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Original Article

Efficacy of Trans-2-Hydroxycinnamic Acid Against Trichlorfon-Induced Oxidative Stress in Wistar Rats

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ABSTRACT

Trichlorfon is an organophosphate insecticide used to control cockroaches, crickets, silverfish, bedbugs, fleas, cattle grubs, flies, ticks, leaf miners, and leaf-hoppers. It is also used to treat domestic animals for control of internal parasites. Trans-2-hydroxycinnamic acid (T2HCA) is a hydroxyl derivative of cinnamic acid. The present study highlights trichlorofon-induced toxicity and the protective role of T2HCA in the liver, kidney, and brain of female Wistar rats. The rats were given a single dose of trichlorofon (150 mg / kg bw) and pre- and post-treatment T2HCA (50 mg / kg bw) for seven days. Trichlorofon enhanced oxidative stress in liver, kidney, and brain of the rats, which was evident from the elevation of lipid peroxidation (LPO). The reduced level of non-enzymatic antioxidant glutathione (GSH) also indicated the presence of an oxidative insult. The activity of enzymatic antioxidants like superoxide dismutase (SOD), catalase (CAT), glutathione-s-transferase (GST), glutathione reductase (GR), and glutathione peroxidase (GPx) was significantly decreased on trichlorfon administration. Pre and post treatment with T2HCA decreased the LPO level and increased SOD, CAT, GST, GR, GPx, and GSH in the brain, liver, and kidney. Trichlorfon-induced reduction in acelylcholinestrase was also ameliorated with T2HCA treatment. In conclusion, trichlorfon-mediated induction in the reactive oxygen species and disturbance in the antioxidant enzymes' defense system was moderately ameliorated by antioxidant trans-2-hydroxycinnamic acid.

Key words: Oxidative stress, trans-2-hydroxycinnamic acid, trichlorfon, Wistar rats

INTRODUCTION

Oxidative stress is responsible for various pathological conditions, such as, cancer, cardiovascular diseases, asthma, arthritis, inflammation, neurodegenerative disorders, and dementia.[1] Pesticides and insecticides are persistent organic pollutants that cause oxidative stress in animals, including humans. Trichlorfon is an organophosphate insecticide used to control cockroaches, crickets, silverfish, bedbugs, fleas, cattle grubs, flies, ticks, leaf-miners, and leaf-hoppers,[2] as well as, for treating domestic animals for the control of internal parasites.[3] Moderate-to-severe symptoms of trichlorfon toxicity have been reported in farm and factory workers, military personnel, and exterminators.[4] The common symptoms of trichlorfon toxicity in humans includes nausea, vomiting, diarrhea, abdominal cramps, headache, dizziness, eye pain, blurred vision, tears, sweating, and confusion. Severe poisoning may affect the activity of the central nervous system leading to in-coordination, slurred speech, loss of reflexes, involuntary muscle contraction, and eventually paralysis of the respiratory muscles and other extremities.[5] Few studies on the toxicity of trichlorfon have been reported in laboratory animals. Teratogenic and embryotoxic toxicity of trichlorfon at a dose of 400 mg / kg bw / day in rat, mouse, and hamster,[6] and neurotoxicity

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DOI: 10.4103/0971-6580.103671

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at a dose 7.5 mg / g bw / day, in female Sprague-Dawley rats,[7] have been reported previously.

Endogenous antioxidants are the essential defense weapons of the cell against free radicals and oxidative damage. However, chronic exposure to pesticides has led to the induction of oxidative stress beyond the protecting efficiency of the endogenous antioxidants. Exogenous antioxidants from natural plant sources have been widely used to counteract pesticide-induced oxidative stress.[8] Phenolic acids are widespread in the plant kingdom and are known to possess a number of biological activities.[9] The antioxidant activity of phenolic acids, including that of hydroxycinnamic acid derivatives, has been reported.[10]

Trans-2-hydroxycinnamic acid (T2HCA) is a derivative of cinnamic acid, obtained from the oil of cinnamon. No reports on the antioxidant activity of T2HCA are available, hence, this study was planned to evaluate the antioxidative effect of T2HCA on trichlorfon-induced oxidative stress in the liver, kidney, and brain of Wistar rats.

MATERIALS AND METHODS

Chemicals

Trichlorfon (97.8%) and T2HCA (97%) were purchased from the Sigma Chemicals (St. Louis, MO, USA). All other chemicals used in this study were of high purity and purchased locally.

Animals

The adult female Wistar rats were obtained from the Animal Research Division, Indian Institute of Toxicological Research (IITR), Lucknow, (India). The animals were kept in an animal house at the Bundelkhand University, Jhansi, for acclimatization, under standard conditions, for one week before the start of the experiment. All animal experiments were carried out as per the guidelines of the Institutional Ethical Committee.

Experimental plan

Thirty-six rats, weighing 200-250 g were divided into six groups as per the given experimental plan [Table 1]. Trichlorfon and T2HCA were dissolved in water and Dimethyl sulfoxide (DMSO), respectively, and administered by gavaging.

At the end of the study, the animals were sacrificed. The liver, kidney, and brain were dissected, washed with 0.9% NaCl, and used for various biochemical estimations

Table 1: Experimental plan

Group A	Control I Normal diet and distilled water for seven days
Group A-1	Control II Normal diet and DMSO for seven days
Group B	Exposure Single dose exposure (150 mg / kg bw) of trichlorfon for 24 hours
Group C	Pre-treatment T2HCA (50 mg / kg bw) for seven days followed by single-dose exposure of trichlorfon (150 mg / kg bw) for 24 hours
Group D	Post-treatment Trichlorfon (150 mg / kg b.wt) for 24 hours followed by T2HCA (50 mg / kg bw) for seven days
Group E	Antioxidant T2HCA (50 mg / kg bw) for seven days

Biochemical estimations

Tissue homogenate preparation

The liver, kidney, and brain were separately homogenized in 10% (w / v) ice cold 0.1 M Phosphate Buffered Saline (PBS) (pH 7.4). A part of this homogenate was used for biochemical estimations and the other part was centrifuged at 9,000 rpm for 20 minutes to obtain the supernatant 'S,' which was used for SOD, CAT, GPx, GR, GST, and protein estimations.

Lipid peroxidation

Lipid peroxidation (LPO) was estimated as described by Okhawa *et al.*[11] One milliliter of homogenate was incubated at 37°C for 10 minutes. One milliliter of 10% (w / v) chilled trichloroacetic acid (TCA) was added to it and centrifuged at 2500 rpm for 15 minutes at room temperature. One milliliter of 0.67% thiobarbituric acid (TBA) was added to 1 ml of supernatant and kept in a boiling water bath for 10-15 minutes. The tubes were cooled under tap water, and followed by an addition of 1 ml of distilled water. Absorbance was recorded at 530 nm and the results were expressed as n moles MDA / hr / g tissue.

Reduced glutathione

Glutathione (GSH) was estimated by the method described by Ellman.[12] One milliliter of 10% crude homogenate was mixed with 1 ml of 5% TCA (w / v). The mixture was allowed to stand for 30 minutes and centrifuged at 2500 rpm for 15 minutes; 0.5 ml of the supernatant was taken and 2.5 ml of 5′5′-dithionitrobenzoic acid (DTNB) was added, mixed thoroughly, and the absorbance was recorded at 412 nm. The results were expressed as μmoles / g tissue.

Superoxide dismutase

Superoxide dismutase (SOD) was estimated by the method described by Kakkar *et al.*[13] Sodium pyrophosphate buffer of 650 μl, 50 μl phenazine methasulfate (PMS), 150 μl of nitroblue tetrazolium chloride (NBT), and 100 μl NADPH were added to 50 μl of 'S'. The mixture was vortexed thoroughly, incubated for 90 seconds, and 500 μl glacial acetic acid was added to stop the reaction. Two milliliters of n-butanol was added to the mixture, vortexed thoroughly, and kept at room temperature for 10 minutes. Absorbance

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was measured at 560 nm and the results were expressed as μmoles / min / mg protein.

Catalase

Catalase (CAT) was estimated by the method of Sinha.[14] One milliliter of phosphate buffer and 0.4 ml water were added to 0.1 ml of 'S'. The reaction was started by adding 0.5 ml H_2O_2, and the mixture was incubated at 37°C for 1 minute. The reaction was stopped by adding 2 ml of dichromate: acetic acid reagent, and kept in a boiling water bath for 15 minutes. The mixture was cooled and absorbance was read at 570 nm. The CAT activity was calculated in terms of μmoles / min / mg protein.

Glutathione-S-transferase

Glutathione-s-transferase (GST) was estimated as per the method of Habig *et al.*[15] The reaction mixture consisting of 1.425 ml phosphate buffer (0.1 M, pH6.5), 1.475 ml GSH (1.0 mM), 20 μl 1-chloro-2,4-Dinitrobenzene (CDNB,1 mM), and 60 μl water was added to 20 μl of 'S' to give a 3.0 ml solution. Absorbance was recorded at 340 nm and the GST activity was calculated as μ moles 1-chloro-2,4-dinitrobenzene (CDNB) conjugate formed / min / mg protein using a molar extinction coefficient of $9.6 \times 10^3 M^{-1} cm^{-1}$.

Glutathione peroxidase

Glutathione peroxidase (GPx) was estimated by the method of Rotruck *et al.*[16] Tris HCl buffer of 0.4 ml, 0.2 ml GSH, 0.1 ml water, and 0.2 ml H_2O_2 were added to 0.1 ml 'S'. The mixture was incubated at 37°C for 15 minutes and 0.5 ml TCA (10%) was added. The mixture was centrifuged at 2000 rpm for 15 minutes, 0.5 ml of the supernatant was taken, and 2 ml di-sodium hydrogen phosphate buffer and 0.5 ml Ellman's Reagent were added. The absorbance was read at 420 nm. The results were expressed as nmoles / min / mg protein.

Total protein

Protein was estimated by the method of Lowry.[17]

Acetylthiocholine esterase assay

The acelylcholinestrase assay was estimated by Ellman.[18] The brain was weighed and homogenized in 0.1 M phosphate buffer (pH 8.0). A 0.4 ml aliquot of the homogenate was added to a cuvette containing 2.6 ml phosphate buffer (0.1 M, pH 8.0) and 100 μl DTNB. The contents of the cuvette were mixed thoroughly by bubbling air and the absorbance was measured at 412 nm. When the absorbance reached a stable value, it was recorded as the basal reading. Substrate of 20 μl, that is, acetylthiocholine, was added, and the change in absorbance was recorded for a period of 10 minutes at two minute intervals. Changes in the absorbance per minute were determined and the results were expressed as nmole / min / g tissue.

Statistical analysis

Mean and standard error were determined for all the parameters and the results were expressed as Mean ± SEM. The data was analyzed employing the 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 the control was performed, to determine the significant differences among the groups.

RESULTS

Lipid peroxidation and non-enzymatic antioxidant

The lipid peroxidation (LPO) levels in groups A1 and A2 were the same, indicating that DMSO was non-toxic at a concentration of 0.5 ml per rat, hence, the mean values of these groups were taken as the control and designated as group A. All comparisons were made with group A, unless mentioned otherwise. The LPO level was significantly increased ($P < 0.05$) in exposure group B in the liver, kidney, and brain, as compared to the control group A. A non-significant ($P > 0.05$) increase in LPO was observed in pre- and post-T2HCA treatment groups C and D. Treatment with T2HCA in group E, non-significantly ($P > 0.05$) reduced the LPO level, as compared to the control [Figure 1].

The level of GSH was depleted significantly ($P < 0.05$) in groups B and D, in the brain, kidney, and liver. A non-significant ($P > 0.05$) decrease in the GSH level was observed in group C, while a non-significant ($P > 0.05$) increase was observed in group E [Figure 2].

Enzymatic antioxidants

The SOD activity decreased significantly ($P < 0.01$) in group B in the brain, kidney, and liver, as compared to the control. A significant decrease ($P < 0.05$) in SOD activity was observed in groups C and D, while a non-significant ($P > 0.05$) increase was seen in group E [Figure 3]. The CAT activity was decreased very significantly ($P < 0.01$) in group B and significantly ($P < 0.05$) in group D. The CAT activity was non-significantly ($P > 0.05$) decreased in group C and increased in group E [Figure 4]. The GPx activity in groups B and D was significantly ($P < 0.05$) lowered as compared to the control, while a non-significant ($P > 0.05$) decrease in group C and increase in group E was observed [Figure 5].

The GST activity was decreased significantly ($P < 0.05$) in groups B and D and non-significantly ($P > 0.05$) in group C. A non-significant ($P > 0.05$) increase in GST activity was observed in group E [Figure 6]. The protein level in all groups, except group E, were decreased non-significantly ($P > 0.05$) as compared to the control [Figure 7].

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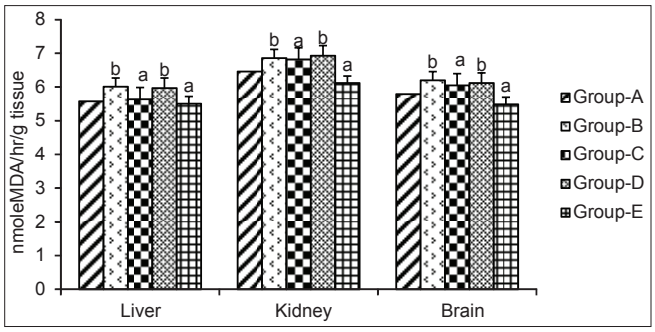


Figure 1: Effect of T2HCA and trichlorfon on the lipid peroxidation level. The value represents the Mean ± SEM ($n = 6$). b = $P < 0.05$, a = $P > 0.05$ as compared to the control value. Group A: Control, Group B: Trichlorfon, Group C: Pre-treatment, Group D: Post-treatment, Group E: Hydroxicinnamic acid

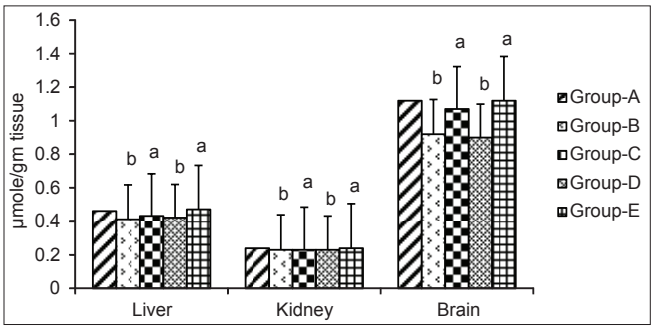


Figure 2: Effect of T2HCA and trichlorfon on the glutathione level. The value represents the Mean ± SEM ($n = 6$). b = $P < 0.05$, a = $P > 0.05$, as compared to the control value. Group A: Control, Group B: Trichlorfon, Group C: Pre-treatment, Group D: Post-treatment, Group E: Hydroxicinnamic acid

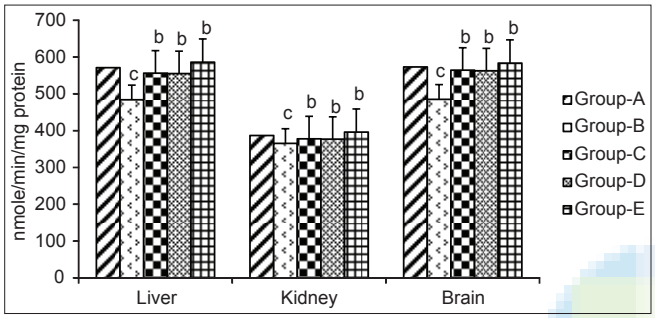


Figure 3: Effect of T2HCA and trichlorfon on superoxide dismutase activity. The value represents the Mean ± SEM ($n = 6$). c = $P<0.01$, b = $P < 0.05$ as compared to the control value. Group A: Control, Group B: Trichlorfon, Group C: Pre-treatment, Group D: Post-treatment, Group E: Hydroxicinnamic acid

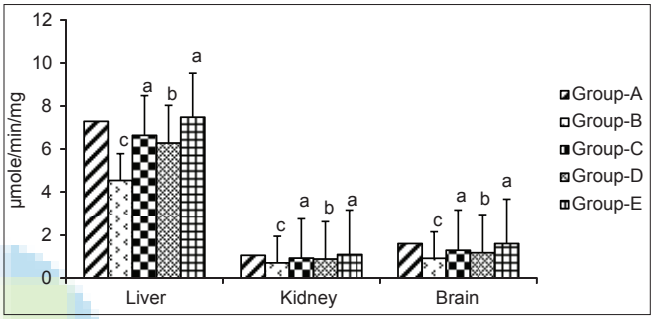


Figure 4: Effect of T2HCA and trichlorfon on catalase activity. The value represents the Mean ± SEM ($n = 6$). c = $P < 0.01$, b = $P<0.05$, a = $P > 0.05$ as compared to the control value. Group A: Control, Group B: Trichlorfon, Group C: Pre-treatment, Group D: Post-treatment, Group E: Hydroxicinnamic acid

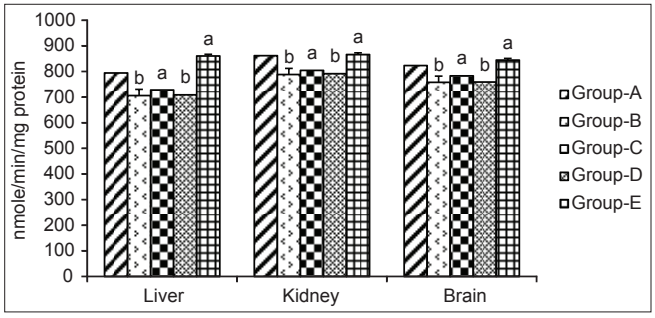


Figure 5: Effect of T2HCA and trichlorfon on glutathione-S-transferase activity. The value represents the Mean ± SEM ($n = 6$). b = $P < 0.05$, a = $P > 0.05$ as compared to the control value. Group A: Control, Group B: Trichlorfon, Group C: Pre-treatment, Group D: Post-treatment, Group E: Hydroxicinnamic acid

Acelylcholinestrase activity

The acelylcholinesterase activity was significantly ($P < 0.01$) decreased in group B. Pre- and post-treatment of T2HCA in groups C and D significantly ($P < 0.05$) lowered the acelylcholinesterase activity. In group E, the acelylcholinesterase activity was non-significantly ($P > 0.05$) increased, as compared to the control [Figure 8].

DISCUSSION

Lipid peroxidation and non-enzymatic antioxidant

A significant increase in the MDA level was observed on trichlorfon exposure in the liver, kidney, and brain. Increase in MDA was an indicator of enhanced oxidative stress.[19] It was previously reported that organophosphate pesticides induced oxidative stress evidenced by enhanced MDA production.[20] Trichlorfon induced an increase in LPO, and disturbance in the integrity of the cell membranes leading to inhibition of the membrane-bound enzymes has already been reported.[21] Increase in ROS and LPO resulted in the depletion of GSH in the liver, kidney, and brain of exposed rats, in this study. GSH is an endogenous, peptidal, antioxidant, which prevents damage to the cellular components by ROS and peroxides.[22] In addition to working as a direct free-radical scavenger, GSH also functions as a substrate for GPx and GST. The reduction in GSH level may be due to the direct conjugation of GSH, with electrophiles generated on trichlorfon exposure. Decrease in the GSH level has already been reported on exposure to other organophosphate pesticides like dichlorvos.[23,24]

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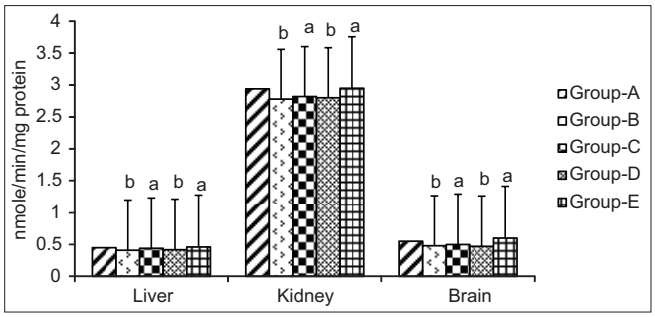


Figure 6: Effect of T2HCA and trichlorfon on glutathione peroxidase level. The value represents the Mean ± SEM ($n = 6$). b = $P < 0.05$, a = $P > 0.05$ as compared to the control value. Group A: Control, Group B: Trichlorfon, Group C: Pre-treatment, Group D: Post-treatment, Group E: Hydroxicinnamic acid

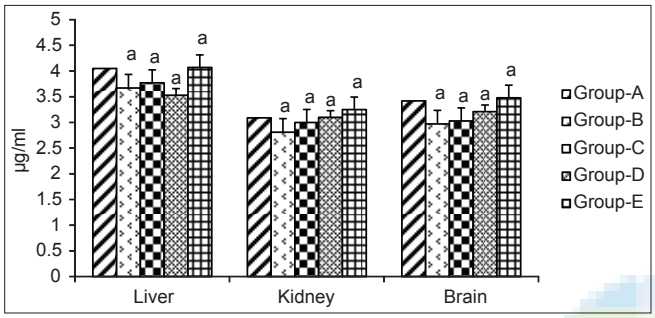


Figure 7: Effect of T2HCA and trichlorfon on total protein level. The value represents the Mean ± SEM ($n = 6$). A = $P > 0.05$ as compared to the control value. Group A: Control, Group B: Trichlorfon, Group C: Pre-treatment, Group D: Post-treatment, Group E: Hydroxicinnamic acid

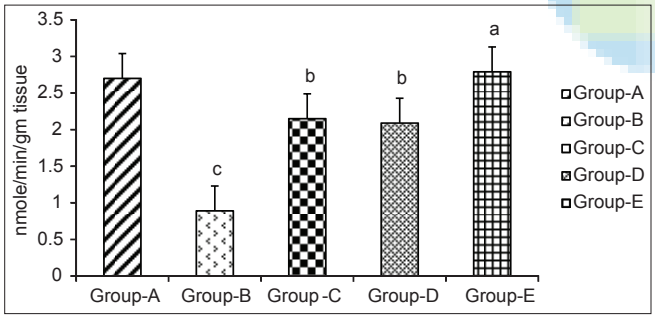


Figure 8: Effect of T2HCA and trichlorfon on acetylecholinesterase activity. The value represents the Mean ± SEM ($n = 6$). c = $P < 0.01$, b = $P < 0.05$, a = $P > 0.05$ as compared to the control value. Group A: Control, Group B: Trichlorfon, Group C: Pre-treatment, Group D: Post-treatment, Group E: Hydroxicinnamic acid

Enzymatic antioxidants

Mammalian cells are equipped with antioxidant enzymes to minimize the cellular damage resulting from intracellular ROS or pesticide-induced oxidative stress.[25] SOD, CAT, and GP_X work in a coherent manner to inactivate the ROS generated by pesticide exposure. SOD is a class of enzymes that catalyze the binding of ROS with water to generate H_2O_2 and it is the first enzymatic defense against the superoxide anion. CAT is responsible for the breakdown of H_2O_2 to water and oxygen, protecting the cell from the damaging action of H_2O_2 and the hydroxyl radical. GP_X catalyzes the reaction of hydroperoxides with reduced glutathione to form glutathione disulfide (GSSG) and the reduction product of the hydroperoxide. The SOD, CAT, and GPx activities in the liver, kidney, and brain, were decreased after trichlorfon exposure, in this study. Organophosphates dichlorvos was previously reported to decrease the activity of these enzymes in rat blood[26] and rat brain.[27] It was proposed that a decrease in SOD activity would accumulate ROS, which in turn would inactivate CAT.[28] As GPx used GSH as a substrate, depletion in the GSH level on trichlorfon exposure could have decreased the GPx activity. GST catalyzed the conjugation of electrophiles generated by the pesticides to GSH via a sulfhydryl group. This activity of GST helped in accelerated metabolism and excretion of the electrophilic molecules. GST might also bind to the toxins and function as transport proteins. In the present study, GST decreased in the liver, kidney, and brain of the rats exposed to trichlorfon. Decrease in the GST activity might be either due to a decrease in GSH or due to an increase in the concentration of electrophiles generated on trichlorfon exposure. Decrease in the GST activity was previously reported in the liver[8] and testes[29] of rats on lindane exposure. The total protein contents in the liver, kidney, and brain of trichlorfon-exposed rats were decreased. Depletion in the total protein content could be due to the accelerated apoptosis of a large number of cells of the exposed tissue and also due to depletion in the enzyme levels. Pesticide-exposed depletion in the total protein content in animal models was reported earlier.[21,24]

Acetylcholinesterase activity

Acelylcholinesterase (AChE) is a key component of cholinergic brain synapses and neuromuscular junctions. In the present study, the AChE activity was decreased on trichlorfon exposure. The decrease in AChE activity could be due to trichlorfon-induced neurotoxicity. The results indicated that trichlorfon exposure resulted in enhanced oxidative stress and reduced antioxidant defense in the brain. These conditions could have induced apoptosis in the neurons, resulting in absolute deficiency of AChE and marked neurotoxicity. There are few earlier reports of decrease in AChE activity on the organophosphate pesticide exposure.[30,31]

Role of Trans-2-hydroxycinnamic acid

The antioxidant activity of cinnamic acid and its derivatives is well known in literature.[32] Among of hydroxycinnamic acid derivatives, caffeic acid has been reported to exhibit good antioxidant and free radical scavenging activities.[33] The antioxidant activities of different cinnamic acid derivatives have been reported earlier, and p-coumeric acid, bearing a structural similarity to T2HCA, possesses moderate antioxidant activity (Jin-Chun *et al.*, 2007).[34] The MDA level was brought to a normal level by pre- and

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post-treatment of T2HCA, in this study. Pre- and post-treatment with T2HCA replenished the deleted GSH level, possibly due to its capability of scavenging the free radicals generated on trichlorfon exposure. Scavenging of ROS by T2HCA may be responsible for the improvement in SOD and CAT activity, and replenishment of GSH may have helped in regaining the GPx activity. Pre- and post-treatment with T2HCA helps in regaining the GST activity. The AChE activity in the brain is also replenished by T2HCA treatment. This study shows that T2HCA possesses moderate antioxidant activity in the liver, kidney, and brain of trichlorfon-exposed rats. The antioxidant activity is not organ-specific. Treatment of normal rats with T2HCA does not result in any type of oxidative stress-related toxicity.

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How to cite this article: Sharma P, Singh R. Efficacy of trans-2-Hydroxycinnamic acid against Trichlorfon-induced oxidative stress in wistar rats. Toxicol Int 2012;19:295-300.

Source of Support: Bundelkhand University, Jhansi, INDIA. **Conflict of Interest:** None declared.