The Ameliorating Role of Geraniol Oil on Renal Toxicity Induced by Some Pesticides in Rats

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ABSTRACT

The Defensive impact of geraniol (GeoH) against renal oxidative injury and nephrotoxicity induced by beta-cyfluthrin, (β-Cyf), fipronil(FPN). and their combined effects on the male rats were investigated. Eight categories, each category of male rats were used contain six rats. Category I as control, Category 2 GeOH (100 mg/kg bwt in corn oil). Categories 3, 4 and 5 rats have presented a single daily oral dose of (FPN) fipronil (4.85 mg/kg bwt), (β-Cyf) beta-Cyfluthrin (19 mg/kg bwt)) and their combination. Categories 6, 7 and 8 rats have presented the same doses as Categories 3, 4 and 5 with GeOH (100 mg/kg) for 28 consecutive days, respectively. Rats which was exposed insecticides compared to control recorded significant decrease in body weight and rise in kidney weight. Treatment rats recorded significant renal function disruption by increase in uric acid and serum creatinine level. Also, insecticide-treated rats revealed renal oxidative damage was spotted in insecticide-treated rats through an increase in kidney lipid peroxidation (LPO) also, kidney appeared the decrease in antioxidant enzymes. Histopathological analysis of the kidney appeared that tubular destruction with multiple vacuolations, hyaline degeneration in glomeruli, and the thick arterial wall, and irregular glomerular lining in treated groups (FPN, β-Cyf, FPN + β-Cyf). In conclusion, the use of Geraniol (GeOH) seemed to be useful to rats, to a great extent by alleviation and decrease the damage sustained by insecticide exposure.

Keywords: Geraniol; fipronil; beta-cyfluthrin; nephrotoxicity; oxidative stress; histopathology

INTRODUCTION

There are many types of Pollution sources as the pesticides that contain a big group of dangerous chemicals which using for agricultural protection (Hardersen and Wratten, 1998). It is found Major target organs of pesticides are liver and kidney which causes damage and toxicity (Mansour and Mossa, 2010; Abdel Rasoul and Marei, 2016). Insecticides encourage the induction of reactive oxygen species (ROS) and causing damage to lipids, proteins, enzymes, carbohydrates and nucleic acids (Fraga et al., 1996; Kartheek and David, 2018). Cyfluthrin is a synthetic pyrethroid vastly used in agriculture against grasshoppers and pests. Cyfluthrin is also used in human hygiene (FAO, 1999). After its first use in 1987 in the USA. UU (EPA, 1987), studied its effect toxic in the environment and observed that it had genotoxic and cytotoxic effects on human lymphocytes (Ila *et al*., 2008), genotoxic effects on human mucosal epithelial cells (Tisch *et al.,* 2005) and DNA injury in fish (Marinowic *et al.*,2012). It has been discovered mutagenic and genotoxic effects in mammals by Some pyrethroid insecticides (Herrera and Laborda, 1998; Hour *et al*., 1998; Shukla and Taneja, 2002; Giri *et al*., 2002; Cavas and Ergene-Gozukara, 2003).

Fipronil (FPN, 5-amino-1-(2,6-dichloro-4-(trifluoromethylphenyl)-4-(trifluoro-methylsulfinyl) pyrazole-3-carbonitrile) is a phenylpyrazole insecticide which is a relatively new and massively used to kill insects that cause damage to the plant crops (Mcmahen *et al.,* 2015; Pisa *et al*., 2015). Around the world, FPN use to protect rice, cotton, sorghum, corn, cereals barley, oats, rye, triticale, wheat, grass, straw, and so on. FPN controls a broad spectrum of insects such as cockroaches, mosquito, lobster, termites, thrips, rootworms, ticks, and fleas in the larval and adult stages (Gunasekara *et al*.2007).

Although FPN showed lower toxicity in mammals than in insects, FPN was documented to have reverse effects such as the liver, thyroid, and influenced reproductive function in nontarget species (Ohi *et al*., 2004; Das *et al.,* 2006; Roques *et al.,* 2013). exposure rats to FPN led to the harm of the thyroid, liver, and kidney (Tingle *et al.,* 2003).

recently, essential oils have been used by researchers as free radical scavengers or antioxidants. (Choi *et al.,* 2000). Geraniol has many pharmacological effectiveness such as antimicrobial (Lorenzi *et al.* 2009), anticancer (Pattanayak *et al.* 2009), anti-lipid peroxidative (Chen and Viljoen 2010), and antioxidant (Tiwari and Kakkar 2009).

Therefore, this study aimed to evaluate the adverse effects of sub-chronic exposure to formulated FPN, β-Cyf and their combination on the oxidative damage and the renal toxicity. In addition, the efficiency of geraniol oil was studied for ameliorating harmful effect of these insecticides.

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MATERIALS AND METHODS

Animals

Male Wistar rats weighing 170 ± 5 g were obtained from the animal house, Faculty of Medicine, Alexandria University, Egypt. The local committee confirmed the design of the experiments and the protocol adapts to the guidelines of the National Institutes of Health (NIH). and put it in cages (6 rats / cage) in the laboratory animal at room temperature. water ad libitum every day until finish the experment, In a standard pellet diet. It has been acclimatized the rats for 1 week.

Chemicals

Geraniol (99% pure) was purchased from Acros Organics Company, New Jersey, USA. The fipronil commercial formulation (Fipral 5% SC) and beta-cyfluthrin (beta-s 10%) were provided by Agricontact Agricultural Service Company, Alexandria, Egypt. Chemicals and kits have been obtained from Bio-diagnostics Co., Dokki, Giza, Egypt. Other reagents used were of analytical grade. Solvents were of analytical grade.

Experimental design

It has been split rats into 8 groups every including 6 animals (6 rats/cage).

Category 1: Was given Corn oil and kept as a control.

Category 2: Was given 100 mg/kg GeOH in corn oil (0.5 ml/rat).

Category 3: Was given (1/20 LD_{50}) (Tomlin 2005), FPN at a daily dose of 4.85 mg/kg b.wt.

Category 4: Was given (1/20 LD_{50}) (Tomlin 2005), β-Cyf at a daily dose of 19 mg/kg b.wt.

Category 5: Was given FPN (4.85 mg/kg b.wt.) and β-Cyf (19 mg/kg b.wt.).

Category (6- 8): Was given 100 mg/kg GeOH in corn oil and the same doses of insecticides as in categories (3-5). It has been registrated the body weights for rats, during expermintal, and the doses modify according to the weight gaining weekly body. After completion of the treatment period, blood samples were centrifuged at 1500 ×g for 10 min and the serum was extracted and stored at -20 ºC for biochemical measurements by using Shimadzu UV- VIS Recording 2401 PC (Japan). It has been removed, cleaned and weighed the both kidneys for histological and biochemical evaluation. Samples are kept in ice-cold buffered saline (154 mM NaCl, 5 mM Tris–HEPES (Tris-HCl buffers and phosphates in PBS, pH 7.5). It was prepared 10% (w/v) homogenate in 0.1 M Tris–HCl buffer, pH 7.5, by using homogenizer Potter-Elvehejem. It has been centrifuged the homogenate at 3000 x g at 4 ºC for 15 min and it has been saved the supernatant in aliquots and stored at -20 ºC for testing protein concentration, lipid peroxidation (LPO) and antioxidant enzymes efficiency.

Measurement of biochemical parameters

It has been estimated total protein, creatinine, and uric acid according to the methods of (Gornall et al.,1949; Larsen, 1972; Barham andTrinder, 1972; Tietz, 1995), orderly.

Oxidative stress evaluation

Thiobarbituric acid reactive substances (TBARS) content is an indicator of lipid peroxidation in the kidney homogenate was measured by (Tappel and Zalkin,1959). Reduced glutathione content (GSH), a tripeptide (γ-glutamylcysteinyl glycine), in tissues was assayed by the method of Jollow et al. (1974) and the concentration expressed as a µmoles of GSH /mg protein.

Renal antioxidant enzymes:

Catalase assay (CAT): Catalase (CAT; EC 1.11.1.6) was estimated (Aebi, 1984) by examination the hydrolysis of H_2O_2 and the resulting reduced in absorbance at 510 nm over a 3 min period at 25C◦.

Assay of superoxide dismutase (SOD): Superoxide dismutase effectiveness (SOD; EC 1.15.1.1) was estimated (Nishikimi *et al.*, 1972).

Assays of glutathione peroxidase (GPx): Glutathione peroxidase (GPx) efficiency was determined using H2O2 as a substrate (Paglia and Valen-tine, 1987).

Histopathological studies

Histopathological has been checked according to (Bancroft et al., 1996). samples from kidney were fixed in 10% phosphate buffer formalin, dehydrated in alcohols and firmed in paraffin, and

checked by light microscopic.

Statistical analysis

The Statistical Package for Social Sciences ver. 21.0 were used. Analysis of variance (ANOVA) has been estimated by using one-way followed by Duncan's test for comparison between different treatment groups.

RESULTS

Marks of toxicity

During the experiment, it has not been detected death in any of the experimental categories. Rats in the control category and in geraniol (GeOH) treated group did not show any mark of toxicity. But, CPF and Cyr+CPF treated rats showed different degrees of clinical signs few minutes after dosing. The signs inclusive huddling, mild tremor and diarrhea. The

observed marks were related to the cholinergic crisis and an abnormal walk.

Body and relative kidney weights

Result, in (Table 1) cleared that there was no significant difference in body, absolute and relative kidney weights between GeOH and untreated rats. However, body weight was significantly decreased by 5.27%, 5.9% and 7.83% for FPN, β-Cyf and FPN + β-Cyf - treated groups, respectively. Relative kidney weight significantly raised by 12.3%, 17.9% and 20% for FPN, β-Cyf and FPN + β-Cyf - treated groups, respectively when compared to control. The treated with GeOH to pesticide-treated groups ameliorated the loss of body weight and the rise of relative kidney weight in pesticide-treated animals (Table 1).

Oxidative stress parameters.

The results cleared that FPN, β-Cyf and FPN + β-Cyf gave a significant increase ($p < 0.05$) in lipid peroxidation as evidenced by the increase in kidney tissue TBRAS levels by58.32, 66.62, and 74.68%, respectively when compared to the control category. However, using GeOH to treated rats reduced the augmentation in TBRAS levels to 44.2, 118.7 and 196.8% for FPN, β-Cyf and FPN + β-Cyf treated rats, respectively (Fig. 1A). Glutathione (GSH), in the reduced form (GSH), acts as one of the major detoxifiers in the body. A significant decrease of glutathione (GSH) level in kidney was evident in FPN, β-Cyf and FPN + β-Cyf treated groups by –54.8%, –61.6% and –73.3%, respectively when compared to control (Fig. 1A). However, co-administration of GeOH to treated rats ameliorated the decrease in kidney GSH levels to –46.2%, –30.5% and –55.8% for FPN, β-Cyf and FPN + β-Cyf treated rats, respectively (Fig. 1B).

Table 1. Effect of FPN and/or β-Cyf on body and relative kidney weights of rats and the role ameliorating of geraniol

Groups	Body weight			Weight absolute of kidney (g)	Weight relative of kidney (g/100g body weight)
	Initial (g)	Final (g)	% Change/week		
Control	165.62±0.63	195.57±1.92^{ab}	4.52±0.39^{a}	1.25±0.02	0.64±0.01^{d}
GeOH	168.25±0.83	200±0.82^{a}	4.71±0.03^{a}	1.23±0.01	0.61±0.01^{d}
FPN	170±1.22	185.25±1.7^{c}	2.78±0.36^{b}	1.36±0.04	0.73±0.02^{abc}
β-Cyf	165±0.71	184±0.81^{cd}	2.88±0.19^{b}	1.41±0.04	0.78±0.02^{ab}
FPN + β-Cyf	173±1.22	180.25±1.03^{d}	1.05±0.27^{c}	1.49±0.02	0.81±0.01^{a}
FPN + GeOH	166.75±1.43	197.25±0.47^{a}	4.58±0.32^{a}	1.36±0.03	0.68±0.01^{cd}
B-Cyf + GeOH	167.75±1.03	186.25±1.03^{c}	2.76±0.3^{b}	1.37±0.04	0.73±0.02^{abc}
FPN + β-Cyf + GeOH	173±1.22	191.50±0.95^{b}	2.68±0.32^{b}	1.38±0.02	0.72±0.01^{bc}

a, b, c, d Duncan's test, $p < 0.05$

FPN: Fipronil; β-Cyf: β- Cyfluthrin; GeoH: Geraniol

The percent of body weight change/week = [(final b .w t. – initial b .wt.)/ initial b .wt.]/no of weeks X 100

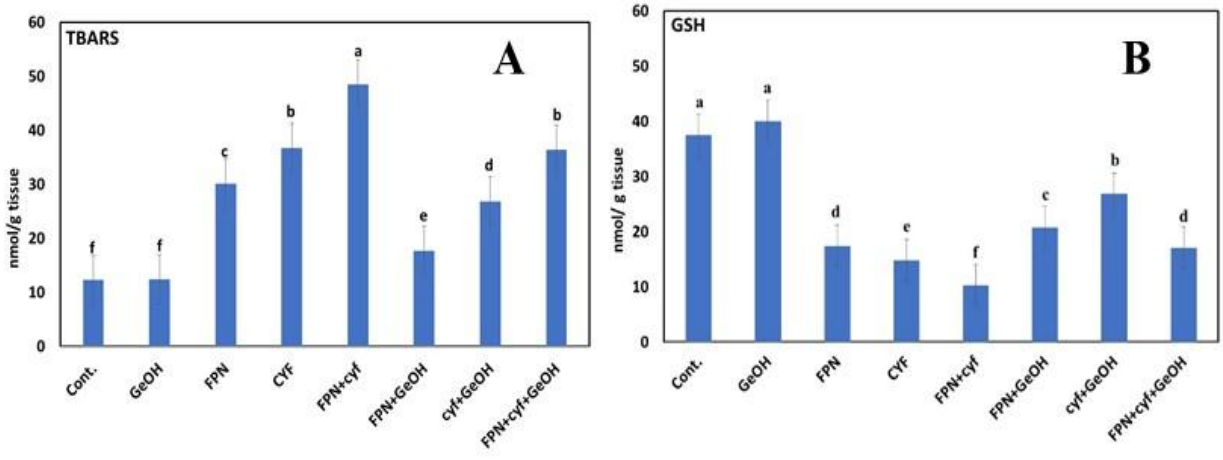

Fig.1. Effect of FPN and β-Cyf on oxidative stress by product TBARS (A) and kidney tissue GSH (B) of rat in the non-attendance and attendance of GeOH.

Markers of renal function

Results in Table 2 illustrated that no significant changes between the untreated control and GeOH treated in serum creatinine, uric acid, and total protein, while level of FPN, β-Cyf and FPN + β-Cyf treated rats were significant increase in creatinine 48.9%, 34.24% and 70.83 and uric acid 131.9%, 146.7% and 204%, respectively. But reduced by -15.3%, -18.15% and -23.3% in the total protein. There is amelioration in the level of Cre and uric acid due to using of GeOH to tested groups.

Effects on activities of kidney antioxidant enzymes

Results in Table 3 showed the effect of FPN, β-Cyf and FPN + β-Cyf treated rats on the activities of CAT, SOD, and GPx. There was damage in rats by the significant alteration in these enzymes when using subacute levels of the tested pesticides due to a state of kidney damage and extensive oxidative. GeOH alone has a significant variation in GPx and CAT effectiveness compared to control, while the effect of GeOH alone on SOD enzyme no significant difference compared to control. Also, therapy with GeOH had mitigated from the injury effect as it was more efficient with a significant improvement in oxidative stress markers and antioxidant enzymes.

Study of histopathological

The histopathological studies in the kidney are appeared in Figure 2 (A-I). the control category rats and GeOH-treated rats appeared that the normal tissue and intact glomeruli**.** However, there were abnormalities in the kidney of treated rats in glomeruli and tubular destruction with multiple vacuolations, hyaline degeneration in glomeruli, and the thick arterial wall, and irregular glomerular lining in (Figure 2B-I) compared to those of controls (Figure 2A). The major characteristic was finding the appearance of renal tissue with hypocellular, hemorrhagic and irregular glomerular lining, arterial wall its thick, congested dilated artery, and destructed glomeruli. However, treatment of the GeOH with FPN or β-Cyf showed clear amelioration with the compare to (FPN, β-Cyf and FPN + β-Cyf) alone.

Table 2. Effect of FPN, β-Cyf and their incorporation on serum creatinine, uric acid and total protein of male rat in the absence and presence of GeoH

Groups	Creatinine mg/dL	Uric Acid mg/dL	TP g/dL
Control	0.960 ±.021^{d}	3.98±0.120^{f}	7.44±0.062^{a}
GeOH	0.890±0.008^{d}	3.71±0.057^{f}	7.49±0.056^{a}
FPN	1.43±0.029^{b}	9.23±0.176^{c}	6.30±0.081^{c}
β-Cyf	1.46±0.042^{b}	9.82±0.102^{b}	6.13±0.062^{c}
FPN + β-Cyf	1.64±0.021^{a}	12.12±0.095^{a}	5.70±0.108^{d}
FPN + GeOH	1.21±0.053^{c}	7.17±0.081^{e}	6.76±0.042^{b}
B-Cyf + GeOH	1.20±0.038^{c}	7.58±0.077^{de}	6.85±0.021^{b}
FPN + β-Cyf + GeOH	1.38±0.041^{b}	7.90±0.334^{d}	6.10±0.040^{c}

a, b, c, d Duncan's test, $p < 0.05$

FPN: Fipronil; β-Cyf: β- Cyfluthrin; GeoH: Geraniol oil

Table 3. Effect of FPN, β-Cyf and their incorporation on antioxidant enzymes in kidney tissue of male rats in the absence and presence of GeOH

Treatments	SOD mU/mg protein	GPx mU/mg protein	CAT U/mg protein
Control	47.66±0.694^{a}	17.88±0.411^{b}	24.38±0.647^{b}
GeOH	49.33±1.177^{a}	20.66±0.771^{a}	26.60±0.647^{a}
FPN	26.98±0.844^{c}	12.78±0.146^{d}	13.79±0.615^{c}
β-Cyf	23.71±0.742^{d}	10.75±0.236^{e}	10.15±0.228^{f}
FPN + β-Cyf	15.99±0.353^{e}	8.36±0.334^{f}	8.85±0.230^{f}
FPN + GeOH	37.62±0.762^{b}	17.24±0.516^{b}	19.06±0.251^{c}
B-Cyf + GeOH	36.17±0.400^{b}	14.71±0.285^{c}	17.24±0.489^{d}
FPN + β-Cyf + GeOH	27.14±0.620^{c}	12.36±0.432^{d}	16.24±0.286^{d}

a, b, c, d Duncan's test, $p < 0.05$

FPN: Fipronil; β-Cyf: β- Cyfluthrin; GeoH: Geraniol oil

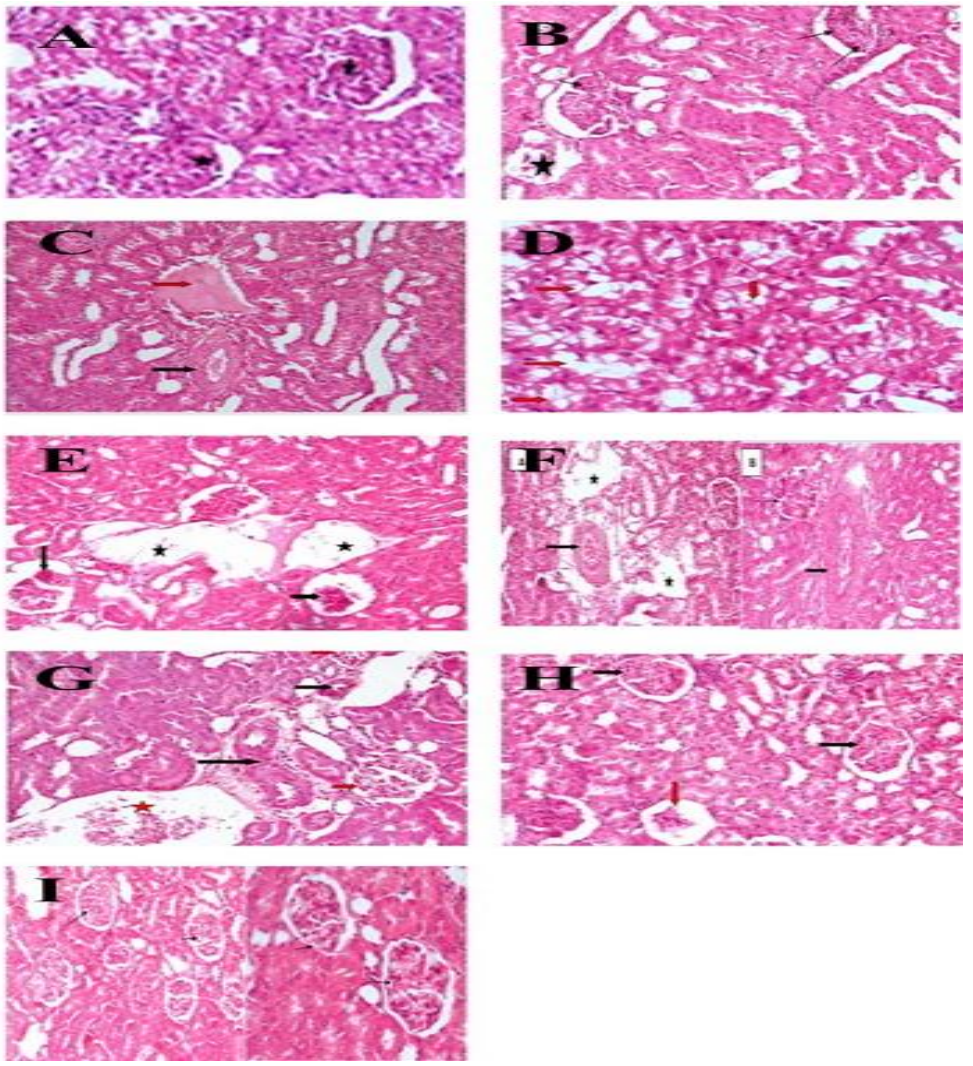

Fig. 2. A photomicrography of kidney tissue stained by haematoxylin and eosin (H&E 200). Control category [A] showing showing normal renal tissue with normal appearing glomeruli (star), FPN-treated group [B &C] showing renal tissue with hypocellular and hemorrhagic glomeruli (thin arrow), and one disturbed glomeruli (star) and hyaline degeneration in glomeruli (red arrow), and thick arterial wall (black arrow) (H&E 100), β -Cyf- treated group [D &E] showing tubular destruction with multiple vacoulation (red arrow) and destructed glomeruli (star), and hypocellular glomeruli (black arrow) (H&E 100), FPN & β-Cyf- treated category [F] showing thickened arterial wall (thick arrow), destructed glomeruli (star) and irregular glomerular lining (thin arrow) (H&E 100), GeOH & FPN - treated category [G] showing thickened arterial wall (black arrow), disturbed glomeruli (star) and partially appearing normal glomeruli (rad arrow) (H&E 100), GeOH & β-Cyf - treated group [H] showing three normal glomeruli (black arrow) and one disturbed glomeruli (rad arrow) (H&E 100), GeOH & FPN & β-Cyf treated category[I] showing normal glomeruliwith tiny vacoulation (arrow) (H&E 100, 200)

DISCUSSION

Renal toxicity occurs due to pesticides exposure and environmental pollutants. This work represents the ameliorating effect of kidney function by using GeOH with FPN, β-Cyf or their combination of FPN and β-Cyf. The results showed that a significant decrease in body weight perhaps due to the joint impact of cholinergic and oxidative stress. As well, the results showed the high in relative kidney weight (saafi *et al.*, 2011; Heikal *et al.*, 2012; Mehmet *et al.*, 2015; Abdel Rasoul and Marei, 2016 ; Turkmen *et al.*, 2019).

Results showed that FPN, β-Cyf and FPN + β-Cyf treatments caused oxidative stress in the kidney of male rats. There are deranged the integrity of cellular membranes cause various kidney injuries due to thiobarbituric acid reactive substances (TBARS) content. These results consent with (Yu *et al.,* 2008; Sadowska-Woda *et al.* 2010; Maran *et al.,* 2010; Khan *et al.* 2015; Lopez- Antia *et al.* 2015; Turkmen *et al.,* 2019).

Enzymatic and non-enzymatic antioxidants work with each other to protection against oxidative cell harms by ROS according to (Iqbal *et al.,* 1999; Romero *et al.,* 2016). In the current study, the oral administration of FPN, β-Cyf and FPN + β-Cyf to adult male rats resulted in an increase in serum creatinine and uric acid in rats. The kidney is the main site of elimination of xenobiotics (Matos et al., 2009). The serum increase levels of uric acid and Cre work as an indicator of the diagnosis of renal failure (El-Demerdash *et al.,* 2013; Turkmen *et al.,* 2019). In addition, the decrease of total protein in FPN, β-Cyf and FPN + β-Cyf treated rats may be due to the kidney dysfunctions, partially because of the high of the serum enzymes (Mansour and Mossa, 2010; Heikal *et al.,* 2012).

FPN, β-Cyf and FPN + β-Cyf treatment increased oxidative stress by modifying the enzyme activities linked with antioxidant defense mechanisms in the kidney of male rats. These pesticides reducing in the effeciency of antioxidant enzymes SOD, CAT, and GPx. according (Mansour and Mossa, 2010; El-Demerdash *et al.,* 2013; Abdel Rasoul and Marei, 2016; Turkmen *et al.,* 2019).

Kidney biomarkers in rats exposed to the FPN, β-Cyf and FPN + β-Cyf corroborated the histopathological lesions observed in this study, renal tissue with hypocellular, hemorrhagic, and irregular glomerular lining, arterial wall its thick, congested dilated artery, and destructed glomeruli. These changes could be due to FPN, β-Cyf and FPN + β-Cyf cause injury the various membrane components of the cell. Also, histological studies on the kidney of FPN, β-Cyf and FPN β-Cyf treated rats were similar with other studies like malathion (Bolton *et al.,* 2000), fenitrothion (Kalender *et al.,* 2007), chlorpyrifos (Mansour and Mossa, 2009) , methyl parathion (El-Desoky *et al.,* 2012) , abamectin (Fahmi *et al.,* 2017) and glyphosate-based herbicide (Turkmen *et al.,* 2019) thus, the insecticides are responsible for the damage which its occurs of histopathological changes in the kidney.

furthermore, Using GeOH had mitigated from the injury effect in the kidney as it was more efficient with a significant improvement in oxidative stress markers , antioxidant enzymes and the histopathological studies gave better healing (Badgujar et al., 2015b; Elguindy et al., 2018).

CONCLUSION

In this study, it can be conclude that FPN, β-Cyf and FPN + β-Cyf induced kidney injury that corroborated with the histopathological lesions. The changes in kidney functions could be due to the generation of ROS, which caused damage to the membrane and all cell components. In opposite, GeOH decreases oxidative damage where it has antioxidant properties thus ameliorative the structural safety of cell membrane and finally alleviates the histopathological changes as well as the biochemical disorders.

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الملخص العربي

الدور التحسيني للجيرانيول على السمية الكلوية الناجمة عن بعض المبيدات في الفئران

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الهدف من هذه الدراسة، دراسة التأثير المعالج لـ Geraniol (GeoH) ضد التلف التأكسدي الكلوي والتسمم الكلوي الناجم عن Fipronil (FPN)، بيتا Cyfluthrin (β-Cyf) -، وتأثيراتها المشتركة على ذكور الفئران. يشمل البحث ثماني مجموعات من الفئران المعاملة، كل مجموعة تحتوي على ستة جرذان. المجموعة الأولى غير معاملة، المجموعة ٢ (GeoH) (١٠٠ ملغم / كغم من وزن الجسم من زيت الذرة). وقد تمت معالجة الجرذان ٣ و٤ و٥ جرعات يومية عن طريق الفم من FPN 4.85ملجم/ كجم من وزن الجسم (، β-Cyf)= ١٩ملجم/ كجم من وزن الجسم). وقد قدمت المجموعات ٦ و٧ و٨ جرعات نفس الجرعات مثل المجموعات ٣ و ٤ و ٥ مع GeOH = 100ملجم / كجم) لمدة ٢٨ يوما متتالية، على التوالي. سجلت الفئران التي تعرضت للمبيدات الحشرية مقارنة بالكونترول انخفاضًا ملحوظًا في وزن الجسم وارتفاعًا في وزن الكلى. الفئران المعاملة سجلت اضطراب كبير في وظيفة الكلى بزيادة في حمض اليوريك ومستوى كرياتينين المصل. أيضا، أظهرت الفئران المعالجة بمبيدات الحشرات أن الأضرار المؤكسدة الكلوية شوهدت في الفئران المعالجة بمبيدات الحشرات من خلال زيادة في بيروكسيد الدهون في الكلى (LPO) أيضا، ظهرت الكلى انخفاض في الإنزيمات المضادة للأكسدة. كاتالاز (CAT) ، ديسموتاز الفائق (SOD) وجلوتاثيون بيروكسيداز .(GPx) ظهر التحليل النسيجي المرضي للكلية هذا التدمير الأنبوبي مع عدة فجوات، انحلال هيلي في الكبيبات، وجدار الشرايين السميك، وبطانة الكبيبات غير المنتظمة في المجموعات المعاملة FPN، β-Cyf، .(FPN + β-Cyf في الختام، يبدو أن استخدام Geraniol (GeOH)مفيد للفئران، إلى حد كبير عن طريق التخفيف وتقليل الضرر الذي لحق من التعرض بالمبيدات الحشرية.