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Study of Protective Effect of Curcumin and Quercetin Against Subacute Toxicity of Fipronil in Rats

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Fipronil is belonged to phenyl pyrazole class of pesticides, used in the veterinary, public health, and agricultural fields to control a variety of pests. Numerous researchers have looked into the possibility that long-term exposure to fipronil causes liver and renal disease. It has been shown that curcumin and quercetin provide protection against the toxicity caused by numerous pesticides. The purpose of our study was to investigate the possible preventive role of quercetin and curcumin in hepatic and renal damage caused by fipronil. The rats were divided into five groups, with six rats in each group. Group I was not given any medication and treated as control, while rats of treatment groups were orally administered with the fipronil at dose 10 mg·kg^{-1}b.wt to group I, fipronil and curcumin (10 mg·kg^{-1}b.wt +100 mg·kg^{-1}b.wt) to group III, fipronil and quercetin (10 mg·kg^{-1}b.wt +100 mg·kg^{-1}b.wt) to group IV and combination of fipronil, curcumin and quercetin (10 mg·kg^{-1}b.wt +100 mg·kg^{-1}b.wt +100 mg·kg^{-1}b.wt) to group V. After exposure, biochemical markers were measured on days 0, 14, and 28th day of study period. Body weight of rats significantly decreased throughout the course of 28 days of exposure to fipronil. Hepatic and renal damage caused by fipronil was indicated by significant increase in the serum levels of AST, ALT, ALP, LDH, BUN, and creatinine, which were recorded at different intervals during the study period. Nevertheless, the negative effects of fipronil were significantly reduced by supplementing with curcumin and quercetin, both separately and together. This was demonstrated by a considerable drop in the raised level of serum biochemical markers. The current study concludes that quercetin and curcumin may function as effective protective agents against toxicity generated by fipronil.

Keywords: Fipronil, Flavonoid, Protective effect, Rats, Turmeric

Introduction

Insecticides are substances that are used to eliminate insects pests in livestock and agriculture industry and public health sector. The insecticides contribute indirectly to economic growth in agriculture and the livestock industry, but, their judicial use is also essential. They alter ecosystem components by their toxicity potential as well as toxic to man and animals. Fipronil is a class of phenyl pyrazole pesticide that is categorized by World Health Organization (WHO) as class II moderately hazardous pesticide.[1] It is used to control various types of pests in agriculture, public health, and livestock sector.[2] It is shown to act effectively on pests that have become nonresponsive to the commonly used insecticides.[3] Fipronil blocks inhibitory action of GABA by binding noncompetitively to $GABA_A$-gated chloride channels in the central nervous system of insects, that leads to death of insects by causing hyperexcitation and paralysis.[4,5] Fipronil is used extensively in home applications, veterinary care, and agriculture, which increases the likelihood of contamination of food, water, and air as well as exposure of humans, domestic animals, and the environment.

Furthermore, fipronil is also reported to produce changes in hematological, biochemical, oxidative stress and histopathological parameters in various studies during long-term exposure in experimental animals.[6–8] However, no antidote is available for neutralizing its toxicity. Therefore, there is a need to find out some remedial agents which are of natural origin that may attenuate the toxic effects of fipronil.

Curcumin is a polyphenolic chemical that is extracted from turmeric (*Curcuma longa*). In addition to its antioxidant action, it also has anti-microbial, anti-tubercular, anti-cancer, hepatoprotective, neuroprotective, nephroprotective, anti-diabetic, anti-inflammatory, antirheumatic, and antiviral properties.[9,10] A flavonoid called quercetin can be found in various fruits and vegetables. In addition to its biological properties as an antioxidant, it also has

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hepatoprotective, neuroprotective, cardioprotective, anti-inflammatory, reproductive system-protective, antiviral, anticancer, antibacterial, and anti-obesity properties.[11–13]

Previous studies have shown that quercetin protects against pyrethroides, organophosphate, and neonicotinoids-induced toxicity.[10,14,15] In a similar way, curcumin has also been demonstrated to be efficacious against pyrethroids, neonicotinoids, and organochlorine poisoning.[10,16,17] On the other hand, no research could be found on the ability of quercetin and curcumin to protect against fipronil toxicity. Thus, the aim of this study was to assess how well quercetin and curcumin guard against the toxicity caused by fipronil.

Material and Methods

Experimental Animals

Thirty male Wistar albino rats (6–8 weeks) weighing 150–200 gm were obtained from animal house of Veterinary college, Mhow, Indore (M.P.) The animals were housed in a room maintained under a 12/12 h light– dark cycle, an ambient temperature of 23–30°C with a relative humidity of 45 (±15)%. Animals were provided with food with free access standard pellet diet and water *ad libitum*. All rats were housed for duration of 1 week for acclimatization before initiation of the experiments. The maintenance of experimental rats and all the procedures implemented are in accordance with standard guidelines issued by CPCSEA followed with approval of the Institutional Animal Ethics Committee (IAEC) of the institute.

Chemicals

Fipronil (Trade name frontline) was obtained from local market and curcumin and quercetin from S.V. agro foods limited, Mumbai (Maharashtra) India.

Dose and Administration

Fipronil was administered orally at dose rate of 10 $mg{\cdot}kg^{-1}$b.wt (1/10th of LD_{50} of fipronil) and curcumin and quercetin at dose rate of 100 $mg{\cdot}kg^{-1}$b.wt.[10] of each for 28 days.

Experimental Design

After acclimatization to the laboratory conditions, the animals were randomly divided into five groups (6 rats each) placed in individual cages and classified as follow:

Group I (**normal control group**): Rats received no drugs, served as control.

Group II (**FPN treated group**): Rats received fipronil at dose rate of 10 $mg{\cdot}kg^{-1}$b.wt. orally daily for 28 days.

Group III (FPN+ CUR treated group): Rat received fipronil at dose rate 10 $mg{\cdot}kg^{-1}$b.wt. and curcumin at 100 $mg{\cdot}kg^{-1}$b.wt. orally daily for 28 days.

Group IV (FPN+QUER treated group): Rat received fipronil at dose rate 10 $mg{\cdot}kg^{-1}$b.wt. and quercetin at 100 $mg{\cdot}kg^{-1}$b.wt. orally daily for 28 days.

Group V (**FPN+CUR+QUER treated group):** Rat received fipronil at dose rate 10 $mg{\cdot}kg^{-1}$b.wt. and curcumin and quercetin at 100 $mg{\cdot}kg^{-1}$b.wt. of each orally daily for 28 days.

Collection of Blood Samples

Blood samples were collected from rats of different groups at 0, 14th and 28th day. About 1 mL blood was collected in sterile vial containing anticoagulant EDTA @ 2 $mg{\cdot}mL^{-1}$ of blood for haematology and remaining 1 mL of blood was collected in a centrifuge tube without anticoagulant for serum separation. After clotting of blood the vial was centrifuged @ 2000 rpm for 5 minutes and serum was collected in a sterile vial and was preserved at −20°C for biochemical estimation.

Serum Biochemical Parameters

Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), blood urea nitrogen (BUN) and creatinine were determined by method described by Teitz (1999).[18]

Statistical Analysis

The results of the experiment were presented as mean ± SE and subjected to one-way analysis of variance and Tukey's test for post hoc analysis and value of $p < 0.05$ was considered significant. SPSS software (Version 20.0) was used to perform statistical analysis.

Results and Discussion

Signs of Toxicity

Rats of control and all treatment groups didn't exhibit any signs of toxicity and mortality during exposure period. Kartheek and David (2018)[3] also reported similar findings, when rats were administered orally with fipronil @ 6.46 $mg{\cdot}kg^{-1}$b.wt. for period of 90 days.

Effect on Body Weight

The rats, that received only fipronil treatment showed a significant ($P < 0.05$) decrease in body weight on days 7, 14, 21, and 28 as compared to the values on day zero. However, when compared to values on "0" days, the difference in body weight at

different weeks was not significant in groups III, IV, and V (Fig. 1). Over the course of a 28-day treatment with fipronil, when body weight of rats was measured at different week intervals, it was found to be decreased. This may have been caused by the oxidative stress that the fipronil induced. However, the toxicity caused by the fipronil was lessened by the supplementation of quercetin and curcumin alone; the combination of the two nutrients had a greater effect on the recovery of body growth rate. However, body weight of rats did not change significantly when they were given fipronil orally for 45 days at a dose rate of 2 $mg \cdot kg^{-1}$b.wt.[8] The deviation in results from our study may be due to administration of lower dose of fipronil to rats.

Effect on Biochemical Parameters

Liver Function Biomarkers

Significant ($P < 0.05$) elevation in levels of both, AST and ALT was observed following fipronil exposure (group II) on 14th and 28th day, and in groups III, IV and V, on 28th day of exposure compare to '0' day values and when AST and ALT levels were compared with untreated (control) group on 28th day, values were increased to 110.18% and 69.7% in fipronil treated group, respectively, whereas, it was

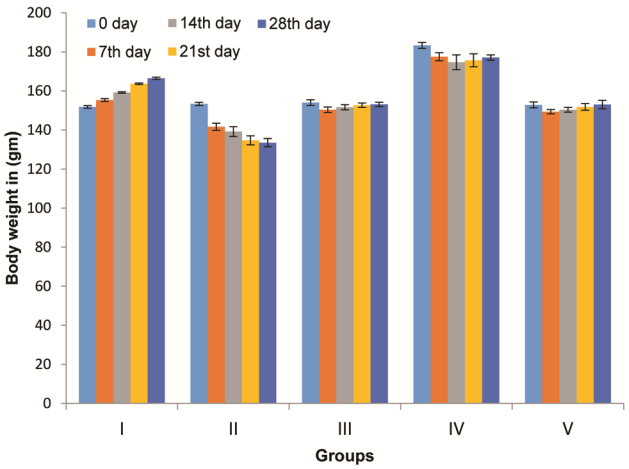

Fig. 1 — Changes in body weight (gm) in rats of different groups at 0, 7th, 14th, 21st and 28th day of exposure

increased by 42.32, 65.32 and 25.13% AST and 19.21, 22.18 and 9.40% in ALT level in groups III, IV and V respectively (Table 1 and 2).

Activity of ALP increased significantly ($P < 0.05$) in groups II, III and IV at 14th and 28th day of application compare to value of '0' day, and in group V at 28th day, it showed significant difference with '0' day value, ALP activity in groups II. III. IV and V was increased by 156.42, 64.52, 94.5 and 60.35%, respectively, when compared with value of control group on 28th day (Table 3). Significant ($P < 0.05$) rise in LDH level was found in group II, III, IV and V at 14th and 28th day of application compare to '0' day values and when compared with control group on 28th day, LDH level was increased to 55.59, 22.43, 25.22 and 13.82% respectively in groups II, III, IV and V, respectively (Table 4). Significant elevation of serum marker enzymes; ALT AST, ALP and LDH, indicated fipronil induced liver damage. Similar findings were recorded in previous studies also.[6,8,19]

Serum marker enzymes, like ALT, AST, ALP, and LDH are involved in detoxification procedures, metabolism, and the creation of energy macromolecules for several vital tasks and they are specific markers of liver injury. Liver dysfunction leads to increase in level of these enzymes. Hepatocelluar necrosis may cause an increase in LDH activity.[8] ALP is a cytoplasmic marker enzyme, used to assess tissue and cell damage caused by toxic compounds.[20]

Curcumin and quercetin are plant based chemicals which possess antioxidant and cyto-protective activities.[10] The elevated levels of ALT, AST, ALP, and LDH were significantly reduced by co-administration of curcumin and quercetin. Both the herbal agents, alone and together, demonstrated their action in fipronil toxicity as protective agents. Al-Ananay *et al.* (2015)[(20)] and Sharma *et al.* (2018)[(10)] also observed ameliorative effect of curcumin in nicotine induced hepatotoxicity and in reproductive impairment caused by deltamethrin and cypermethrin respectively, alone and in combination, in male rats.

Table 1 — Effect of FPN, FPN+ CUR, FPN+QUER and FPN+CUR+QUER exposure on Aspartate aminotransferase activity (IU/L) at 0, 14th and 28th day in rats

Groups	0 day	14th day	28th day	Percent increase
I	47.57 ± 2.05^{a}	48.50 ± 2.79^{a}	49.45 ± 2.57^{a}	—
II	52.62 ± 1.70^{c}	81.74 ± 4.53^{b}	104.33 ± 3.64^{a}	110.98
III	51.83 ± 1.30^{b}	65.16 ± 2.21^{a}	70.38 ± 1.71^{a}	42.32
IV	68.64 ± 3.35^{b}	70.80 ± 1.98^{b}	81.95 ± 2.57^{a}	65.32
V	54.26 ± 1.29^{b}	58.76 ± 1.39^{ab}	61.88 ± 1.26^{a}	25.13

*Mean values bearing common superscripts within rows (within groups) did not differ significantly ($P < 0.05$)

Curcumin and quercetin alone also have found to be effective against various pesticides induced hepatotoxicity in earlier studies.[21–24]

Kidney Function Biomarkers

Group II exhibited a significant ($P < 0.05$) increase in BUN values on days 14 and 28 when compared to the "0" day level. Additionally, groups III and IV demonstrated a significant ($P < 0.05$) difference in their BUN levels on day 28 when compared to the value on day 0. On the other hand, BUN values of group V at the 14th and 28th day of exposure did not significantly differ from the "0" day value. Groups II, III, IV, and V had increases in BUN levels of 105.71, 45.24, 64.35, and 23.67%, respectively on day 28 as compared to the control group (Table 5). Group II showed significant ($P < 0.05$) increase in creatinine levels on days 14 and 28 as compared to the values on 0th day, however, level of creatinine changed nonsignificantly in group III, IV and V at 14th and 28th day of exposure. The percent rise in creatinine in groups II, III, IV and V was 99.0, 29.41, 34.31 and 12.74, respectively, when compared with control group on 28th day (Table 6).

Mossa *et al*. (2015)[8] observed an increase in BUN and creatinine levels in rats given with fipronil, at a dose 2 $mg \cdot kg^{-1}$b.wt, orally for a duration of 45 days. Curcumin and quercetin supplements, both separately and together, have the potential to lessen kidney impairment by lowering increased BUN and creatinine levels. Curcumin was also found to have a protective effect against nephrotoxic effects of

Table 2 — Effect of FPN, FPN+ CUR, FPN+QUER and FPN+CUR+QUER exposure on Alanine aminotransferase activity (IU/L) at 0, 14th and 28th day in rats

Groups	0 day	14th day	28th day	Percent increase
I	40.95 ± 3.04^{a}	43.17 ± 1.99^{a}	42.15 ± 2.18^{a}	—
II	47.14 ± 1.97^{c}	64.43 ± 1.91^{b}	71.57 ± 1.58^{a}	69.70
III	42.85 ± 2.63^{b}	41.16 ± 2.49^{b}	50.25 ± 3.26^{a}	19.21
IV	33.01 ± 3.46^{b}	39.01 ± 3.11^{b}	51.50 ± 2.56^{a}	22.18
V	36.82 ± 1.65^{b}	49.44 ± 2.11^{a}	46.83 ± 2.20^{a}	9.40

*Mean values bearing common superscripts within rows (within groups) did not differ significantly ($P < 0.05$)

Table 3 — Effect of FPN, FPN+ CUR, FPN+QUER and FPN+CUR+QUER exposure on Alkaline phosphatase activity (IU/L) at 0, 14th and 28th day in rats

Groups	0 day	14th day	28th day	Percent increase
I	45.16 ± 2.09^{a}	46.03 ± 1.28^{a}	45.53 ± 1.82^{a}	—
II	56.54 ± 0.83^{c}	81.15 ± 2.16^{b}	116.28 ± 0.84^{a}	156.42
III	46.50 ± 1.48^{c}	58.38 ± 1.04^{b}	74.91 ± 1.58^{a}	64.52
IV	54.71 ± 1.18^{c}	76.82 ± 2.17^{b}	88.56 ± 1.96^{a}	94.50
V	60.06 ± 2.32^{b}	66.19 ± 1.78^{ab}	73.01 ± 1.81^{a}	60.35

* Mean values bearing common superscripts within rows (within groups) did not differ significantly ($P < 0.05$)

Table 4 — Effect of FPN, FPN+ CUR, FPN+QUER and FPN+CUR+QUER exposure on Lactate dehydrogenase activity (IU/L) at 0, 14th and 28th day in rats

Groups	0 day	14th day	28th day	Percent increase
I	219.33 ± 1.80^{a}	220.33 ± 1.02^{a}	220.66 ± 1.47^{a}	—
II	211.83 ± 1.72^{c}	288.66 ± 2.67^{b}	343.33 ± 2.16^{a}	55.59
III	216.66 ± 0.95^{c}	237.16 ± 3.40^{b}	270.16 ± 1.57^{a}	22.43
IV	215.50 ± 2.09^{c}	237.50 ± 1.66^{b}	276.33 ± 1.80^{a}	25.22
V	215.00 ± 1.15^{c}	231.50 ± 1.11^{b}	251.16 ± 1.40^{a}	13.82

*Mean values bearing common superscripts within rows (within groups) did not differ significantly ($P < 0.05$)

Table 5 — Effect of FPN, FPN+ CUR, FPN+QUER and FPN+CUR+QUER exposure on level of Blood urea nitrogen ($mg \cdot dL^{-1}$) at 0, 14th and 28th day in rats

Groups	0 day	14th day	28th day	Percent increase
I	38.16 ± 2.26^{a}	41.58 ± 2.71^{a}	33.95 ± 4.22^{a}	—
II	31.05 ± 1.65^{c}	54.62 ± 3.17^{b}	69.78 ± 1.79^{a}	105.71
III	39.89 ± 5.59^{b}	45.31 ± 5.55^{ab}	49.31 ± 1.20^{a}	45.24
IV	41.61 ± 2.63^{b}	43.72 ± 0.58^{b}	55.75 ± 2.09^{a}	64.21
V	35.48 ± 3.92^{a}	37.45 ± 2.77^{a}	41.95 ± 4.21^{a}	23.56

*Mean values bearing common superscripts within rows (within groups) did not differ significantly ($P < 0.05$)

Table 6 — Effect of FPN, FPN+ CUR, FPN+QUER and FPN+CUR+QUER exposure on level of Creatinine (mg·dL^{-1}) at 0, 14th and 28th day in rats

Groups	0 day	14th day	28th day	Percent increase
I	1.31 ± 0.02^{a}	1.13 ± 0.23^{a}	1.02 ± 0.05^{a}	—
II	1.22 ± 0.07^{b}	1.45 ± 0.05^{b}	2.03 ± 0.04^{a}	99.01
III	1.03 ± 0.02^{a}	0.99 ± 0.07^{a}	1.32 ± 0.07^{a}	29.41
IV	1.13 ± 0.09^{a}	1.12 ± 0.06^{a}	1.37 ± 0.06^{a}	34.31
V	0.91 ± 0.04^{a}	1.08 ± 0.07^{a}	1.15 ± 0.06^{a}	12.74

*Mean values bearing common superscripts within rows (within groups) did not differ significantly ($P < 0.05$)

metribuzin and lindane in rats.[19,25] And a protective effect of quercetin against nephrotoxicity caused by thiamethoxam and organophosphate insecticide in rats have also been demonstrated.[14,15]

Conclusions

The present outcome suggested hepatic and renal toxicity potential of fipronil, as shown by alterations in biomarkers of liver and kidney function at present dose of fipronil, when administered for 28 days. However, co-administration of curcumin and quercetin, alone and in combination alleviated the toxic effects of fipronil by significantly decreasing the raised level of liver and kidney function biomarkers. The data also suggests that the combination of curcumin and quercetin may provide better protection than each alone. But the active chemicals present in curcumin and quercetin needs to be isolated and require further molecular study to make them patent as protective agents in fipronil toxicity. Also, proper precautions should be taken during application of fipronil in household sectors, veterinary and agriculture field and during occupational exposure.

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