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

Gehan I. Kh. Marei

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 GeoOH (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 GeoOH (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-Gozkara, 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 experiment, 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_{soo}) (Tomlin 2005), FPN at a daily dose of 4.85 mg/kg b.wt.
Category 4: Was given (1/20 LD_{soo}) (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 experiment, 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 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 and Trinder, 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-glutamlycysteinyl 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_{2}O_{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 by 58.32, 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%, 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

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

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.w t.)/ initial b.w t.] 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.](image-url)
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 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

<table>
<thead>
<tr>
<th>Groups</th>
<th>Creatinine mg/dL</th>
<th>Uric Acid mg/dL</th>
<th>TP g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.960 ± .021d</td>
<td>3.98 ± 0.120f</td>
<td>7.44 ± 0.062a</td>
</tr>
<tr>
<td>GeOH</td>
<td>0.890 ± .008d</td>
<td>3.71 ± 0.057f</td>
<td>7.49 ± 0.056a</td>
</tr>
<tr>
<td>FPN</td>
<td>1.43 ± 0.029b</td>
<td>9.23 ± 0.176c</td>
<td>6.30 ± 0.081c</td>
</tr>
<tr>
<td>β-Cyf</td>
<td>1.46 ± 0.042b</td>
<td>9.82 ± 0.102b</td>
<td>6.13 ± 0.062c</td>
</tr>
<tr>
<td>FPN + β-Cyf</td>
<td>1.64 ± 0.021a</td>
<td>12.12 ± 0.095a</td>
<td>5.70 ± 0.108d</td>
</tr>
<tr>
<td>FPN + GeOH</td>
<td>1.21 ± 0.053c</td>
<td>7.17 ± 0.081c</td>
<td>6.76 ± 0.042b</td>
</tr>
<tr>
<td>B-Cyf + GeOH</td>
<td>1.20 ± 0.038c</td>
<td>7.58 ± 0.077de</td>
<td>6.85 ± 0.021b</td>
</tr>
<tr>
<td>FPN + β-Cyf + GeOH</td>
<td>1.38 ± 0.041b</td>
<td>7.90 ± 0.334d</td>
<td>6.10 ± 0.040c</td>
</tr>
</tbody>
</table>

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

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

a, b, c, d Duncan’s test, p < 0.05
FPN: Fipronil; β-Cyf: β- Cyfluthrin; GeoH: Geraniol oil
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 efficiency 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 paraoxon (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.

**ACKNOWLEDGMENTS**

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الملخص العربي

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

جيهان إبراهيم خليل مرعى

الهدف من هذه الدراسة، دراسة التأثير المعالج لـ Geraniol (GeoH) ضد التلف التأكسدي الكلوي والتسمم الكلوي الناجم عن Cyfluthrin (β-Cyf) و Fipronil (FPN)، وتآثرهما المشتركة على ذكور الفئران، يشمل البحث ثماني مجموعات من الفئران المعالمة، كل مجموعة تحتوي على ستة جرذان. المجموعة الأولى غير معالمة، المجموعة (GeoH)100ملغم/ كلغم من وزن الجسم. وتمت معالجة الجرذان 3 و 4 و 5 جرعات يومية من FPN4.85ملغم/ كلغم من وزن الجسم، β-Cyf19ملغم/ كلغم من وزن الجسم، وقد قدمت المجموعات 6 و 7 و 8 جرعات منSAME ϕ + β-Cyf geometrically. في الختام، يبدو أن استخدام Geraniol (GeOH) في الفئران، إلى حد كبير عن طريق التخفيف وتقليل الضرر الذي لحق من التعرض بالمبيدات الحشرية.

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