

Repeated administration of fenitrothion alters renal functions via oxidative stress mechanism without inhibiting acetylcholinesterase activity in rats

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ABSTRACT

Background: The main mechanism of fenitrothion (FNT) toxicity is by inhibiting the acetylcholinesterase enzyme, though studies have shown that FNT might also develop other toxicological manifestations, including oxidative stress. However, the kidney functions as well as oxidative stress status after repeated exposure to FNT is not well documented. **Objective:** The present study was conducted to evaluate the kidney functions and oxidative stress status after exposure to low doses of FNT. **Materials and Methods:** 24 male Sprague-Dawley rats were divided randomly into three groups (n = 8/group): control, which received 1 mg/ml corn oil; FNT 10, which received 10 mg/kg (BW) FNT; and FNT20 which received 20 mg/kg (BW) FNT. The corn oil and FNT were fed orally for 28 consecutive days. At the end of the study, the blood was taken, and the kidney was obtained for biochemistry evaluation and histological observation. **Results:** The AChE activity was significantly inhibited in the FNT20 group ($p \leq 0.05$) compared to the control group and FNT10 and the rats exhibited the signs and symptoms of toxicity such as lacrimation, piloerection, hypoactivity, and tremor. Plasma creatinine and BUN levels showed a significant increase ($p \leq 0.05$) in FNT treated groups, but the superoxide dismutase and glutathione level were significantly reduced ($p \leq 0.05$). The malondialdehyde and protein carbonyl level were elevated significantly ($p \leq 0.05$) in FNT treated groups. Histopathological observation revealed morphological changes, including atrophy of the glomerulus and presence of non-amyloid substances in FNT treated groups. **Conclusion:** Even at the dose that did not inhibit the AChE activity, FNT was found to reduce the renal function and induce oxidative damage on the kidney of male *Sprague Dawley* rats.

Keywords: Antioxidant; non-amyloid; oxidative stress; organophosphate; oxidative damage

INTRODUCTION

Fenitrothion (FNT) is an organophosphate (OP) insecticide which was first introduced in 1959 (Wang et al., 2012). In Malaysia, FNT is widely used in agriculture for pest control and in the public health sector to control vector-borne diseases such as malaria and filariasis (Nazni et al., 2005). Extensive usage of FNT in both fields has eventually led to the persistence of FNT in the environment. Therefore, continuous exposure of FNT to animals and humans are unavoidable, via inhalation, oral and dermal routes. FNT is a lipid soluble molecule which can be easily absorbed and distributed among vital organs, especially organs that are surrounded by fat. Absorption of FNT will potentially initiate changes to the normal physiology of the body (Surur et al., 2015), thus causing acute or chronic toxicity in humans and animals (Taib et al., 2013).

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Received: 24 August 2020

Revised: 29 October 2020

Accepted: 10 November 2020

Published: 11 November 2020

doi

<https://doi.org/10.28916/lsm.4.9.2020.70>

Generally, FNT is converted to an active metabolite called fenitrooxon by the CYP1A1/2 and CYP2B6 hepatic enzymes. This active metabolite is believed to cause acute neurotoxic effects in comparison to the parent compound (Wang et al., 2012). Like other OPs, inhibition of the acetylcholinesterase (AChE) enzyme is the main mechanism of FNT toxicity. The inhibition of AChE activity causes accumulation of acetylcholine at nicotinic and muscarinic receptors, initiating the presence of cholinergic syndromes such as piloerection, tremor, hypoactivity and salivation (Taib et al., 2013). Furthermore, repeated exposure to FNT also exerts toxicological effects via the oxidative stress mechanism. The metabolism of FNT increases the formation of reactive oxygen species (ROS) and decreases the enzymatic and non-enzymatic antioxidants in several organs such as the liver, kidneys (Elhalwagy et al. 2008; Budin et al. 2013) and testes (Taib et al. 2013). Oxidative stress causes tubular cell injury that leads to tubular cell loss, which is known to be one of the mechanisms involved in chronic kidney disease progression (Daenen et al., 2019; Forbes et al., 2008).

The kidney is the main organ responsible in eliminating waste products and xenobiotic compounds such as OPs. However, the kidney is also rich in mitochondria, thus making this organ more susceptible to oxidative damage (Daenen et al., 2019; Shen et al., 2019). Repeated exposure to FNT reduces kidney functions, which was proven by an increment in urea and creatinine levels (Elhalwagy et al., 2008). Moreover, the administration of FNT in rats also caused degenerative changes in kidney tissues, characterised by congestion and haemorrhage in the renal cortex as well as mild shrinkage of the glomerulus (Budin et al., 2013).

According to Lee et al. (2015), OP toxicity not only causes the inhibition of AChE activity, but also increased the acute kidney injury cases by 6.17-fold. Furthermore, repeated exposure to OPs also induced oxidative stress in many organs (Lukaszewicz-Hussain, 2010; Taib et al., 2013). However, daily occupational exposure to FNT is rarely reported to cause AChE inhibition in humans. Moreover, the status of oxidative stress, as well as the kidney function is also not well documented in daily occupational exposure to FNT. Therefore, the current research aimed to study the effects of repeated exposure to FNT on the renal function and oxidative stress status in an animal model.

MATERIALS AND METHODS

Chemicals

In the present study, the reagents and chemicals were purchased from Sigma-Aldrich (USA), except for fenitrothion (FNT). FNT with 98.66% purity (Lot No. G144531) was purchased from LGC Labor GmbH (Augsburg, Germany).

Animals

A total of 24 male Sprague Dawley rats weighing between 240-270 g were obtained from the Laboratory Animal Resource Unit, Universiti Sains Malaysia, Malaysia. The handling protocol was approved by Universiti Kebangsaan Malaysia Animal Ethics Committee (UKMAEC) with ethical number: FSK/2016/IZATUS/23-NOV./807-NOV.-2016-FEB.-2019. Polycarbonate cages were used to house two rats in each cage, and the temperature was maintained at 20-24°C with reversed 12-hours light and dark cycle and the relative humidity was maintained at 30-70%. A standard rat chow palette and water was given to the rat *ad libitum* which was supplied by the Universiti Kebangsaan Malaysia (UKM) animal house.

Rats were randomly divided into three groups: control, FNT10, and FNT20 (eight rats per group). The control group received 1 ml/kg corn oil, FNT10 received 10 mg/kg (1/60 LD50) FNT while FNT20 received 20 mg/kg (1/30 LD50) FNT. FNT was diluted in corn oil to obtain the final concentration of 10 mg/kg and 20 mg/kg of body weight. The doses were chosen based on previous studies done by Ito et al. (2014) and Taib et al. (2013). The treatments were administered by oral force-feeding once daily, between 9.00 am to 10.00 am for 28 consecutive days. After 28 days, the rats were fasted overnight and anesthetized with a single

intraperitoneal injection of ketamine and xylazine (KTX). The blood was withdrawn for further kidney function test while the kidney was obtained for oxidative stress evaluation and histological observation.

Sample collection

The blood samples were collected via cardiac puncture and transferred into a heparin tube to obtain the plasma for further renal function and acetylcholinesterase analysis. Both left and right kidneys were excised, weighed, and washed using buffer. The right kidneys were then homogenized (10% w/v) in homogenate buffer, 1.15% potassium chloride. The homogenate was centrifuged at 8,000 rpm for 20 minutes at 4°C and stored at -80°C for further biochemical analysis. The left kidney samples were immersed in 10% formalin for histological observation.

Acetylcholinesterase activity

Briefly, the plasma samples were prepared using an AChE reagent kit following the manufacturer's instructions prior to analysis. The AChE enzyme activity was measured using a BioSystems semi-automated biochemical analyser (BioSystems S.A., Barcelona, Spain). The AChE enzyme activity was measured spectrophotometrically at 405 nm, and the calculated values were expressed in U/L.

Renal function

For renal function evaluation, plasma blood urea nitrogen (BUN) and creatinine levels were analysed following the methods described in previous studies (Rosenthal 1955; Jaffé 1986). The BUN level was measured using the diacetyl monoxime method where the urea in the hot solution of diacetyl monoxime condenses to form a diazine derivative which is a pink chromogen. This pink chromogen was measured by using a spectrophotometer at 480 nm. For creatinine analysis, the creatinine in the plasma was reacted with picric acid in an alkaline medium to form a yellowish, reddish complex. The coloured multiplex compound was measured at 520 nm. The BUN and creatinine were calculated, and expressed in mmol/L.

Oxidative stress status

Superoxide dismutase measurement

The superoxide dismutase (SOD) activity was measured based on the method described in a previous study (Beyer and Fridovich 1987). Briefly, a mixture of kidney homogenate and substrate was incubated in an aluminium box and exposed to a 20-watt lamp for 7 minutes. The SOD activity was measured spectrophotometrically at 560 nm. The SOD unit was defined as one unit of an enzyme that inhibits 50% of the nitro blue tetrazolium (NBT) reduction. The SOD activity was calculated and expressed in U/mg protein.

Glutathione measurement

The determination of glutathione (GSH) was based on the method described in a previous study with some modifications (Ellman 1959). Kidney homogenate was deproteinized using a metaphosphoric acid solution to obtain a supernatant. Then, the reaction buffer (pH 8.0) and DTNB were mixed with the obtained supernatant, incubated in the dark for 15 minutes and measured at 412 nm by using a BioRad iMark microplate reader (BioRad, United States of America). The GSH content was calculated and expressed as mmol/mg protein.

Malondialdehyde measurement

The malondialdehyde (MDA) level was measured based on the method described in a previous study (Stocks & Dormandy 1971). Briefly, the MDA in the sample reacted with thiobarbituric acid to form

a pink chromogen containing thioBarbituric acid reactive substances (TBARS). The TBARS were measured using a spectrophotometer at 532 nm. The concentration of MDA was calculated as mM/mg of tissue protein.

Protein carbonyl measurement

The protein carbonyl (PC) level was measured based on the method described in a previous study (Levine 1990). Briefly, kidney homogenate was mixed (1:1) with trichloroacetic acid (TCA) for protein precipitation. The mixture was incubated in ice for 15 minutes, and then centrifuged at 14,000 rpm for five minutes at 4°C to obtain the pellet. The pellet was incubated in 10 mM DNPH for one hour in the dark at 25°C. The protein precipitation process was repeated two times. The final pellet was washed using ethanol and ethyl acetate (1:1) mixtures and was diluted with 6 M guanidine hydrochloride. The carbonylated protein was measured at 366 nm and expressed as nmol/mg of tissue protein.

Histopathological observation

The fixation of kidney tissues was done by passing it in a series of gradually increasing concentration (100%, 100%, 95%, 80%, 70%, 50%) of alcohol and water before being cleared in xylene. Then, the processed tissues were embedded in paraffin wax, cut into sections of 4–5 µm thick and stained with haematoxylin and eosin (H&E). Congo Red was also applied to the other sections. Histological slides were observed under a light microscope and the abnormalities were validated by histopathological experts.

Statistical analysis

The obtained data were analysed by using Statistical Package for Social Sciences (SPSS) version 25. The data were tested for normality using Shapiro Wilk and were found to be normally distributed.

Then, the data were analysed using one-way analysis of variance (one-way ANOVA) and post hoc test. The data was considered significant when the p value is ≤ 0.05 . All data were expressed as mean \pm standard error mean.

RESULTS

Body and organ weight and food and water intake

The body and kidney weight, as well as food and water intake in experimental rats are shown in Table 1. At the end of the study, the final body weights of FNT10 and FNT20 groups were significantly lower compared to the control group at $p \leq 0.05$. The weight gains of both FNT groups were also significantly lower compared to the control group ($p \leq 0.05$). The FNT20 group had significantly decreased in absolute kidney weight compared to the control group ($p \leq 0.05$). There was no significant difference in the relative weight of the kidney among all experimental groups. Both FNT groups showed a decreased food and water intake as compared to the control group. However, the food and water intake in rats could not be statistically analysed because two rats were housed in every cage.

Toxicity signs and symptoms

Table 2 shows the toxicity signs and symptoms observed in experimental rats. Only rats from the FNT20 group showed the toxicity signs and symptoms of OP poisoning such as lacrimation, hypoactivity, tremoring, and piloerection. The toxicity signs and symptoms occurred within the first 20 minutes of treatment in which these signs can remain for 3 hours. No mortality was recorded during the treatment period.

Acetylcholinesterase activity

The AChE activity is shown in Table 2. The results showed that the AChE activity was significantly decreased in the FNT20 group ($p \leq 0.05$) compared to the control and FNT10 groups.

Table 1: Body weight, absolute and relative organ weights and food and water intake of experimental rats

Parameters	Experimental Groups		
	Control	FNT 10 (10 mg/kg BW)	FNT 20 (20 mg/kg BW)
Initial body weight (g)	249.09 \pm 0.64	254.14 \pm 1.88	253.64 \pm 0.73
End of body weight (g)	468.39 \pm 2.61	426.89 \pm 3.09 ^a	404.03 \pm 3.24 ^a
Weight gain (g)	219.27 \pm 2.51	172.75 \pm 1.96 ^a	150.39 \pm 3.34 ^a
Kidneys absolute weight (g)	2.26 \pm 0.05	2.14 \pm 0.05	2.02 \pm 0.05 ^a
Kidneys relative weight (%)	0.48 \pm 0.01	0.50 \pm 0.01	0.50 \pm 0.01
Food intake (g)	353.14 \pm 16.62	319.19 \pm 16.69	275.96 \pm 9.23
Water intake (ml)	621.34 \pm 47.81	552.66 \pm 33.73	440.81 \pm 32.82

^a indicates statistical significance ($p \leq 0.05$) compared to the control group

Table 2: Toxicity signs and symptoms, including the acetylcholinesterase activity of experimental rats

Groups	Mortality Rate (n/T)	Toxicity Signs (n/T)	Toxicity Signs	Observation Time (hour(s))	AChE Plasma Activity (U/L)
Control	0/8	0/8	Nil	Nil	704.65 \pm 28.25
FNT 10	0/8	0/8	Nil	Nil	711.31 \pm 18.25
FNT 20	0/8	6/8	Tremor	0.25 – 3	519.12 \pm 38.60 ^{a,b}
			Lacrimation	0.75 – 1	
			Piloerection	0.30 – 3	
			Hypoactivity	1 – 2	

(n/T) is number of rats calculated/total of rats in a group.

^a indicates statistical significance ($P \leq 0.05$) compared to the control group;

^b indicates statistical significance ($p \leq 0.05$) compared to the FNT10 group

Renal function test

Table 3 shows the plasma creatinine and BUN levels in all experimental groups. The creatinine levels of FNT10 and FNT20 were significantly increased compared to the control group ($p \leq 0.05$). Meanwhile, the plasma BUN level of FNT10 and FNT20 were significantly increased compared to the control group at $p \leq 0.05$ and $p \leq 0.01$, respectively.

Oxidative stress status

Table 4 shows the oxidative stress status of the kidney in experimental groups. The FNT20 group showed significantly lowered SOD activity ($p \leq 0.05$) compared to the control group, though no significant difference was found between the control and FNT10 groups. Meanwhile, the FNT10 and FNT20 groups showed significant depletion in the GSH level in comparison to the control group ($p \leq 0.05$).

Furthermore, for lipid peroxidation, the FNT20 group showed a significantly elevated ($p \leq 0.05$) MDA level in comparison to the control and FNT10 groups.

However, no significant difference was found between the control and FNT10 groups. Meanwhile, for the protein oxidation, the PC level was significantly increased in both FNT10 and FNT20 groups in comparison to the control group at $p \leq 0.05$.

Histological observations

Figure 1 shows the renal histology of all experimental groups using H&E staining at 400X magnification. The control rat shows a normal structure of glomerulus, Bowman's space, and Bowman's capsule. Besides, there were no changes in the morphology of proximal convoluted tubules and distal convoluted tubules (Figure 1a). On the other hand, FNT10 (Figure 1b) revealed atrophy of the glomerulus causing the widening of Bowman's space. The glomerulus atrophy is more obvious in the FNT20 group compared to the FNT10 and control groups. Besides, an amorphous pink substance was found deposited in the glomeruli, as seen in Figure 1c. Therefore, a Congo Red stain was applied to confirm whether the materials are amyloid. The finding shows negative results for Congo Red stain in the FNT20 group, which revealed that the substance was non-amyloid (Figure 2).

Table 3: Plasma creatinine and blood urea nitrogen levels of all experimental rats

Parameters	Experimental Groups		
	Control	FNT 10 (10 mg/kg BW)	FNT 20 (20 mg/kg BW)
Creatinine (mmol/L)	0.60 ± 0.01	0.80 ± 0.07 ^a	0.89 ± 0.09 ^a
Blood Urea Nitrogen (BUN)(mmol/L)	130.79 ± 9.78	171.97 ± 11.47 ^a	201.75 ± 12.55 ^b

^a indicates statistical significance ($p \leq 0.05$) compared to the control group; ^b indicates statistical significance ($p \leq 0.01$) compared to the control group.

Table 4: The oxidative stress parameters in kidney of all experimental rats.

Parameters	Experimental Groups		
	Control	FNT 10 (10 mg/kg BW)	FNT 20 (20 mg/kg BW)
SOD Activity (u/mg protein)	0.22 ± 0.01	0.19 ± 0.01	0.16 ± 0.01 ^a
GSH Level (nmol/mg protein)	0.32 ± 0.04	0.19 ± 0.03 ^a	0.18 ± 0.02 ^a
MDA level (nmol/mg protein)	8.81 ± 0.71	9.27 ± 0.52	11.75 ± 0.75 ^{a,b}
PC Level (nmol/mg protein)	0.06 ± 0.02	0.19 ± 0.04 ^a	0.24 ± 0.06 ^a

^a indicates statistical significance ($p \leq 0.05$) compared to the control group; ^b indicates statistical significance ($p \leq 0.05$) compared to the FNT10 group

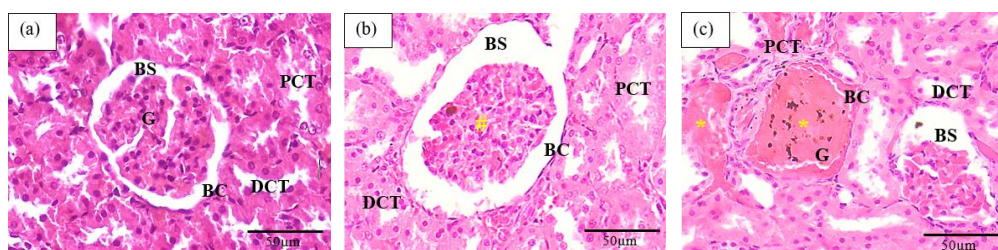


Figure 1: Histology of kidney of experimental rats using H&E Staining with 400X magnification (a - c). The control group shows normal structure of kidney consists of glomerulus (G), proximal convoluted tubules (PCT), distal convoluted tubules (DCT), Bowman's capsule (BC) and Bowman's space (BS) (Fig. 1a). Fig. 1b shows the kidney of FNT10 group with atrophy of glomerulus (#) and widening of Bowman's space (BS). The kidney of FNT20 group also showed atrophy of glomerulus (#) with widening of Bowman's space (BS) (Fig. 1c). The asterisk (*) glomerulus also showed acellular with materials deposition.

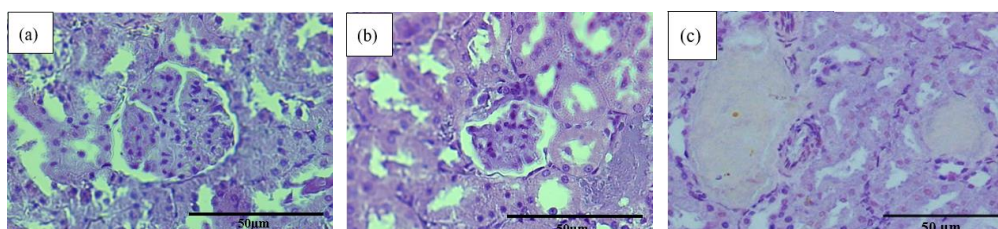


Figure 2: Histology of kidney of experimental rats using Congo Red stain (400X). Fig. 2a, 2b and 2c show histology of control, FNT10 and FNT20 groups, respectively. All figures show a negative result for Congo Red stain. Negative staining in Congo Red stain indicates absence of amyloids.

DISCUSSION

The putative implication of kidney dysfunction and oxidative stress in repeated administration of FNT in male rats were evaluated in the current study. Firstly, the FNT caused a significant reduction in weight gain and absolute weight of kidneys in rats. These findings are in line with previous findings that demonstrated decreased weight gain following OP exposure (Budin et al., 2014; Saafi et al., 2011). The main mechanism of OP toxicity is by inhibition of AChE activity, which in turn causes accumulation of acetylcholine (ACh) at the muscarinic and nicotinic junctions (Saafi et al., 2011). This accumulation leads to activation of muscarinic and cholinergic receptors causing some of the toxicity signs and symptoms such as lacrimation, tremor, piloerection and hypoactivity to develop in affected rats (Lukaszewicz-Hussain, 2010). The signs and symptoms of toxicity cause a reduced feeding appetite of the intoxicated rats, characterised by a reduction in food and water intake (Budin et al., 2014; Saafi et al., 2011). This might also explain the changes in body weight gain, food and water intake as well as the toxicity signs and symptoms in FNT-intoxicated rats.

Both doses of FNT caused kidney dysfunction by increasing the creatinine and blood urea nitrogen (BUN) levels. These discoveries are consistent with previous findings that found FNT caused a significant increase in BUN and creatinine levels (Elhalwagy et al., 2008; Zeid & Khalil 2014). George et al. (2017) stated that the accumulation of the xenobiotic compound would lead to direct effects on the kidney. Since the function of the glomerulus is to filter all of the metabolism products including the OP, gradual retention of these toxins may damage the glomerular structures. Besides, this glomerular damage causes a decrease in glomerular filtration rate (GFR), which ultimately affects the kidney functions by increasing the creatinine and BUN levels (Fuentes-Delgado et al., 2018).

Both doses of FNT not only caused kidney dysfunction, but also induced oxidative stress in the rat kidney. This was proven by the increased MDA and PC levels and decreased SOD activity and GSH level in the FNT intoxicated rats. These findings are in agreement with previous studies that also demonstrated oxidative stress in several organs of intoxicated rats (Budin et al., 2014; Kalender et al., 2007; Taib et al., 2013). SOD is an enzymatic antioxidant responsible for converting the superoxide anion into the less reactive metabolite, hydrogen peroxide (Ighodaro & Akinloye 2018). GSH is a multifunctional non-enzymatic antioxidant that also acts to combat free radicals (Kurutas, 2016). Therefore, the increasing formation of free radicals leads to the depletion of enzymatic and non-enzymatic antioxidants, causing lipid peroxidation and protein oxidation (Ighodaro & Akinloye 2018; Kurutas, 2016). This mechanism might explain the oxidative stress in the kidney of FNT-treated rats.

All of these changes, including the kidney dysfunction as well as oxidative damage were also seen in the FNT10 group, but with neither inhibition of AChE nor neurotoxic signs being observed. Other than the liver, the kidney also plays an important role in FNT metabolism (Elhalwagy et al., 2008). Therefore, fenitrooxon, which is the reactive metabolite of FNT might accumulate in the kidney, leading to the initiation of oxidative stress mechanism. Moreover, the kidney is also a highly metabolic organ responsible for filtering all of the reactive metabolites in the blood circulation. This might explain the kidney dysfunction and oxidative damage having occurred in the FNT10 group without inhibition of the AChE activity.

The biochemical findings are supported by the histological observation in the present study. Morphological changes of the kidney such as glomerulus atrophy and widening of Bowman's space were observed in FNT administered rats. Besides, some of the glomeruli in the FNT20 group also showed acellular and protein deposition that were negative for Congo Red staining, suggesting that the type of protein deposition in the kidney of FNT administered rats was non-amyloid. Furthermore, according to Budin et al. (2013), the morphological changes that were observed in the kidney of FNT administered rats were due to tissue degeneration.

CONCLUSION

In conclusion, the present study demonstrated that FNT at the dose of 10 mg/kg has reduced the kidney function in rats by significantly increasing the level of creatinine and BUN, without inhibiting the AChE activity. Moreover, it also induced oxidative stress by reducing the enzymatic and non-enzymatic antioxidants and increased the formation of lipid peroxidation and protein oxidation. Further studies can be done to evaluate the molecular oxidative stress mechanism by evaluating the reactive oxygens species (ROS) formation as well as the Nrf2-ARE pathway in rats induced by FNT.

DISCLOSURES

The authors declare that there is no conflict of interest.

ACKNOWLEDGEMENT

This research was fully supported by the research grant, GGPM-2016-084. The authors would like to express their appreciation to the staff of the Biomedical Sciences Programme, Faculty of Health Sciences, Universiti Kebangsaan Malaysia for helping in preparing research materials and facilities. Acknowledgement is extended to all the research assistants, postgraduate students, lecturers, and those who directly or indirectly supported this research.

REFERENCES

- Beyer Jr, W.F. & Fridovich, I. (1987). Assaying for superoxide dismutase activity: some large consequences of minor changes in conditions. *Analytical Biochemistry*. 161(2): 559- 566.
[https://doi.org/10.1016/0003-2697\(87\)90489-1](https://doi.org/10.1016/0003-2697(87)90489-1)
- Budin, S.B., Han, K.J., Jayusman, P.A., Taib, I.S., Ghazali, A.R. & Mohamed J. (2013). Antioxidant activity of tocotrienol rich fraction prevents fenitrothion-induced renal damage in rats. *Journal of Toxicology Pathology*. 26(2): 111-118.
<https://doi.org/10.1293/tox.26.111>
- Budin, S.B., Taib, I.S., Jayusman, P.A., Chiang, H.H., Ramalingam, A. & Ghazali, A.R. (2014). Ameliorative effect of palm oil tocotrienol rich fraction on brain oxidative stress in fenitrothion-administered rats. *Sains Malaysiana*. 43(7): 1031-1036.
- Daenen, K., Andries, A., Mekahli, D., Van Schepdael, A., Jouret, F. & Bammens, B. (2019). Oxidative stress in chronic kidney disease. *Pediatric Nephrology*. 34(6): 975-991.
<https://doi.org/10.1007/s00467-018-4005-4>
- Elhalwagy, M.E., Darwish, N.S. & Zaher, E.M. (2008). Prophylactic effect of green tea polyphenols against liver and kidney injury induced by fenitrothion insecticide. *Pesticide Biochemistry and Physiology* 91(2): 81-89.
<https://doi.org/10.1016/j.pestbp.2008.01.006>
- Fadzil, N.I., Ahmad, S.A., Yasid, N.A., Sabullah, M.K., Mohd Daud, H. & Khalid, A. (2019). Characterisation of cholinesterase and histopathological features of brain of *Clarias gariepinus* following exposure to cadmium. *Journal of Environmental Biology* 40(2): 133-142.
- Forbes, J.M., Coughlan, M.T. & Cooper, M.E. (2008). Oxidative stress as a major culprit in kidney disease in diabetes. *Diabetes* 57(6): 1446-1454.
<https://doi.org/10.2337/db08-0057>
- Fuentes-Delgado, V.H., Martínez-Saldaña, M.C., Rodríguez-Vázquez, M.L., Reyes-Romero, M.A., Reyes-Sánchez, J.L. & Jaramillo-Juárez, F. (2018). Renal damage induced by the pesticide methyl parathion in male Wistar rats. *Journal of Toxicology and Environmental Health, Part A* 81(6): 130-141.
<https://doi.org/10.1080/15287394.2017.1394948>
- George, B., You, D., Joy, M.S. & Aleksunes, L.M. (2017). Xenobiotic transporters and kidney injury. *Advanced Drug Delivery Reviews* 116: 73-91.
<https://doi.org/10.1016/j.addr.2017.01.005>
- Ighodaro, O.M. & Akinloye, O.A. (2018). First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. *Alexandria Journal of Medicine* 54(4): 287-293.
<https://doi.org/10.1016/j.ajme.2017.09.001>
- Ito, Y., Tomizawa, M.H., Suzuki, H., Okamura, A., Ohtani, K., Nunome, M., Noro, Y., Wang, D., Nakajima, T. & Kamijima, M. (2014). Fenitrothion action at the endocannabinoid system leading to spermatotoxicity in Wistar rats. *Toxicology and Applied Pharmacology* 279: 331-337.
<https://doi.org/10.1016/j.taap.2014.06.023>

- Jaffé, M. & Ueber Den Niederschlag. (1886). Welchen pikrinsäure in normalem harn erzeugt und über eine neue reaction des kreatinins. *Zeitschrift Für Physiologische Chemie* 10(5): 391-400.
- Kalender, S., Kalender, Y., Durak, D., Ogutcu, A., Uzunhisarcikli, M. & Sitki, B. (2007). Methyl parathion induced nephrotoxicity in male rats and protective role of vitamins C and E. *Pesticide Biochemistry and Physiology* 88(2): 213-218.
<https://doi.org/10.1016/j.pestbp.2006.11.007>
- Kurutas, E.B. (2016). The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. *The Journal of Nutrition* 15: (71): 1-22.
<https://doi.org/10.1186/s12937-016-0186-5>
- Lee, F.Y., Chen, W.K., Lin, C.L., Lai, C.Y., Wu, Y.S., Lin, I.C. (2015). Organophosphate poisoning and subsequent acute kidney injury risk: a nationwide population-based cohort study. *Medicine* 94(47): e2017.
<https://doi.org/10.1097/MD.0000000000002107>
- Levine, R.L., Garland, D., Oliver, C.N., Amici, A., Climent, I. & Lenz, A.G. (1990). Determination of carbonyl content in oxidatively modified proteins. *Method Enzymology* 186(49): 464-478.
[https://doi.org/10.1016/0076-6879\(90\)86141-H](https://doi.org/10.1016/0076-6879(90)86141-H)
- Lukaszewicz-Hussain, A. (2010). Role of oxidative stress in organophosphate insecticide toxicity-short review. *Pesticide Biochemistry and Physiology* 98(2): 145-150.
<https://doi.org/10.1016/j.pestbp.2010.07.006>
- Nazni, W., Lee, H. & Azahari, A. (2005). Adult and larval insecticide susceptibility status of *Culex quinquefasciatus* (say) mosquitoes in Kuala Lumpur Malaysia. *Tropical Biomedicine* 22(1): 63-68. PMID: 16880755.
- Rosenthal, H.L. (1955). Determination of urea in blood and urine with diacetyl monoxime. *Analytical Chemistry* 27(12): 1980-1982.
<https://doi.org/10.1021/ac60108a039>
- Saafi, E.B., Louedi, M., Elfeki, A., Najjar, M.F., Hammami, M. & Achour, L. (2011). Protective effect of date palm fruit extract (*Phoenix dactylifera* L.) on dimethoate induced-oxidative stress in rat liver. *Experimental and Toxicology Pathology* 63(5):433-441.
<https://doi.org/10.1016/j.etp.2010.03.002>
- Sarikaya, R., Selvi, M. & Erkoç, F. (2004). Investigation of acute toxicity of fenitrothion on peppered corydoras (*Corydoras Paleatus*). *Chemosphere* 56(7): 697-700.
<https://doi.org/10.1016/j.chemosphere.2004.04.008>
- Shen, H., Scialis, R.J. & Lois-McKeeman, L. (2019). Xenobiotic transporters in the kidney: function and role in toxicity. *Seminars Nephrology* 39(2): 159-175.
<https://doi.org/10.1016/j.semnephrol.2018.12.010>
- Stocks, J. & Dormandy, T. (1971). The autoxidation of human red cell lipids induced by hydrogen peroxide. *British Journal of Haematology* 20(1): 95-100.
<https://doi.org/10.1111/j.1365-2141.1971.tb00790.x>
- Surur, A.S., Alemayyehu, A. & Esho, T.B. (2015). Analysis of 3-methyl-4-nitrophenol, a major metabolite of fenitrothion, in mice urine using HPLC. *Pharmaceutical Methods* 6(1): 35-41.
<https://doi.org/10.5530/phm.2015.6.4>
- Taib, I.S., Budin, S.B., Ghazali, A.R., Jayusman, P.A., Louis, S.R. & Mohamed, J. (2013). Fenitrothion induced oxidative stress and morphological alterations of sperm and testes in male Sprague-dawley rats. 68(1): 93-100. h
[https://doi.org/10.6061/clinics/2013\(01\)OA15](https://doi.org/10.6061/clinics/2013(01)OA15)
- Wang, D., Naito, H. & Nakajima, T. (2012). The Toxicity of fenitrothion and permethrin. In: Farzana, P. Eds. *Insecticides-Pest Engineering*, London, UK: InTech Open Limited, Pp: 85-98.
<https://doi.org/10.5772/27884>
- Zeid, E.H.A. & Khalil, A.S.A. (2014). Effects of acute fenitrothion insecticide exposure on DNA damage and oxidative stress biomarkers and health of Nile tilapia fingerlings, *Oreochromis niloticus*. *World Journal of Fish and Marine Sciences* 6(4): 361-370.

Citation:

Yusoff, N. A. ., Juremi, I. I. ., Budin, S. B. ., & Taib, I. S. (2020). Repeated administration of fenitrothion alters renal functions via oxidative stress mechanism without inhibiting acetylcholinesterase activity in rats. *Life Sciences, Medicine and Biomedicine*, 4(9).
<https://doi.org/10.28916/lsm.4.9.2020.70>



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