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# Hepatorenal protective action of curcumin against chlorantraniliprole-induced subacute exposure in Wistar rats

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## ABSTRACT

**Background:** Chlorantraniliprole is a widely used anthranilic diamide insecticide considered relatively safe for non-target organisms; however, prolonged exposure may induce hepatic and renal toxicity. Curcumin, a natural polyphenolic compound derived from *Curcuma longa*, possesses potent antioxidant and tissue-protective properties. **Objective:** The present study was undertaken to evaluate the ameliorative potential of curcumin against chlorantraniliprole-induced hepato-renal toxicity following 28 days of oral exposure in Wistar rats. **Materials and Methods**: Forty adult male Wistar rats were randomly divided into five groups (n=8). Group A served as the normal control and received distilled water, while Group B received corn oil as vehicle control. Group C was administered curcumin (100 mg/kg), Group D received chlorantraniliprole (250 mg/kg), and Group E received chlorantraniliprole (250 mg/kg) along with curcumin (100 mg/kg) orally for 28 days. Liver and kidney function biomarkers were estimated, followed by histopathological examination of hepatic and renal tissues. **Results:** Chlorantraniliprole administration caused marked alterations in liver and kidney function biomarkers. AST and ALT levels increased from 91.25±7.12 U/L and 48.62±3.34 U/L in the control group to 122.50±8.10 U/L and 65.50±7.09 U/L, respectively, in chlorantraniliprole-treated rats. Similarly, blood urea nitrogen (BUN), creatinine, and uric acid levels increased to 78.13±13.81 mg/dl, 0.83±0.06 mg/dl, and 1.38±0.18 mg/dl, respectively, compared to control values of 37.25±8.22 mg/dl, 0.73±0.03 mg/dl, and 1.08±0.10 mg/dl. Histopathological examination revealed congestion, bile duct epithelial proliferation, hepatocellular degeneration, necrosis, and periportal fibroplasia in the liver, while kidneys showed congestion, focal hemorrhage, glomerular cellular proliferation, tubular dilatation, and tubular degeneration. Co-administration of curcumin significantly ameliorated these alterations, reducing AST and ALT levels to 114.13±6.67 U/L and 59.12±4.03 U/L, respectively, and improving renal biomarkers and tissue architecture toward normal. **Conclusion:** The findings of the present study demonstrate that curcumin exerts protective effects against chlorantraniliprole-induced hepato-renal toxicity, possibly through its antioxidant and free radical scavenging properties. Curcumin may therefore serve as a promising therapeutic agent for mitigating pesticide-induced organ damage.

**Keywords:** Chlorantraniliprole, Curcumin, Hepatotoxicity, Nephrotoxicity, Histopathology, Wistar rats.

## INTRODUCTION

Chlorantraniliprole belongs to Ryanodine receptor blocker [1,2] and can be used as alternate of organophosphate, organochlorine, carbamates, pyrethroids and neonicotinoids insecticides due to low toxic effect to non-target organisms such as birds, mammals, earthworms etc. [3-6]. Chlorantraniliprole selectively binds to insect nicotinic acetylcholine receptors and has very less affinity for mammalian [7,8], non-target insects and vertebrates to RyR [9-12]. Following ingestion/contact by insect it increases the release of calcium from sarcoplasmic reticulum into the cytoplasm as a result impairment in muscle contraction regulatory activity leading to feeding cessation, lethargy, paralysis, and death of target organisms [1]. This type of calcium-induced muscle-contraction mode of action is selective toxicity for insect ryanodine receptors. However, aquatic animals (fish) are susceptible to toxic effect [13] but Daphnia magna is highly susceptible to toxic effect of Chlorantraniliprole [14].

It has been observed that RyR plays a vital role in $Ca^{2+}$ signaling in the body, which is responsible for its effects on mammal's tissues. According to [15], chlorantraniliprole come under category IV toxic compound (acute oral $LD_{50}$ i.e. 5000 mg/kg body weight), has no acute mammalian toxicity; no adverse short-term effects; no neurotoxic, immunotoxin, carcinogenic, genotoxic, or a developmental toxicant. It did not show effects on maternal or fetal rats and rabbits in oral exposure studies. Chlorantraniliprole is use on several agriculture crops such for control of moths, beetles, and caterpillars etc. [13].

Curcumin (diferuloylmethane) derived from the rhizome of *Curcuma longa L. (Zingiberacae* family), chemically-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione and a molecular weight of 368.38 [16]. It is most commonly called as turmeric powder, extensively use in ayurvedic medicine for centuries due to possesses variety of therapeutic properties including anti-oxidant, analgesic, anti-inflammatory, antiseptic [17]. The antioxidant mechanism of curcumin is attributed to its unique conjugated structure, which includes two methoxylated phenols and an enol form of β-diketone; the structure shows typical radical trapping ability as a chain-breaking antioxidant.

Several authors reported hepato and geno-protective action of curcumin against pesticide due to decreased the serum markers of liver function, lipid peroxidation, proinflammatory mediators and proapoptotic p53 expression, and DNA damage in hepatocytes, prevent alteration in enzymatic and non-enzymatic antioxidants defense mechanism and tissue structure in rats [18,19]. Based on availability of a few research data on hepato-renal protective potential of curcumin against chlorantraniliprole subacute exposure effect in rat, present study was conducted.

## MATERIAL AND METHODS

### Chemicals and Diagnostic kits

All chemicals and diagnostic kits used in the present study were of analytical grade and procured from standard commercial sources. Chlorantraniliprole (98% technical grade) was obtained from Wanhua Chemicals, China. Curcumin was procured from Molychem India (Cat. No. 31495; 10 g). Diagnostic kits for glucose, total cholesterol, triglycerides, HDL cholesterol, urea, uric acid, creatinine, total protein, albumin, total bilirubin, and direct bilirubin were purchased from ERBA Diagnostics India. Diagnostic kits for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were obtained from SPAN Diagnostics, India. Acetone AR, benzene AR, and xylene AR were procured from Molychem India.

### Experimental Animals

Adult male Wistar rats were obtained from Lab Animal Facility (LAR), ICAR-Indian Veterinary Research Institute (IVRI) Izatnagar-243122 and maintained under standard managemental conditions in the Small Animal House Facility, Department of Animal Biotechnology, College of Biotechnology, Sardar Vallabhbhai Patel University of Agriculture and Technology, Meerut-250110. Animals had free access to pelleted feed (Savion Software and Technologies, Meerut), clean and deionized drinking water. Daily light and dark cycle of 12 h was ensured. Before start of the experiment, an acclimatization period of fifteen days was allowed. All the experimental animals were kept under constant observation before and during the entire period of study. The study was approved from Institutional Animal Ethics Committee (IAEC Approval no. IAEC/SVPUAT/2024/137), COVAS, SVPUA&T, Meerut.

### Experimental Design

Forty male Wistar rats were included in current study and they were divided in five groups of eight animals each. Animals of different groups (C to E) was treated with curcumin, chlorantraniliprole alone and/or combination of both and while group A and B served as negative and vehicle controls, respectively. Details of the experimental design are summarized in Table 1.

**Table 1:** Group allocation and treatment schedule of experimental rats

| Groups | Treatment | Mode of administration | Duration of exposure |
|---|---|---|---|
| A | Normal control (n= 8) | Deionized water (Oral) | 28 days |
| B | Vehicle control (Corn oil) (n= 8) | Oral | |
| C | Rats treated with Curcumin @ 100 mg/kg; (n= 8) | Oral | |
| D | Rats treated with Chlorantraniliprole 1/20$^{th}$ of $LD_{50}$ @ 250 mg/kg; (n= 8) | Oral | |
| E | Chlorantraniliprole1/20$^{th}$ of $LD_{50}$ @ 250 mg/kg with Curcumin @100 mg/kg; (n= 8) | Oral | |

- $LD_{50}$ value of chlorantraniliprole is > 5000 mg/kg oral [13,15]
- Chlorantraniliprole and Curcumin was dissolved in corn oil

### BIOCHEMICAL PARAMETERS STUDIES

### Collection of Blood

Blood from experimental rats was collected on 29$^{th}$ day in EDTA tubes from inner canthus of eye through retro-orbital plexus puncture with the help of glass capillary tubes after overnight fasting [20] for determination biochemical parameters. Blood samples were centrifuged at 2500 rpm for 15 min. Plasma was separated and transferred into plastic vials and was stored at -20 ºC for biochemical parameters analysis.

### Blood Biochemical Studies

Different biochemical tests namely-total proteins, albumin, direct bilirubin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, uric acid and blood urea nitrogen (BUN) in plasma of different treatment group of rat samples was estimated by using the commercially available kits of ERBA and SPAN Diagnostics.

### Histopathological Studies

Liver and kidneys were collected in 10% formal saline and was processed as per standard procedure. Biefly, these organs were cut into small pieces, washing was done under running tap water overnight, dehydration of tissues was done into ascending grades of alcohol (50%, 70%, 80% and 90% ethanol for one h), absolute alcohol I and absolute alcohol II for 1 h, respectively. Thereafter, all the tissues were kept in acetone I and acetone II for 45 min, and fat was removed from the tissue by putting the tissues in Benzene I and Benzene II for 45 min each, respectively. Waxing was done in melted paraffin wax then blocking of tissue and cooling of tissue done in refrigerator. 5-6-micron thick sections of tissue were cut with the help of a microtome (SLEE 5062) and H&E (Hematoxylin & Eosin) staining helps in examination of tissue section in light microscope.

### Statistical Analysis

Statistical difference between respective means for various parameters was evaluated by using one way ANOVA followed by Tukey's multiple post hoc tests with the help of SPSS software 20. Comparisons were made among the treatment groups. Data was presented as Mean ± SE and significant difference was considered at $P<0.05$.

## RESULTS

### Effect of Curcumin on Liver Function Biomarkers Following Exposure of Chlorantraniliprole

Liver function marker parameters of rats of different treatment groups are presented in Table 2 revealed that no significant alteration was observed in total protein, albumin and globulin levels in rats of different treatment groups. However, total bilirubin level was higher in rats of chlorantraniliprole –alone exposed group and concurrent treatment of rats with chlorantraniliprole and curcumin reduced the total bilirubin level towards the value of rats of control group. Similarly, as compared to control group rats (A), direct bilirubin level in rats of chlorantraniliprole alone exposed group (D) was more and simultaneous treatment of rats of chlorantraniliprole and curcumin group (E) decreased the curcumin level towards the value of control group (A). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in rats of chlorantraniliprole group was moderately higher and co-treatment of rats with chlorantraniliprole and curcumin decreased the AST and ALT level.

### Effect of Curcumin on Kidney Function Biomarkers Following Exposure of Chlorantraniliprole

Kidney function biomarkers of rats of different treatment group are presented in Table 3 and revealed that BUN, creatinine and uric acid levels was moderately higher in rats of chlorantraniliprole alone exposed group further co-treatment of rats with chlorantraniliprole and curcumin decreased the level of BUN, creatinine and uric acid levels as the values observed in rats of control groups.

### Effect of Curcumin on Histology of Liver Following Exposure of Chlorantraniliprole

Histological alteration of liver of rats of different treatment groups following 28 days oral exposure of chlorantraniliprole and its amelioration by curcumin are presented in Figure 1. Microphotograph of liver of control group A showed normal histology with the presence of normal hepatocytes, bile duct and interconnected plates of epithelial cells. Chlorantraniliprole exposure in rats' liver showed congestion, proliferation of bile duct epithelium, and single cell necrosis & degeneration of hepatocytes and mild periportal fibroplasia (Stain H&E; 400X). Co-treatment of rats with chlorantraniliprole and curcumin improved in histoarchitectural of liver and showed moderate recovery having moderate congestion and normal hepatocytes (Stain H&E; 400X).

### Effect of Curcumin on Histology of Kidney Following Exposure of Chlorantraniliprole

Histological changes in kidneys of rats of different treatment groups following 28 days oral exposure of chlorantraniliprole alone and co-treatment of chlorantraniliprole and curcumin are presented in Figure 2. Microphotograph of renal tissue of group showing normal histology (Stain H&E; 100X) with the presence of glomerulus, proximal convoluted tubule and bowman capsule etc. Renal tissue of rats of chlorantraniliprole-alone exposed group showed congestion, focal hemorrhage, proliferation of meningeal cells of glomerulus, tubular dilatation, single cell necrosis and mild tubular degeneration (Stain H&E; 100X). Following concurrent treatment of rats of group E with chlorantraniliprole and curcumin showing ameliorative potential of curcumin as observed in the form of moderate improvement having mild congestion, mild increased glomerular cellularity and normal tubule.

**Table 2:** Effect of curcumin (100 mg/kg) on liver function parameters of rats of different treatment groups following 28 days oral exposure to chlorantraniliprole (250 mg/kg) alone and both in combination (curcumin (100 mg/kg) + chlorantraniliprole (250 mg/kg))

| Groups | Treatment | Total Protein (g/dl) | Albumin (g/dl) | Globulin (g/dl) | Total Bilirubin (mg/dl) | Direct Bilirubin (mg/dl) | AST (U/L) | ALT (U/L) |
|---|---|---|---|---|---|---|---|---|
| A | Control | 5.60±0.35a | 3.11±0.05a | 2.83±0.10a | 1.40±0.08a | 0.14±0.02a | 91.25±7.12a | 48.62±3.34a |
| B | Vehicle control (Corn oil) | 5.93±0.12a | 3.58±0.46a | 2.35±0.49a | 1.55±0.03a | 0.12±0.01a | 102.00±13.87a | 59.25±3.93a |
| C | Curcumin (100 mg/kg) | 6.20±0.33a | 3.93±0.16a | 2.29±0.37a | 1.39±0.11a | 0.11±0.03a | 102.37±12.28a | 48.50±2.41a |
| D | Chlorantraniliprole (250 mg/kg) | 5.77±0.11a | 2.90±0.28a | 2.86±0.30a | 1.58±0.09a | 0.17±0.01a | 122.5±8.10a | 65.50±7.09a |
| E | Chlorantraniliprole (250 mg/kg) + Curcumin (100 mg/kg) | 5.94±0.09a | 3.62±0.15a | 2.33±0.18a | 1.43±0.08a | 0.11±0.02a | 114.13±6.67a | 59.12±4.03a |

Values (mean ± SEM; n=8) bearing different superscripts in the same column differed significantly (P<0.05)

**Table 3:** Effect of curcumin (100 mg/kg) on kidneys function parameters of rats of different treatment groups following 28 days oral exposure to Chlorantraniliprole (250 mg/kg) alone and both in combination (curcumin (100 mg/kg) + chlorantraniliprole (250 mg/kg))

| Groups | Treatment | BUN (mg/dl) | Creatinine (mg/dl) | Uric acid (mg/dl) |
|---|---|---|---|---|
| A | Control | 37.25±8.22[a] | 0.73±0.03[a] | 1.08±0.10[a] |
| B | Vehicle control (Corn oil) | 42.00±5.67[a] | 0.78±0.08[a] | 1.20±0.09[a] |
| C | Curcumin (100 mg/kg) | 55.37±5.02[a] | 0.74±0.04[a] | 1.05±0.15[a] |
| D | Chlorantraniliprole (250 mg/kg) | 78.13±13.81[a] | 0.83±0.06[a] | 1.38±0.18[a] |
| E | Chlorantraniliprole (250 mg/kg) + Curcumin (100 mg/kg) | 70.63±13.73[a] | 0.73±0.04[a] | 1.31±0.19[a] |

Values (mean ± SEM; n=8) bearing different superscripts in the same column differed significantly (P<0.05)

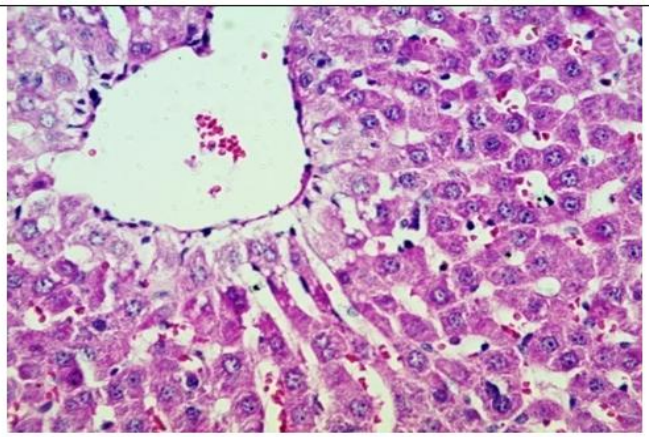

**Figure 1.1:** Microphotograph of liver of group-A showing normal histology (Stain H&E; 400X)

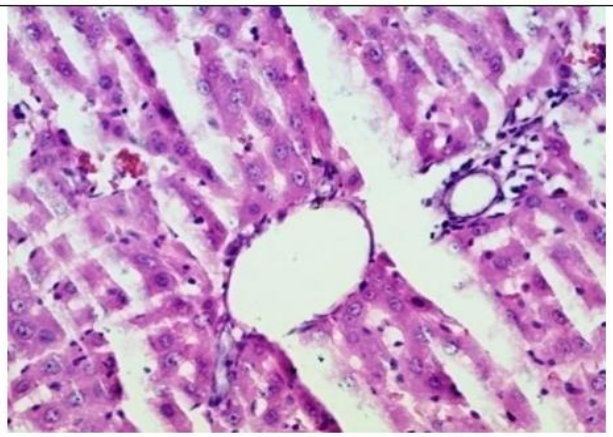

**Figure 1.2:** Microphotograph of liver of curcumin treated group C @ 100 mg/kg showing normal histology (Stain H&E; 400X)

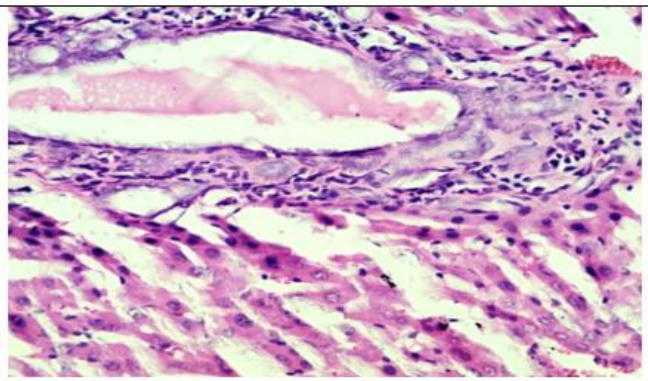

**Figure 1.3:** Microphotograph of liver of group-D (chlorantraniliprole @ 250 mg/kg) showing congestion, proliferation of bile duct epithelium, and single cell necrosis & degeneration of hepatocytes and mild periportal fibroplasia (Stain H&E; 400X)

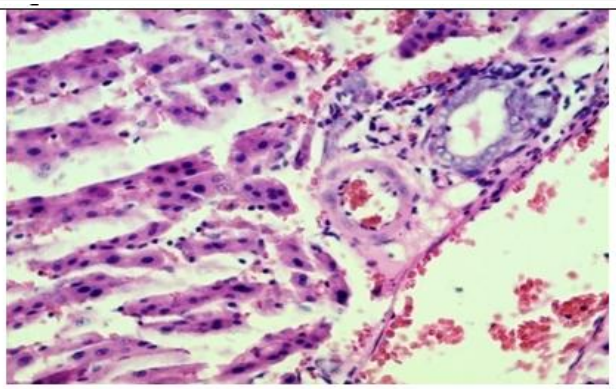

**Figure 1.4:** Microphotograph of Liver of group-E (Chlorantraniliprole @ 250 mg/kg + Curcumin @ 100 mg/kg) showing moderate recovery having moderate congestion and normal hepatocytes (Stain H&E; 400X)

**Figure 1:** Effect of curcumin (100 mg/kg) on histology of liver rats of different treatment groups following 28 days oral administration of Chlorantraniliprole (250 mg/kg) alone and combination of both (Chlorantraniliprole @ 250 mg/kg + Curcumin @ 100 mg/kg)

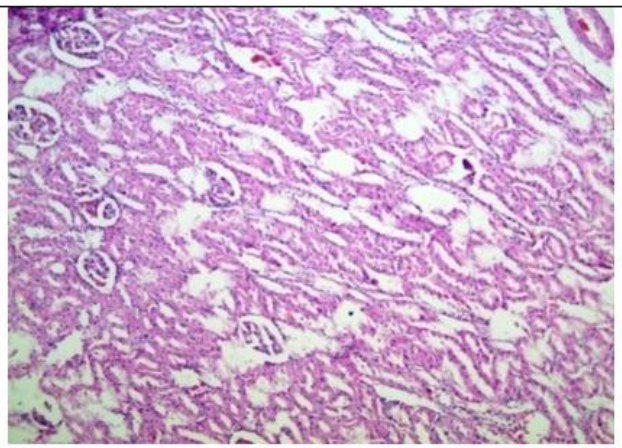

**Figure 2.1**: Microphotograph of renal tissue of group-A rats showing normal histology (Stain H&E; 100X)

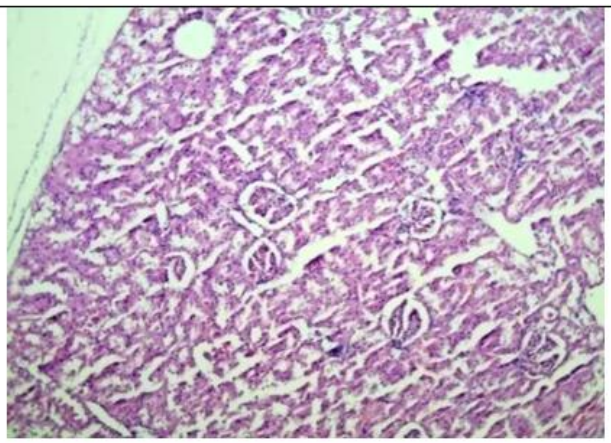

**Figure 2.2:** Microphotograph of renal tissue of curcumin treated showing normal histology (Stain H&E; 100X)

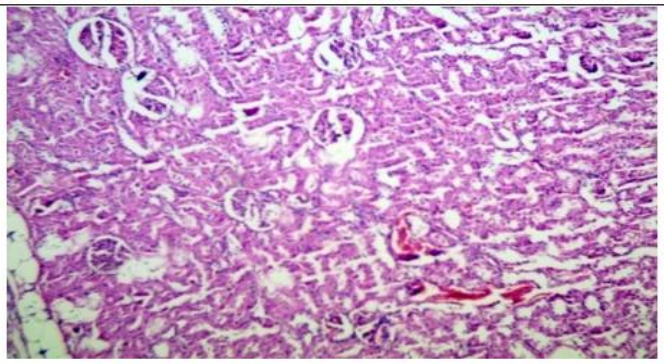

**Figure 2.3:** Microphotograph of renal tissue of group-D rats (Chlorantraniliprole @ 250 mg/kg) showing congestion, focal hemorrhage, proliferation of meningeal cells of glomerulus, tubular dilatation, single cell necrosis and mild tubular degeneration (Stain H&E; 100X)

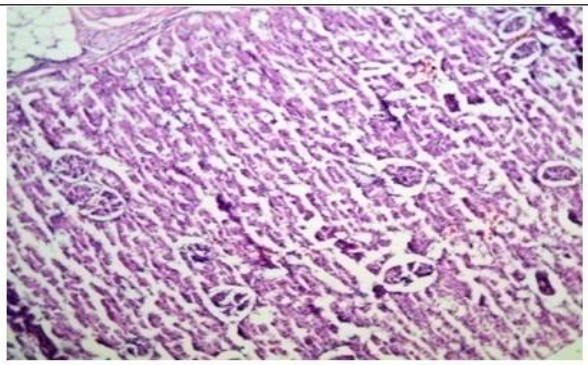

**Figure 2.4:** Microphotograph of renal tissue of group-E rats (Chlorantraniliprole @ 250 mg/kg + Curcumin @ 100 mg/kg) showing moderate improvement having mild congestion, mild increased glomerular cellularity and normal tubule (Stain H&E; 100X)

**Figure 2:** Effect of curcumin (100 mg/kg) on histology of kidneys rats of different treatment groups following 28 days oral administration of Chlorantraniliprole (250 mg/kg) alone and combination of both (Chlorantraniliprole -250 mg/kg + Curcumin – 100 mg/kg)

## DISCUSSION

Liver is most important vital organ of the body and involved in excretion of xenobiotics from body by detoxification mechanism. Thus, liver is more prone to toxic effect of xenobiotics. Result of albumin level in present study are in accordance of several authors following exposure of chlorantraniliprole, chlorpyrifos, imidocloprid and captan in rats [21-24]. While result of increased globulin level was corroborated with the observation of previous studies [21,25] following exposure of chlorantraniliprole and carbaryl which may be due to inflammation, acute infection and chronic liver disease induced by xenobiotic. Further increased levels of total and direct bilirubin levels indicated hepatic damaging effect of chlorantraniliprole and impaired excretion of bile which can be substantiated by histopathological examination. Bilirubin is a degradation product of haemoglobin (RBCs) and increased level of bilirubin in the present study may be due impairment in intra-hepatic excretion of unconjugated or conjugated bilirubin from hepatocytes [26]. Result of present study are in agreements of other studies [27-28] who reported significant to marked increase in total and direct bilirubin level in flubendiamide exposed rats.

AST present in mitochondria and cytosol of hepatocytes while presence of ALT is located in cytosol of hepatocyte [29]. Aspartate amino transferase activity (AST) and alanine aminotransferase (ALT) activities in rats of chlorantraniliprole group was increased which are in agreement of the observation of other researchers [30,31,21]. The increased in the level of AST and ALT in the present study is due to hepatocytes injury and hepatotoxic effect of chlorantraniliprole which can be further substantiated by histopathological examination. Similar observation was reported by Aprioku *et al.,* [32] following exposure of mancozeb in rats which may be due to loss of hepatocyte membrane integrity, leading increase membrane permeability in liver and resulting leakage of these enzymes in blood. Several studies reported that increased level of AST, ALT and liver function markers following exposure of pesticides [32-35]. Histological examination of liver of chlorantraniliprole exposed rats of group showed congestion, proliferation of bile duct epithelium, and single cell necrosis & degeneration of hepatocytes and mild periportal fibroplasia.

Kidneys is one of the important organs of the body involved in removal of waste, extra fluid and maintain the water and electrolyte balance of the body. Function of kidneys is judged by estimation of blood urea nitrogen (BUN), creatinine and uric acid level. In the present study, blood urea nitrogen level, creatinine and uric acid levels were increased in the chlorantraniliprole exposed rats which is due to decreased in water intake during the IVth week of exposure period leads to reduction in glomerular filtration which can be substantiated by histological examination. Increase in the values of these parameters are indicative of kidneys injury effect of chlorantraniliprole in rats and are in accordance with agreements of previous studies [31,21] while increased creatinine level may be due to impaired kidney function and nephrotoxic effect [36]. Similar observation was reported by Dutta K *et al*. [30] following coragen administration in rats where significantly increased the urea and creatinine level indicating adverse effect of coragen on kidney. [34] reported significant increase in serum urea level indicative of marked renal failure following oral exposure of pesticides. Result of present study are in agreement of Saoudi M *et al.* [37] who reported significant increase in urea, creatinine and uric level in chlorpyrifos exposed rats which may be due degradation of purines and pyrimidine and impaired kidney's function. Several authors reported increased level in blood urea nitrogen, creatinine and uric acid in rats following exposure of pesticides [38-40]. Histopathological examination of renal tissue of rats of chlorantraniliprole-alone exposed group showed congestion, focal hemorrhage, proliferation of meningeal cells of glomerulus, tubular dilatation, single cell necrosis and mild tubular degeneration.

Concurrent administration of curcumin and chlorantraniliprole increased the albumin and decreased the globulin, total and direct bilirubin level and activities of ALT and AST may be due to hepatoprotective effect of curcumin. Hepatoprotective effect of curcumin in the present study is due to prevention in oxidative damaging effect of chlorantraniliprole by curcumin in line with previous investigations [32,41]. who reported antioxidant restoration effect of curcumin in fenitrothion induced liver damage along with diminished expression of hepatic CYP1A1 and CYP1A2 levels and produced ameliorative effect of curcumin which can be further confirmed by histopathological examination. Co-treatment of rats with chlorantraniliprole and curcumin improved in histoarchitectural of liver and showed moderate recovery having moderate congestion and normal hepatocytes. Curcumin inhibits lipid peroxidation and acts as a chain-breaking antioxidant at the 3' position, has free radical-scavenging activity and down regulates the iNOS activity in macrophages, thus reducing the amount of reactive oxygen species (ROS) generated in response to oxidative stress.

Concurrent administration of curcumin with chlorantraniliprole decreases the BUN, creatinine and uric acid levels in rats suggesting reparative potential of curcumin against toxicity manifestation by chlorantraniliprole. Renal protective effect of curcumin was reported by Huang S *et al.* [42] may be due to curcumin involved in decreases in

BUN level and activation of miR-181a/PTEN axis against cisplatin-induced renal toxicity in mice. Result of present study are in agreement of findings of Aslanturk A *et al*. [43] who reported nephroprotective effect of curcumin against methomyl-induced nephrotoxic effect possibly due to inhibition of lipid peroxidation and improving antioxidant enzyme activities. Similar nephroprotective effect of curcumin was reported by Uzun MH *et al.* [44] against fipronil-induced nephrotoxic rats possibly due alteration in renal function markers and antioxidant enzyme activities. Co-administration of chlorantraniliprole and curcumin showing ameliorative potential of curcumin as observed in the form of moderate improvement having mild congestion, mild increased glomerular cellularity and normal tubule. Result of present study are in agreement of Aslanturk A *et al*. [43] who reported nephroprotective effect of curcumin may be due to inhibition of lipid peroxidation, free radical scavenging activity and antioxidant activity of curcumin provide ameliorative effect in renal tissue. Antioxidant properties of curcumin protect rats against parathion, paraquat, and diazinon induced damage and oxidative stress in hippocampus, myocardial ischemia and lung injury and liver, blood, and erythrocytes, respectively [45-47].

Moreover, antioxidant and free radical scavenging activity of curcumin has been proven to ameliorate cypermethrin-induced oxidative stress in liver, kidney and brain of Wistar rats [48,49].

## CONCLUSION

Therefore, result of present study evidently suggest that liver and kidneys are sensitive targets for toxic effects of chlorantraniliprole; and curcumin possesses some reparative potential against chlorantraniliprole as it improved in liver, kidney's function parameters and restored histological changes indicating ameliorative potential of curcumin.

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**Author Contributions**

AK was involved in concept, design, literature review and execution of research work; RM and AK conceptualised the manuscript; SC was involved in statistical analysis and in the data acquisition; VJ was involved in histopathology and examination of histological findings; JMV was involved in haematological examination. All authors have read and agreed to the published version of the manuscript.

**Data Availability Statement**

The data that support the findings of this study are available and will be made available upon request.

**Use of AI in Drafting of Manuscript**

The authors declare that they have not used any generative AI/AI-assisted technologies in the writing of this manuscript.

**Conflict of Interest**

The authors declared no conflict of interest.

**Financial Support**

None declared.

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