS) and promoting oxidative stress. Excess production of ROS can cause oxidative modification of proteins, DNA, and lipids. Endogenous non-enzymatic (glutathione, GSH) and enzymatic (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione S-transferase (GST)) antioxidants detoxify these ROS and protect cells. Due to continuous exposure of pesticides, level of these endogenous antioxidants decreases, leading to accelerated

cell death. Use of cytoprotective agents in the form of exogenous antioxidants may help in scavenging excess ROS, helping in cell survival and longevity.

A number of medicinal plants are reported to possess ROS scavenging and cytoprotective activity.[14-17] Ginger (*Zingiber officinale*) has been used in the Indian traditional system of medicine for digestive disorders, common cold, and rheumatism.[18] Ginger has been shown to posses many pharmacological and physiological activities such as antioxidants, anti-inflammatory, analgesic, anti-carcinogenic, and cardiotonic effects.[19] In this study, we evaluated the effect of a fresh ginger juice in dichlorvos and lindane induced neurotoxcity in male and female wistar rats.

MATERIALS AND METHODS

Chemicals and plant materials

Dichlorvos (CAS 62-73-7) and lindane (CAS 58-89-9) were purchased from the Sigma Chemicals (St. Louis, MO, USA). All other chemicals used in this study were of analytical grade and purchased locally.

Fresh ginger rhizome were purchased from a local market, washed thoroughly, peeled, chopped, and grinded in a mixer grinder to obtain ginger juice. Ginger juice was centrifuged to remove particulate matter and lyophilized to get dry powder. The powder was stored in air tight jars at −40 °C until use. Groundnut oil was used as a vehicle for both the pesticides and distilled water for ginger.

Animals

The adult male and female wistar rats were obtained from animal research division, Central Drug Research Institute (CSIR), Lucknow (India). The animals were kept in the animal house of Department of Biomedical Sciences, Bundelkhand University, Jhansi, under light and dark cycle of 12 h each. The rats were allowed free access to laboratory diet and tap water. Rats were acclimatized for 1 week prior to start of the experiment. All animal experiments were carried out as per the guidelines of Institutional Ethical Committee.

Treatment schedule

Eighty-four adult wistar rats of both the sexes (42 males and 42 females), weighing 200–250 g, were used in the experiment. Rats were divided in seven groups of 12 each (6 males and 6 females) as per the following detail.

Group C	**Control** Normal diet and groundnut oil for 28 days
Group D	**Exposure A** Dichlorvos (8.8 mg/kg bw) for 14 days
Group L	**Exposure B** Lindane (8.8 mg/kg bw) for 14 days
Group D + L	**Exposure C** Dichlorvos + lindane (8.8 mg/kg bw each) for 14 days
Group D + G	**Post-treatment A** Dichlorvos (8.8 mg/kg bw) for 14 days followed by ginger juice (100 mg/kg bw) for 14 days
Group L+G	**Post-treatment B** Lindane (8.8 mg/kg bw) for 14 days followed by ginger juice (100 mg/kg bw) for 14 days
Group D + L + G	**Post treatment C** Dichlorvos + lindane (8.8 mg/kg bw each) for 14 days followed by ginger juice (100 mg/kg bw) for 14 days

At the end of the study, animals were killed, brain were dissected out and washed with 0.9% NaCl and stored at −40 °C for further processing.

Tissue homogenate preparation

Brain was homogenized in 10% (w/v) ice-cold 0.1 M PBS (pH 7.4). The estimation of lipid peroxidation (LPO) and reduced glutathione (GSH) were estimated with a part of crude homogenate and the rest homogenate was centrifuged at 12,000 rpm for 20 min to obtain the supernatant (S) that was used for enzymatic estimations.

Biochemical estimations

Lipid peroxidation

Lipid peroxidation (LPO) was estimated as described by Ohkawa *et al.*[20] One milliliter of homogenate was incubated at 37 °C for 10 min. One milliliter of 10% trichloroacetic acid (TCA) chilled (w/v) was added to it and centrifuged at 2500 rpm for 15 min at room temperature. One milliliter of 0.67% TBA was added to 1 ml of supernatant and kept in a boiling water bath for 10–15 min. The tubes were cooled under tap water. After cooling 1 ml of DDW was added to it and absorbance was taken at 530 nm. The results were expressed as nmoles MDA/h/g tissue.

Non-enzymatic antioxidant-reduced glutathione

Reduced glutathione was estimated by the method described by Ellman.[21] Part of the crude homogenate was centrifuged at 9000 rpm for 20 min to obtain the supernatant. One milliliter of the supernatant was mixed with 1 ml of 5% TCA (w/v), the mixture was allowed to stand for 30 min and centrifuged at 2500 rpm for 15 min. 0.5 ml of the supernatant was taken and 2.5 ml of 5'5 '-dithionitrobenzoic acid (DTNB) was added, mixed thoroughly and absorbance was recorded at 412 nm. The results were expressed as μmol/g tissue.

Enzymatic antioxidants

Superoxide Dismutase: SOD was estimated by the method described by Misra and Fridovich.[22] An aliquot of 0.25 ml ice-cold chloroform was added to 0.1 ml of supernatant (S) followed by addition of 0.15 ml ice-cold

ethanol. The mixture was centrifuged at 3000 rpm for 10 min at 4 °C. 0.2 ml the supernatant was taken and 1.3 ml buffer, 0.5 ml EDTA, and 0.8 ml water were added. Reaction was started by adding 0.2 ml epinephrine. Change in absorbance ΔOD/min at 480 nm was read for 3 min. The results were expressed in terms of n mol/min/mg protein.

Catalase: CAT was estimated by the method of Sinha.[23] One milliliter of the phosphate buffer and 0.4 ml water was added to 0.1 ml of the supernatant (S). Reaction was started by adding 0.5 ml H_2O_2 and the mixture was incubated at 37 °C for 1 min. Reaction was stopped by adding 2 ml of dichromate:acetic acid reagent and kept at a boiling water bath for 15 min. The mixture was cooled, and absorbance was read at 570 nm. CAT activity was calculated in terms of μmols/min/mg protein.

Glutathione-S-Transferase: GST was estimated as per a method of Habig *et al*.[24] The reaction mixture consisting of 1.425 ml phosphate buffer (1 M, pH 6.5), 0.2 ml GSH (1.0 mM), 0.25 ml 1-chloro-2,4-dinitrobenzene (CDNB, 1 mM), 20 μl supernatant (S) and 60 μl water was mixed to give a total volume of 3.0 ml. Absorbance was recorded at 340 nm, and the enzyme activity was calculated as nmol CDNB conjugate formed/min/mg protein using a molar extinction coefficient of 9.6×10^3 M^{-1} cm^{-1}.

Glutathione peroxidase: GPx was estimated by the method of Rotruck *et al*.[25] 0.4 ml Tris–HCl buffer, 0.2 ml GSH, 0.1 ml sodium azide, 0.1 ml water, 0.1 ml H_2O_2, and supernatant (S). Incubated at 37°C for 15 min, 0.5 ml TCA was added and centrifuged. 0.5 ml of supernatant was taken, and 2 ml $Na_2HPO_4 \cdot 2H_2O$ and 0.5 ml Ellman's Reagent was added. Absorbance was noted at 420 nm. The results were expressed as μmol/min/mg protein.

Glutathione reductase: GR was estimated by the method given by Carlberg and Mannervik.[26] Then, 2.5 ml buffer, 0.2 ml NADPH, 0.2 ml GSSG, and 0.1 ml supernatant (S) were mixed and allowed to stand for 30 s. Absorbance was recorded at 340 nm for 3 min at 30 sec intervals. GR was calculated in terms of *n* mol/min/mg protein.

Quinone reductase: QR was estimated by the Benson method.[27] OD was measured at 600 nm for 3 min at 30 s intervals, and NADPH Quinone Reductase was calculated as *n* mol/min/mg protein.

Total protein

Protein was estimated by the method of Lowry's.[28]

Statistical analysis

Mean and standard error were determined for all the parameters, and the results were expressed as a mean ± SEM. The data were analyzed by employing analysis of variance (ANOVA) using statistical software Graph Pad In Stat Software Inc., v. 3.06, San Diego, USA. The Dunnett test for multiple comparisons of groups against control was performed to determine the significant differences among the groups.

RESULTS

The level of LPO was increased in the pesticide treated groups among male and female [Tables 1 and 2]. We observed a significant ($P < 0.01$) increase in LPO in groups D and D + L while a significant ($P < 0.05$) increase in group L as compared to control. In post-treatment group D + G and D + L, there was a non-significant ($P > 0.05$) increase in the LPO level while in group D + L + G, this increase was significant ($P < 0.01$) as compared to control.

The level of GSH, SOD, and CAT was decreased on dichlorvos and lindane exposure in both sexes of rats. The GSH level was decreased significantly ($P < 0.01$) in groups D, D + L, D + L + G, and L ($P < 0.05$). A non-significant decrease in GSH in groups D + G and L + G was observed as compared to control. A SOD level was decreased significantly ($P < 0.01$) in groups D, L, D + L, and D + L + G, while non-significant decrease ($P > 0.05$) was observed in groups D + G and L + G. CAT activity was decreased significantly ($P < 0.01$) D + L and ($P < 0.05$) D + L + G.

We observed a significant ($P < 0.01$) decrease in Gpx activity in groups D, L, D + L and D + L + G. while a non-significant ($P > 0.05$) decrease in group L + G in both the sexes of wistar rats. Decrease in Gpx activity in group D + G was significant ($P < 0.01$) and ($P < 0.05$) in female and male rats, respectively. No significant variation was observed in GST and QR activity in any of the exposure or treatment group.

GR activity was significantly ($P < 0.01$) decreased in groups D + L and D + L + G while a significant ($P < 0.05$) decrease in groups D and L. Decrease in GR activity in groups D + G and L + G was non-significant ($P > 0.05$). No variation was observed in GR activity between two sexes among different groups.

DISCUSSION

The results showed that the oral exposure of dichlorvos and lindane causes a significant increase in oxidative stress in cerebral tissue of male and female wistar rats as evident from increased level of LPO in groups D, L and D + L. Brain is considered highly vulnerable to oxidative stress than

Table 1: The effect of ginger against dichlorvos- and lindane-induced neurotoxicity in male wistar rats

Parameters	C	D	L	D + L	D + G	L + G	D+L + G
LPO (nmole MDA/h/g tissue)	4.752 ± 0.1582	6.280 ± 0.4024 **	5.878 ± 0.2184*	7.000 ± 0.2808**	5.235 ± 0.3949 •	4.830 ± 0.1904***	6.220 ± 0.2194**
GSH (µmole/g tissue)	13.011 ± 0.1439	11.828 ± 0.2213**	11.940 ± 0.1520*	10.908 ± 0.2467**	12.852 ± 0.3447***	12.454 ± 0.2558***	11.782 ± 0.1908**
CAT (µmole/min/mg protein)	74.058 ± 3.975	63.445 ± 3.571***	65.927 ± 4.100***	55.432 ± 3.019**	71.875 ± 3.887***	69.108 ± 4.244***	58.265 ± 3.137*
SOD (nmole/min/mg protein)	174.63 ± 1.844	154.51 ± 2.061**	161.65 ± 2.043**	143.31 ± 1.762**	168.50 ± 2.065***	171.18 ± 1.673***	151.93 ± 1.445**
GPx (nmole/min/mg protein)	21.507 ± 0.3831	17.879 ± 0.3066**	18.927 ± 0.5481**	16.272 ± 0.2711**	19.622 ± 0.4728*	20.570 ± 0.3931***	17.445 ± 0.3377**
GST (nmole/min/mg protein)	652.21 ± 48.178	572.95 ± 38.948***	573.06 ± 43.149***	509.61 ± 34.42***	621.41 ± 44.234***	640.20 ± 45.463***	552.53 ± 40.740***
GR (nmole/min/mg protein)	3.258 ± 0.2047	2.555 ± 0.1539*	2.485 ± 0.1313*	2.052 ± 0.1182**	3.133 ± 0.1950***	3.020 ± 0.1889***	2.338 ± 0.1666**
QR (nmole/min/mg protein)	77.928 ± 3.020	74.062 ± 2.616***	73.087 ± 2.494***	68.713 ± 2.117***	75.532 ± 2.873***	77.023 ± 2.852***	70.657 ± 2.258***
Protein (µg/ml)	5332.7 ± 583.48	4615.3 ± 430.45***	4852.2 ± 289.29***	4477.7 ± 214.06***	4934.3 ± 486.06***	5216.3 ± 361.47***	4649.5 ± 398.53***

Results shown as mean ± SEM. *P < 0.05, **P < 0.01, ***P > 0.05 as compared with control values.

Table 2: The effect of ginger against dichlorvos and lindane induced neurotoxicity in female wistar rats

Parameters	C	D	L	D + L	D + G	L + G	D + L + G
LPO (nmole MDA/h/g tissue)	5.047 ± 0.1610	6.617 ± 0.3094**	6.28 ± 0.2394*	7.372 ± 0.3139**	5.845 ± 0.1348***	5.187 ± 0.1982***	6.305 ± 0.1879**
GSH (µmole/g tissue)	12.985 ± 0.4294	11.636 ± 0.2048**	11.867 ± 0.1669*	10.828 ± 0.2537**	12.758 ± .3305***	12.299 ± 0.2540***	11.652 ± 0.1443**
CAT (µmole/min/mg protein)	73.455 ± 2.971	62.467 ± 3.546***	64.925 ± 3.990***	54.627 ± 3.092**	71.008 ± 3.906***	67.945 ± 3.978***	57.452 ± 3.132*
SOD (nmole/min/mg protein)	173.95 ± 1.675	153.95 ± 1.902**	160.74 ± 1.368**	143.00 ± 1.600**	167.97 ± 1.903***	170.79 ± 1.548***	150.51 ± 0.6392**
GPx (nmole/min/mg protein)	20.895 ± 0.4357	17.207 ± 0.3384**	18.120 ± 0.3639**	15.493 ± 0.1020**	18.388 ± 0.4127**	19.523 ± 0.4331***	16.788 ± 0.3644**
GST (nmole/min/mg protein)	644.04 ± 47.228	564.60 ± 32.061***	563.67 ± 41.352***	499.26 ± 27.200***	606.83 ± 42.235***	633.31 ± 41.381***	539.14 ± 37.423***
GR (nmole/min/mg protein)	3.163 ± 0.1943	2.480 ± 0.1040*	2.420 ± 0.0800*	1.957 ± 0.1304**	2.940 ± 0.2173***	2.873 ± 0.1763***	2.168 ± 0.1527**
QR (nmole/min/mg protein)	74.512 ± 1.973	69.927 ± 2.612***	70.577 ± 2.913***	65.020 ± 1.504***	71.733 ± 2.941***	73.463 ± 3.232***	67.495 ± 2.037***
Protein (µg/ml)	5301.0 ± 575.73	4591.7 ± 436.37***	4827.2 ± 288.09***	4460.5 ± 211.72***	4891.0 ± 489.98***	5196.3 ± 361.75***	4624.5 ± 399.08***

Result shown as Mean ± S.EM, * P < 0.05, ** P < 0.01, ***P > 0.05 as compared with control values.

any other organ of the body as it consumes high amount of oxygen, contains high amount of polyunsaturated fatty acids (PUFA) and low level of antioxidant enzymes. Further, the lipophilic nature of dichlorvos and lindane makes the brain most prone target. An increase in LPO may be due accumulation of dichlorvos and lindane in the cerebral tissue and enhanced production of ROS. Increased ROS leads to excessive membrane damage and cell death. An increase in LPO in cerebral hemisphere of rat brain on lindane exposure has been earlier reported by Sahoo *et al*.[29] Dichlorvos induced more LPO as compared to lindane. In the combination group, D + L increase in LPO was more pronounced as compared to groups D and L, but the effect was not cumulative. An increase in the LPO level was not specific to sex.

The reduction in level of non-enzymatic and enzymatic antioxidants was more in group D + L as compared D and L. Reduction in the GSH level may be due to indirect conjugation with excess electrophiles produced due to dichlorvos and lindane exposure. In previous studies, decrease in GSH level was reported on exposure of dichlorvos and monocrotofos in rat brain,[6] chlorpyrifos in rat brain, kidney and spleen[4] and lindane in mice brain.[12] The reduction in the GSH level in this study may be due to direct conjugation of GSH with electrophiles species which are produced increasingly by dichlorvos and lindane exposure or due to inhibition of enzymes such as GR, GPx, *etc*. which are involved in GSH synthesis and regeneration. The reduction in the SOD and CAT level may be due to the excessive production of superoxide anions after exposure of dichlorvos and lindane. The decreased level of SOD and CAT is previously reported in rats brain exposed to chlorpyrifos[4] and lindane.[29] GPx is a GSH using enzyme and plays an important role in maintaining GSH homeostasis and tissue detoxification. Dichlorvos and lindane exposure lead to decrease in GPx activity in our study, which may be due to the depleted level of GSH. A decrease in SOD, CAT, and GPx depletion was more significant in the combination group D + L as compared to groups D and L indicating that dichlorvos and lindane induced neurotoxicity was synergistic. There was a slight reduction in the GST and QR level on exposure to dichlorvos and lindane alone and in combination but this reduction was non-significant. A decrease in GR activity is already reported in rat brain,[4] and tests exposed to methoxychlor.[30] A decrease in activities of antioxidant enzymes was not specific to any sex.

Total protein levels were decreased non-significantly among exposure groups in both the sexes. The slight reduction in total protein in rat brain observed during the study was not significant. The decrease in the protein level may be due to depletion in the level of various antioxidative enzymes.[13]

In post-treatment groups, ginger showed protective role by decreasing the LPO level in animals exposed to dichlorvos and lindane. Ginger worked as an antioxidant and increased the level of non-enzymatic antioxidant GSH, enzymatic antioxidants CAT, SOD, GPx, GST, GR, and QR and the protein level in animals exposed to dichlorvos and lindane. Ginger reduces the oxidative stress in the animals, by its high ROS scavenging capacity and protecting the antioxidant enzymes from being denatured. Protective role of ginger has also been reported by Nirmala *et al*.[31] and Nabil *et al*.[32] In post-treatment combination group D + L + G, protective effects of ginger were less effective as compared to D + G and L + G groups. Less effectiveness of ginger may be due to the synergistically high toxicity of both the pesticides. In future experiments, higher doses of ginger juice up to no observed adverse effect level (NOAEL) may be tried.

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