NAAS Score: 4.11; IC Value: 74.82; UGC-India Approved
The Journal of Phytopharmacology 2018; 7(1): 33-39
Online at: www.phytopharmajournal.com

Research Article

ISSN 2320-480X
JPHYTO 2018; 7(1): 33-39
January- February
Received: 24-11-2017
Accepted: 05-01-2018

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Understanding the role of quercetin during neurotoxicity induced by Chlorpyrifos

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ABSTRACT

Organophosphate Chlorpyrifos (CPF), a pesticide, is widely used across the world to control worms and insects. It is highly toxic and causes neurobehavioral disorders. Naturally occurring compounds having polyphenols as their structural units are considered beneficial against toxicities inflicted by organophosphates. The present study reports that quercetin, a polyphenol, provides neuroprotection following neurotoxicity induced by chlorpyrifos. To carry out the study, male Sprague Dawley rats weighing 170-200g were segregated into four groups viz: normal control, CPF treated (13.5mg/kg b. wt. alternate day), Quercetin treated (50mg/kg b. wt. every day) and combined CPF +Quercetin treated. All the treatments were carried out for a total duration 60 day. Rota-rod performance test and Actophotometer test were undertaken to evaluate the locomotor activity and muscular strength of animals. Further, experiments were also conducted to assess neurotoxicity and structural alterations of cerebrum and cerebellum of brain, if any, inflicted by chlorpyrifos. The results revealed a significant decrease in locomotor activity as well as muscular strength of animals following chlorpyrifos treatment which however were appreciably improved upon simultaneous supplementation with quercetin. Further, treatment with chlorpyrifos resulted in a significant decrease in the activity of acetyl cholinesterase in serum as well as in cerebrum and cerebellum which however was increased upon co-treatment with quercetin. On the contrary, we noticed a significant increase in the levels of acetylcholine both in cerebrum and cerebellum which were modulated upon supplementation of quercetin. Light micrographs of both cerebrum and cerebellum showed histoarchitectural alterations which were improved upon co-treatment with quercetin. This study therefore concludes that quercetin when used as a prophylactic intervention would provide protection against CPF induced neurotoxicity.

Keywords: Chlorpyrifos, Quercetin, Acetylcholinesterase, Brain and Neurotoxicity.

INTRODUCTION

Pesticides are chemical compounds that are used worldwide to control pests and weeds. The purpose of using pesticides is to enhance agricultural production and also to increase the quality and yield of the produce. Pesticide particles have been found everywhere in atmosphere and they exist in high concentrations especially in the areas where they are applied. They are believed to target both central and peripheral nervous system and can cause neurological disorders [1].

Chlorpyrifos (CPF), a broadly used organophosphate is well known for its action on nervous system and red blood cells by way of inhibiting the activity of enzyme acetylcholinesterase (AChE) and therefore cannot break down acetylcholine for a longer time to choline and acetic acid. As a result, acetylcholine accumulates at synapses in the nervous system and neuromuscular junction and causes neurotoxic effects such as overstimulation of neuronal cells, anxiety, alteration of neurobehavioral action, cognitive dysfunction, Parkinson disease and eventually death [2,3]. Chlorpyrifos pesticide exposure enhances the level of hydrogen peroxide, a reactive oxygen species (ROS) and brings down the level of antioxidant potential of nervous system and results in oxidative stress in neuronal cells [4-6]. Also, various studies have shown that chlorpyrifos produces oxidative stress via binding of phosphate and other oxygen-ligands to form stable complexes thereby interrupting mitochondria activity in brain [7,8]. Neurobehavioral alteration is one of the main impacts of chlorpyrifos exposure on central and peripheral nervous system and is manifested with cognitive deficit, anxiety, long and short-term memory impairment and neuro-developmental delays through inhibition of cholinesterase and alternative cholinergic mechanism such as endocannabinoid, serotonergic and dopaminergic pathways [9,10]. Oxidative stress is recognized as an important factor in a variety of neurodegenerative diseases. Polyphenols act as antioxidant agents and reduce the risk of neurodegeneration.

Quercetin is a polyphenol flavonoid occurring naturally in a variety of brightly colored plant-based foods as glycosides linked to glucose, galactose, xylose and rhamnose. Quercetin is considered to be a strong antioxidant because of its ability to scavenge free radicals and to bind to transition metal ions. The antioxidant character of quercetin is associated with the presence and location of hydroxyl (–OH) substitutions and the catechol-type B-ring [11,12]. Quercetin has been shown to inhibit pro inflammatory enzymes such as cyclooxygenase and lipoxygenase, thereby reducing the production of inflammatory mediators like leukotrienes and prostaglandins [13]. However, the information is lacking with regard to protective effects of quercetin, if any, in containing neurotoxic effects of chlorpyrifos on cerebrum and cerebellum regions of brain.

Therefore, the present study was conducted to explore whether quercetin affords protection against chlorpyrifos induced neurotoxicity in rats.

MATERIALS AND METHODS

Materials

Chlorpyrifos and Quercetin dihydrate were purchased from Sigma-Aldrich Chemical Company. All other chemicals used in this study were of analytical grade and were purchased from the local firms.

Animals

Male Sprague Dawley rats in the weight range 170 to 200g were obtained from the Central Animal House of Panjab University, Chandigarh, India. The animals were kept in plastic cages under hygienic conditions and were given feed in the form of pellets procured from Ashirwad Industries, Kharar, Punjab, India. Before subjecting the animals to different treatments, they were acclimatized for a week in the animal house of the department. The animals were provided free access to drinking water and diet. The animals were treated and housed as per the guidelines approved by the Institutional Animals Ethics Committee, Panjab University, Chandigarh. To carry out various investigations, the animals were randomly divided into four groups.

Experimental design

The animals in Group 1 served as normal controls and were given normal feed and water ad libitum throughout the study. The animals in Group 2 were given chlorpyrifos orally through intubation gavage technique at a dose level of 13.5mg/kg body weight in corn oil every alternate day [14]. The animals in Group 3 were given quercetin every day in the form of quercetin hydrate through gavaging at a dose of 50mg/kg body weight [15]. The animals in group 4 were given a combined treatment with chlorpyrifos as well as quercetin in a similar manner as was given to Group 2 and Group 3 animals, respectively. All the treatments were continued for a total period of 8 weeks.

Record of body weights

A record of body weight changes of all the animals belonging to different groups was kept throughout the investigations. At the initiation of the study, the animals were weighted and there after every 15 days till the completion of the experiments.

Blood Samples

The blood samples were collected under light ether anesthesia from normal and treated rats by puncturing the ocular vein using fine sterilized glass capillaries. The blood samples were kept for some time and thereafter the serum was separated by centrifugation.

Actophotometer performance test

The locomotor activity of the animals was monitored using a computerized Actophotometer (INCORP, India). The animals were placed in Actophotometer individually and an array of 16 infrared emitter/detector pairs measured the animal activity along a single axis of motion. Further, the animals were allowed to acclimatize for 2 minutes in the observation chamber. A count was recorded when the beam of light falling on the photocell was disconnected by the animal. The activity was monitored for a total duration of 3 min. Finally, total locomotor activity was determined as a mean of sum of total ambulant photo beam counts and total rearing photo beam counts for 3 min per animal [16].

Muscular endurance test (Rota-rod performance test)

The muscular strength of rats was evaluated by performing Rota-rod test. The animals were trained to balance on a drum rotating at a speed of 20 revolutions per minute. The animals were subjected to 2 initial training trials of 300 seconds each, nearly 10 minutes apart so as maintain posture on Rota- rod. After the initial trials, a baseline trial of 120 seconds was conducted. The number of falls as well as the time spent by each animal on the Rota-rod was recorded automatically by a trip switch under the floor of each rotating drum [17].

Tissue Preparation

The tissue homogenates (10% w/v) were prepared in ice cold 10 mM phosphate-buffered saline, pH7.4. The homogenates were centrifuged at 2,000g for 10 min at 40C so as to obtain crude homogenates which were devoid of the cell debris and nuclear pellets. The supernatants so obtained were re-centrifuged at 10,000g for 30 min at 40C to obtain the post-mitochondrial supernatants (PMSs). In the present study, PMSs were used to carry out the biochemical estimations.

Acetylcholinesterase activity in serum and tissues

Acetylcholinesterase activity in serum, cerebrum and cerebelum samples was estimated by using acetylthiocholine iodide as a substrate [18]. The reaction mixture comprised of 2.85ml of 0.1M phosphate buffer (pH 7.5), 0.1ml of acetylthiocholine iodide and 50ul of serum or 100ul of tissue homogenate. These samples were allowed to incubate at 370C for 10 min. Thereafter, 0.2ml 10mM 5,5-dithiobisnitrobenzoic acid (DTNB) was added to all the samples. Acetylthiocholine reacts with DTNB and produces 5-mercapto-2-nitrobenzoic acid, a yellow compound whose optical density was measured at 412nm in a double beam spectrophotometer. The activity of the enzyme was expressed in umol of product formed per min per litre of serum or nmol of product formed per min per mg of protein by using an extinction coefficient of 13.6 mM-1cm-1.

Acetylcholine (Ach)

The levels of acetylcholine were estimated by using the method of Hestrin [19]. 0.2ml of alkaline hydroxylamine hydrochloride was added

to 0.4 ml of 10% tissue homogenate and the reaction mixture was kept for 10 min in room temperature. Further, to the reaction mixture, 1ml of HCL(4N) and 1ml of 0.35M ferric chloride were added and the optical densities of the samples were determined at 530 nm in double beam spectrophotometer. A standard graph was prepared with acetylcholine and the values were shown as micromoles of acetylcholine per mg of protein.

Histoarchitectural studies

Histoarchitectural studies were carried out by taking small sections of cerebellum and cerebrum tissues from normal control and treated animals. The tissue samples were washed in ice-cold 0.9% NaCl and then were fixed in 10% formal saline for 48 hours. Following fixation, the tissue samples were dehydrated in ascending grades of alcohol and subsequently were embedded in paraffin wax to prepare blocks. The blocks were cut using microtome to obtain 5 micron thick sections. The sections were finally stained using Hematoxylin and Eosin stain and were viewed under light microscope as described by Pearse [20].

Statistical analysis

The data are expressed as means ± S.D.; n=6. The lowercase alphabet a, b and c represent statistical difference (ap≤0.05, bp≤0.01, cp≤0.001) when comparisons of all treated groups were made with normal control. The lowercase alphabet x, y and z represent statistical difference (xp≤0.05, yp≤0.01, zp≤0.001) when combination group (Quercetin+CPF) was compared with CPF group by using one-way ANOVA followed by Student-Newman-Keuls post hoc test.

RESULTS

Body weight changes

The body weights of the animals exposed to different treatment groups are presented Fig. 1. A steady increase in body weights of normal control rats was observed. Quercetin supplementation alone did not cause any significant change in the body weight when compared to normal control group. However, a significant decrease ($p<0.001$) in body weights was noticed after 30 days CPF treatment when compared to normal control group and the decreasing trend continued till the end of the study. The body weights of CPF treated rats showed marked improvement when rats were simultaneously supplemented with quercetin.

BEHAVIOURAL ACTIVITY

Locomotor activity performance

The locomotor activities of CPF treated animals were observed to be significantly decreased ($p\leq0.01$) after 40 days of treatment when compared to normal control group and the declining trend continued till 60 days of treatment (Figure 2). Interestingly, in the combined CPF and Quercetin treated group, the locomotor activity score was significantly increased($p\leq0.05$) at the end of treatment (60 days). Whereas, no significant change was observed in the Quercetin alone treatment group.

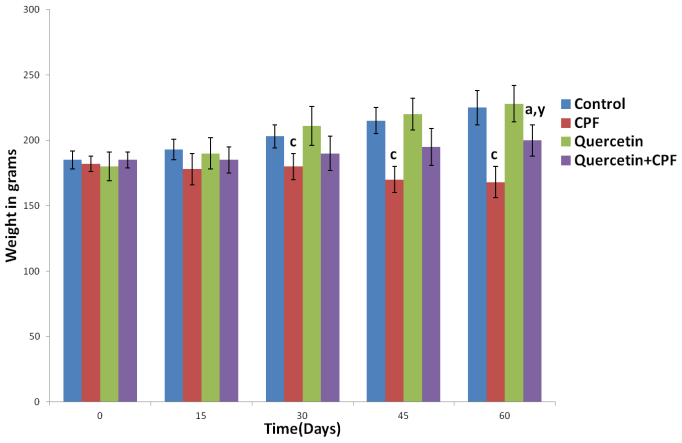

Figure 1: Effects of Quercetin on body weights of rats following 2 months of Chlorpyrifos treatment.

The data are expressed as means ± S.D.; n=7, lowercase alphabet a, b & c represent statistical difference ($^{a}p\leq0.05$, $^{b}p\leq0.01$, $^{c}p\leq0.001$) when comparison of all treated groups was made with control; x, y and z represent statistical difference ($^{a}p\leq0.05$, $^{b}p\leq0.01$, $^{c}p\leq0.001$) when combination group (Quercetin+CPF) is compared to CPF group by using one way ANOVA followed by Student-Newman-Keuls post hoc test.

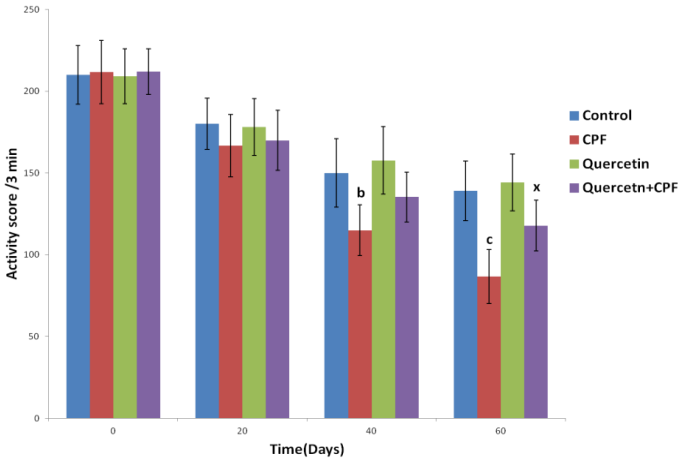

Figure 2: Effects of Quercetin on locomotor activity of rats following 2 months of Chlorpyrifos treatment.

The data are expressed as means ± S.D.; n=6, lowercase alphabet a, b & c represent statistical difference (ap≤0.05, bp≤0.01, cp≤0.001) when comparison of all treated groups was made with control; x, y and z represent statistical difference (ap≤0.05, bp≤0.01, cp≤0.001) when combination group (Quercetin+CPF) is compared to CPF group by using one way ANOVA followed by Student-Newman-Keuls post hoc test.

Rotarod performance test

The Rotarod performance test as an index of muscular activity of rats has revealed a significant decrease ($p\leq0.001$) in the mean fall of time following 40 days and 60 days of CPF treatment in comparison to the normal control group (Figure 3a). On the contrary, a significant increase ($p\leq0.001$) in the number of falls was noticed following CPF treatment at the same time intervals (3b). However, when CPF treated rats were simultaneously supplemented with quercetin, an improvement in mean fall of time and a decrease in number of falls was observed. Quercetin treated group has shown nearly the same muscular activity as compared to the normal control group.

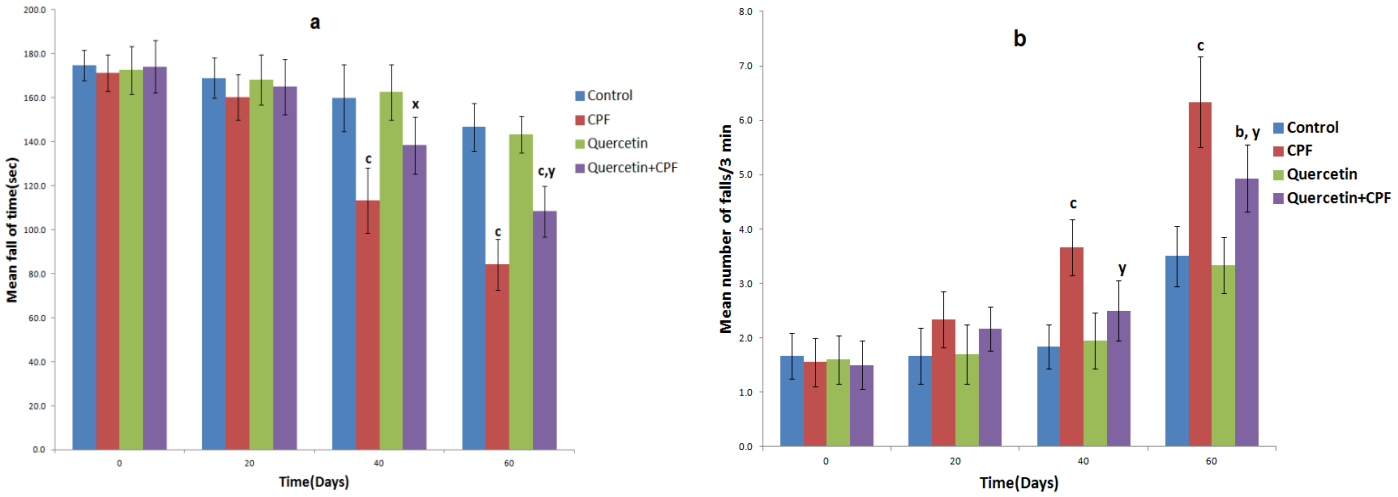

Figure 3: Effects of Quercetin on Muscle activity of animals following 2 months of Chlorpyrifos treatment.

The data are expressed as means ± S.D.; n=6, lowercase alphabet a, b & c represent statistical difference (ap≤0.05, bp≤0.01, cp≤0.001) when comparison of all treated groups was made with control; x, y and z represent statistical difference (ap≤0.05, bp≤0.01, cp≤0.001) when combination group (Quercetin+CPF) is compared to CPF group by using one way ANOVA followed by Student-Newman-Keuls post hoc test.

Brain marker

Acetylcholinesterase activity in serum and brain tissue

Chlorpyrifos treatment to normal rats resulted in a significant decrease (p≤0.001) in the activity of enzyme acetylcholinesterase in serum of CPF treated rats as compared to normal control rats, which however was increased significantly when CPF treated rats were supplemented with quercetin (Table 1). No significant difference in the activity of enzyme acetylcholinesterase was observed in quercetin treated group as compared to normal control group. Further, activity of enzyme acetylcholine esterase was significantly inhibited in cerebrum (p≤0.05) and cerebellum (p≤0.001) in comparison to normal control group which interestingly was increased upon quercetin supplementation.

Table 1: Effect of quercetin on acetylcholinesterase in serum, cerebrum and cerebellum of rats subjected to Chlorpyrifos treatment.

Group	Acetylcholinesterase activity in serum	Acetylcholinesterase activity in tissue	
		Cerebrum	Cerebellum
Normal control	165.25±34.84	19.25±2.70	17.55±4.22
CPF	66.526±12.57^{c}	13.03±2.24^{a}	8.59±2.10^{c}
Quercetin	161.4±14.45	19.12±4.20	17.33±1.35
Quercetin+CPF	93.56±10.26^{c,z}	15.23±1.87	13.88±2.42^{x}

Acetylcholinesterase: nmoles acetylcholine hydrolyzed/min/L serum; Acetylcholinesterase:nmoles acetylcholine hydrolyzed/min/mg Protein.
The data are expressed as means ± S.D.; n=6, lowercase alphabet a, b and c represent statistical difference (ap≤0.05, bp≤0.01, cp≤0.001) when comparison of all treated groups was done with control; x, y and z represent statistical difference (ap≤0.05, bp≤0.01, cp≤0.001) when combination group (Quercetin+CPF) is compared to CPF group by using one-way ANOVA followed by Student-Newman-Keuls post hoc test.

Acetylcholine level

The level of acetylcholine was significantly increased in CPF treated animals in both cerebrum and cerebellum (p≤0.001) as compared to normal control group (Table 2). However, in combined treatment group, the acetylcholine level was found to be appreciably declined in both cerebrum (p≤0.05) and cerebellum (p≤0.01) in comparison to the CPF treated animals. Further, the level of acetylcholine in quercetin treated group was within the same range as compared to normal control rats.

Table 2: Effects of quercetin on acetylcholine in cerebrum and cerebellum of rats subjected to Chlorpyrifos treatment.

Group	Acetylcholine	
	Cerebrum	Cerebellum
Normal control	19.95±3.19	12.67±2.20
CPF	30.13±4.34^{c}	22.23±2.97^{c}
Quercetin	18.19±2.71	12.80±3.07
Quercetin+CPF	23.70±4.12^{x}	16.15±1.75^{y}

Acetylcholine level (nmoles of Ach/mg protein)

The data are expressed as means ± S.D.; n=6, lowercase alphabet a, b and c represent statistical difference (^{a}p≤0.05, ^{b}p≤0.01, ^{c}p≤0.001) when comparison of all treated groups was done with control; x, y and z represent statistical difference (^{a}p≤0.05, ^{b}p≤0.01, ^{c}p≤0.001) when combination group (Quercetin+CPF) is compared to CPF group by using one way ANOVA followed by Student-Newman-Keuls post hoc test.

Histoarchitectural Studies

Cerebrum

The histoarchitectural findings of normal and treated cerebrum are depicted in light photomicrographs (PMG A-D, Figure 4). The photomicrograph of cerebrum of normal control rats shows gray matter which is interspersed with axons, dendrites and glial cells with intact nuclei (PMG- A). The section from CPF treated rats shows gray matter with few enlarged glial cells and the glial cells are seen to be concentrated in a narrow area (PMG-B). Some neurons with pyknotic nuclei are also visible (black arrow). Further, necrosis of some cells was also seen (green arrow). Section of cerebrum from quercetin treated shows intact gray matter with normal population of glial cells (PMG-C). Section from combined CPF + Quercetin treated cerebrum shows near normal structure with mild pyknosis and clearly delineated glial cells intermingled with neurons (arrow, PMG-D).

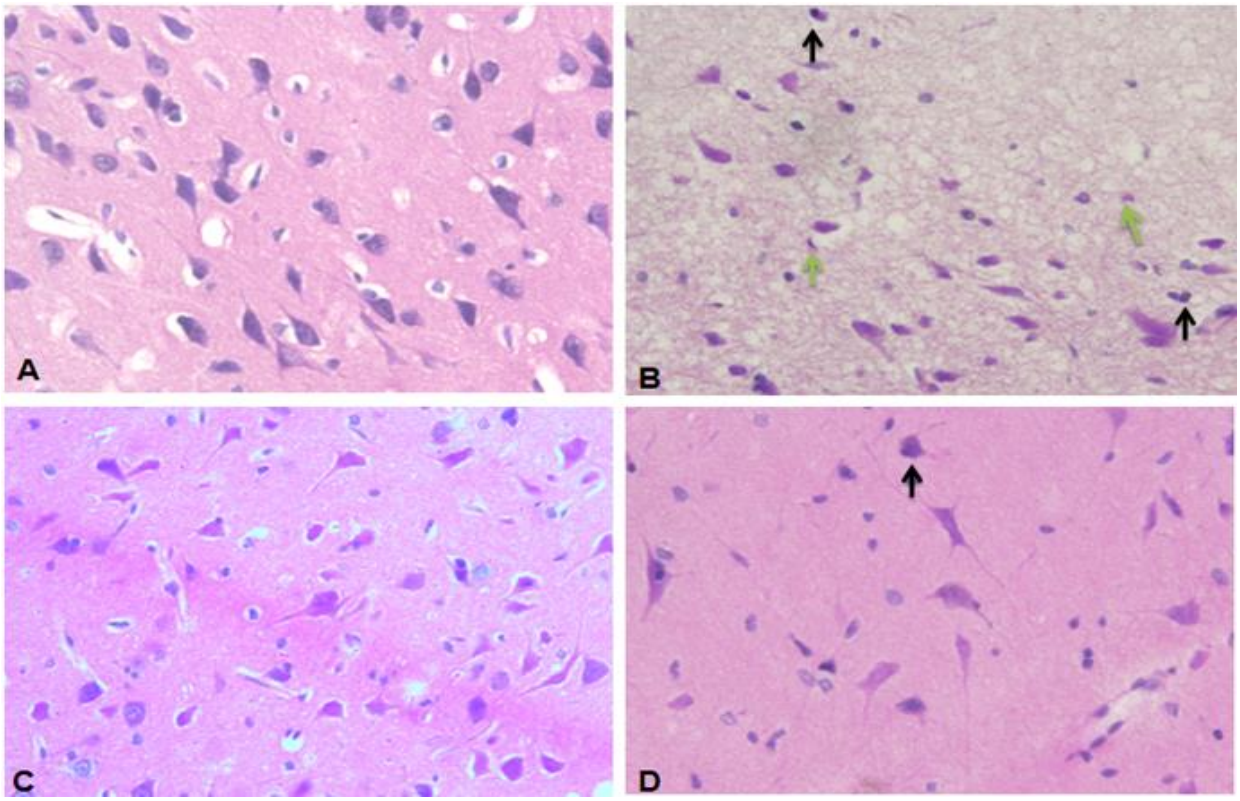

Figure 4: Photomicrographs of cerebrum of Normal Control, CPF, Quercetin and combined CPF + Quercetin treated rats (40X).

Photomicrographs of cerebrum of Normal Control, CPF, Quercetin and combined CPF + Quercetin treated rats, stained by H&E (40 X). (A) Normal Control rat: Section shows intact cerebral gray matter consisting of intermingled axons, dendrites and glial cells with clearly delineated nuclei. (B) CPF Treated rat: Section shows cerebral gray matter with enlarged glial cells which are aligned and are concentrated in a narrow area. Some neurons with pyknotic nuclei are also visible (black arrow). Further, necrosis of some cells was also seen (green arrow). (C) Quercetin treated: Section shows intact gray matter with normal population of glial cells. (D) CPF + Quercetin treated: Section shows near normal structure with mild pyknosis (arrow) and clearly delineated glial cells intermingled with neurons Cytoplasmic vacuolization is sparse.

Cerebellum

The histoarchitectural findings of normal and treated cerebellum are depicted in light photomicrographs (PMG A-D, Figure 5). The normal control section (A) shows normal pattern of three distinct layers viz. Molecular layer (M), Purkinje layer (P) and Granular layer (G). Molecular layer comprises of glial cells, axons of granular cell bodies and dendrites of purkinje cells (black arrow) as well as bergman glia cells (green arrow). Purkinje layer consists of properly aligned cell bodies of neurons above the granular layer (Arrow head). Granular layer comprises of cell bodies of neurons which are closely interspersed. Cerebellum section from CPF treated rats (B) reveals a loss of dendrites of purkinje cells and a change in shapes of cell bodies with a disturbance in their alignment (arrow head) and reduced number of bergman cells. In quercetin treated group (C) the structure of purkinje cells and glial cells are normal. The section from combined treated group (D) shows shrinkage in cell bodies of some purkinje cells (arrow head) with reduction in their number. Further, bergman cells are improved and looking normal (green arrow) and purkinje dendrites are also visible (arrow).

DISCUSSION

In the present study, we conducted investigations to understand the effects of quercetin on various indices related to brain functions and structure that included brain markers, locomotor activity, muscular endurance test and histoarchitecture of chlorpyrifos treated animals. We could notice a significant decrease in body weights of rats following one month of chlorpyrifos treatment and that trend continued till two months. Earlier studies from our lab have also reported a reduction in body weights when animals were subjected to chlorpyrifos treatment [21]. Since, we did not record any change in diet consumption by chlorpyrifos treated rats, thus it can be arguably anticipated that adverse effect on body weights was understandably due to increased peroxidation of lipids. Further, an increase seen in body weights following quercetin supplementation is reasonably due

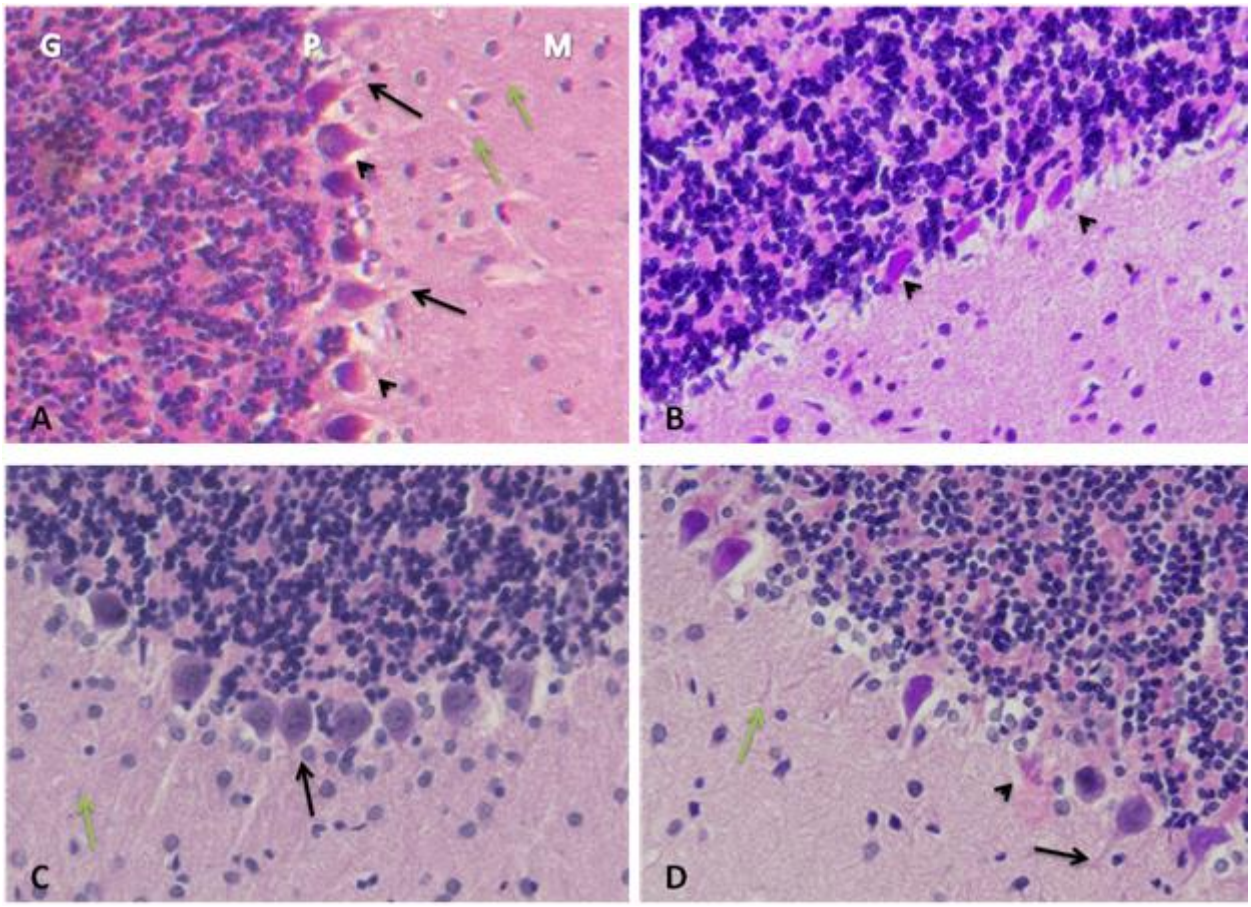

Figure 5: Photomicrographs of cerebellum of Normal Control, CPF, Quercetin and combined CPF + Quercetin treated rats (40X).

In normal control(A) section shows normal structure of purkinje cells (Arrow head) and number of them as well and presence of normal Bergman glial cells in molecular layer (green arrows) and dendrites of purkinje cells (black arrow) whereas in CPF treated rats (B) revealed a decrease in bergman glia cells and loss of purkinje cells dendrites (arrow head). In combined treatment group (D) there is less number of purkinje cells and shrink in cell body of some purkinje cells (arrow head) but bergman cells are improved and looking normal (green arrow) also purkinje dendrites are visible (black arrow) in comparison to CPF treated group. In quercetin treated group (C) structure of purkinji cells and glial cells are normal as compared to control group.

to antioxidative action of phenolic groups of quercetin which could contain reactive oxygen species and prevented oxidative damage.

Further, chlorpyrifos treatment resulted in a significant decrease in muscular strength and locomotor activity of animals. These results indicate the adverse influence of chlorpyrifos on cognitive functioning and motor coordination of the brain as reflected by reduction in activity score and mean fall of time by animals on Rota-rod. Furthermore, number of falls recorded in chlorpyrifos treated animals was increased vis-a-vis normal animals thereby suggesting some loss in grip ability of chlorpyrifos treated rats. Earlier, studies have also shown the adverse effects of chlorpyrifos on locomotor activity of mice and rats [22,23]. The plausible reason is understandably due to interference of chlorpyrifos with cholinergic and dopaminergic system as seen in the present study and evidenced by increased level of acetylcholine as consequence of reduction in acetylcholinesterase activity.

Acetylcholinesterase activity is considered a standard biomarker to study neurotoxic effects of pesticides. Chlorpyrifos causes inhibition of enzyme acetylcholinesterase that leads to accumulation of acetyl choline which consequently prevents conduction of nerve impulse [24,25]. In our study, quercetin supplementation to chlorpyrifos treated animals has resulted in decreasing the level of acetylcholine and increasing the activity of acetylcholinesterase which is arguably due to antioxidative potential of quercetin that checks the onslaught of reactive oxygen species generated by metabolism of chlorpyrifos [26,27]. In the present study, we observed some histoarchitectural disruptions as a consequence of damage inflicted by reactive oxygen species produced due to chlorpyrifos intoxication; however, these changes were mitigated by supplementation of quercetin.

CONCLUSSION

The present study concludes that quercetin has the potential to be used as prophylactic intervention during chlorpyrifos induced neurotoxicity.

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Conflicts of interest

There are no conflicts of interest

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HOW TO CITE THIS ARTICLE

Fereidounni S, Dhawan DK. Understanding the role of quercetin during neurotoxicity induced by Chlorpyrifos. J Phytopharmacol 2018; 7(1):33-39.