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Ameliorating effect of curcumin against fipronil induced subacute toxicity in rats

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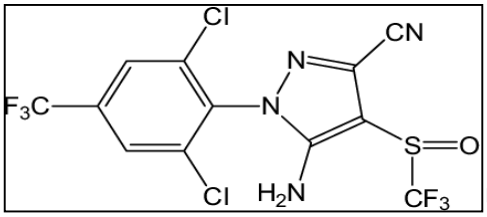
Abstract
Fipronil is a class of phenyl pyrazole pesticides used for the control of a wide range of agricultural, public health and veterinary pests. Curcumin, a polyphenolic compound obtained from turmeric (*Curcuma longa*) possesses a number of pharmacological activities. Present study was conducted to evaluate the ameliorative effect of curcumin against fipronil induced toxicity in rats. Rats were divided in to three groups, having six animals in each group. Group I was treated as control and group II and III received, fipronil (10 mg/kg b.wt) and fipronil + curcumin (10mg/kg b.wt +100mg/kg b.wt) respectively orally daily for 28 days. The results revealed that fipronil caused significant reduction in body weight of rats after 28 days of exposure compared to control group, which may be due to oxidative stress by induced by fipronil. Fipronil also significantly increased the serum level of AST, ALT, ALP LDH, BUN and creatinine on after 28 days of exposure indicated liver and kidney damage by fipronil. However supplementation of curcumin mitigated the adverse effects of fipronil by reducing the elevated level of serum biochemical parameters.

Keywords: Fipronil, curcumin, biochemical biomarkers, protective effect, rats

Introduction
Pesticides are heterogeneous group of substances used for preventing, destroying or repelling pests. Animals are infested by a number of parasitic insects and acarine species causing major economic losses in agriculture and livestock industry. Growing demand of pesticides and their indiscriminate application has led to environmental contamination globally, causing adverse health effects on non-target organisms. Fipronil is a class of phenyl pyrazole pesticides used for the control of a wide range of agricultural, public health and veterinary pests [1]. It has been found to be eff ective even against those pests which have gained resistance to the conventional insecticides [2]. Fipronil is an active ingredient of one of the popular ectoparasiticide veterinary products, Frontline, commonly used on dogs and cats to kill fleas and all stages of ticks and mites [3]. Because fipronil is widely used in agriculture, veterinary sector and household applications, the high rates of possible contamination (e.g., food, water and air) and exposure (e.g., human, domestic animals and environment) are increasing. Therefore, recent concerns for potential adverse public health effects of fipronil have been raised [1].
The toxic action of fipronil is due to its ability to act on gama aminobutyric acid receptor. Fipronil binds noncompetitively to $GABA_A$-gated chloride channels, thereby blocking the inhibitory action of GABA in the central nervous system, which lead to the death of insect by neuronal hyperexitation and paralysis [3, 4]. Fipronil induces hematological, biochemical, oxidative stress and histopathological changes during long-term exposure in rats [5-7].
Curcumin, a polyphenolic compound obtained from turmeric (*Curcuma longa*) is an excellent antioxidant and possesses a number of pharmacological activities such as anti-inflammatory, anti-microbial, anticancer, anti-tubercular, cardioprotective, anti-diabetic, hepatoprotective, neuroprotective, nephroprotective, antirheumatic and anti-viral activities [8, 9].
There has been report of protective effect of vitamin E and vitamin C [10], zinc [1], rosuvastatin [11], Ginseng [12] against fipronil induced toxicity. Curcumin has been found to effective against toxicity induced by pesticides of other groups like pyrethroides, neonicotinoids, and organochlorine [9, 13, 14]. However there are no report regarding protective effect of curcumin against fipronil induced toxicity.

Material and Methods
Experimental animals
Eighteen male Wistar albino rats (6-8 weeks) weighing 150-200gm were obtained from animal house of Veterinary college Mhow, Indore (M.P.) The animals were housed in a room



[15]

Chemical structure of fipronil

Dose and administration

Fipronil was administered orally at dose rate of 10 mg/kg b. wt (1/10th of $LD_{50,}$ [15] and curcumin at 100 mg/kgb. wt of each for 28 days.

Collection of blood samples

Blood samples were collected from rats of different groups at 28th day of study from tail vein with the help of 1ml tuberculine syringe. About 2ml blood was collected 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 ºC for biochemical estimation.

Serum biochemical parameters

Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydogenase (LDH), blood urea nitrogen (BUN) and creatinine were determined by method described by Teitz, [16].

Experimental Design

After acclimatization to the laboratory conditions, the animals were randomly divided into three 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 (**Fipronil exposed group**): Rats received fipronil at dose rate of 10 mg/kg b. wt. orally daily for 28 days.

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

Statistical analysis

Data were reported as mean ± SE. The data were subjected to one-way analysis of variance and further subjected to Tukey's test for post hoc analysis by defining the significance level at $p<0.05$. All statistical analyses were performed using SPSS software (Version 20.0).

Results

Signs of toxicity

No mortality or signs of toxicity were recorded in rats of group I, II and III during study period. No mortality or severe clinical sings of toxicity were observed in rats when fipronil was given @ 32.33, 12.12 and 6.46 mg/kg b.wt. orally for 90 days [2].

Effect on body weight

Body weight of animal in control group increased significantly, but it was significantly in reduced in fipronil treated group after 28th day of exposure, when compared with control group. However in fipronil and curcumin treated group, body weight differed nonsignificantly with the Control. Group but it was significantly higher than the fipronil treated group (Table 1).

Table 1: Effects of fipronil, fipronil and curcumin on body weight of rats after 28 days of treatment.

Groups	Control	FPR	FPR+CUR
Body Weight (g)	166.50±0.60[b]	133.50±2.10[a]	153.13±1.07[b]

FPR: Fipronil, FPR+ CUR: Fipronil + curcumin

Values are given as mean + SE for group of 6 animals each
Mean values with dissimilar superscript (ab) in a row differed significantly at $p<0.05$ level

Effect on biochemical parameters

There was significant increase in the level of ALT, AST, LDH, ALP, BUN and creatinine in fipronil only treated group after 28th day of exposure as compared to control group. Also in group treated with fipronil plus curcumin, the level of biochemical parameters was significantly increased when compared with control group, however, the values were much lower than the fipronil treated group and differed significantly (Table 2)

Table 2: Effects of fipronil, fipronil and curcumin on biochemical parameters of rats after 28 days of treatment

Parameters	Control	FPR	FPR+CUR
AST	49.45±2.57[a]	104.33±3.64[b]	70.38±1.71[c]
ALT	42.15±2.18[a]	71.57±1.58[c]	50.25±3.26[b]
ALP	45.53±1.82[a]	116.28±0.84[c]	74.91±1.58[b]
LDH	220.66±1.47[a]	343.33±2.16[c]	270.16±1.57[b]
BUN	33.95±4.22[a]	69.78± 1.79[c]	49.31±1.20[b]
Creatinine	1.02±0.05[a]	2.03±0.04[b]	1.32±0.07[a]

FPR: Fipronil, FPR+ CUR: Fipronil + curcumin

Values are given as mean + SE for group of 6 animals each.
Mean values with dissimilar superscript (abc) in a row differed significantly at $p<0.05$ level.

Discussion

Increase in body weight of rats in control group indicates normal weight gain of rats but in fipronil group, the body weight of rats was decreased after 28 days of treatment which may be due to oxidative stress induced by fipronil. On the other hand supplimentation of curcumin, attenuated the fipronil induced toxicity. Body weight of rats did not change significantly, when administered with fipronil at dose rate 2mg/kg b. wt, orally for 45 days [1, 7]. The variation in results of present study may be due to higher dose of fipronil.

The results of the study also indicated that fipronil induced liver and kidney damage in treated rats at dose rate 10 mg/kg b.wt. When administered daily for 28 days, as shown by significant increases in serum marker enzymes AST, ALT, ALP, LDH, BUN and creatinine Our findings are in accordance with the previous studies [7, 11, 12, 17].

AST, ALT, ALP and LDH are mainly used in the evaluation of hepatic damage. Transaminases (AST and ALT) play an important role in amino acids catabolism and biosynthesis. They are responsible for detoxification processes, metabolism and biosynthesis of energetic macromolecules for different essential functions and used as specific indicators for liver damage. The increase in these enzymes may be due to liver dysfunction and disturbance in the biosynthesis of these enzymes with alteration in the permeability of the liver membrane takes place. The elevation in LDH activity may be due to the hepatocelluar necrosis and leakage of the enzyme into the blood [7, 12]. Assay of ALP can be used for the prognosis of liver and lung disorder. ALP, cytoplasmic marker enzyme,

is a known indicator of cell and tissue damage by toxic compounds [18].

Curcumin is a phytochemical with proven antioxidant and cyto-protective activities [9]. Co-administration of curcumin decrease the elevated level of AST, ALT, ALP, LDH indicating their protective effect against fipronil induced toxicity. Curcumin has been reported to produce ameliorative effect against deltamethrin and cypermethrin induced reproductive impairement and against nicotine induced liver toxicity in male rats and against various other pesticides induced toxicities in previous studies [18-21].

Supplementation of curcumin may also reduce the renal damage by inducing decline in BUN and creatinine level. Curcumin has been observed to produce ameliorative effect against lindane induced nephrotoxicity in rats [14].

Conclusion

From the present study it can be concluded that fipronil induced liver and kidney damage, as evidenced by changes in liver and kidney function biomarkers, when administered at dose rate of 10 mg/kg b.wt. orally for 28 days. Co-administration of curcumin ameliorated the toxic effects of fipronil by reducing the elevated level of biochemical parameters. The finding suggest that curcumin produced protective effect against fipronil induced subacute toxicity by mitigating the adverse effects of fipronil.

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