EFFECTS OF SEPARATE AND COMBINED EXPOSURE TO CYPERMETHRIN AND CHLORPYRIFOS ON SELECTED REPRODUCTIVE, HAEMATOLOGICAL , SERUM HEPATIC AND RENAL PARAMETERS IN MALE ALBINO RATS

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ABSTRACT
The study aimed to investigate the reproductive toxicity induced by oral exposure to the pyrethroid insecticide (Cypermethrin) and the organophosphorus insecticide (Chlorpyrifos), individually and in combination in male albino rats. Twenty mature male albino rats were divided into four groups of five animals each. The groups received the following treatments: Control group was administered with distilled water, the second group received Cypermethrin (19 mg/kg/day) , the third (Chlorpyrifos (25 mg/kg/day) and the fourth (Cypermethrin (19.0mg/kg) plus Chlorpyrifos (25.0mg/kg) orally daily for 28 days. The results revealed a significant ($p < 0.05$) decrease in the weight of both the right and left epididymis in the combined insecticide treatment group compared to the control and animals exposed to chlorpyrifos and cypermethrin separately Furthermore, the volume of the testis was significantly ($p< 0.05$) lower in the cypermethrin exposed group compared with the control. The results of the oxidative stress and antioxidant parameters revealed a significant ($p< 0.05$) decrease in malondialdehyde (MDA), a measure of lipid peroxidation in the chlorpyrifos plus cypermethrin exposed group compared with the control. While a significant ($p< 0.05$) decrease was also observed between the cypermethrin exposed group and the group administered with the combination of cypermethrin and chlorpyrifos. Markers of liver function enzymes such as ALP, ALT and AST evaluated in this study showed a significant ($p< 0.05$) elevation in the chlorpyrifos exposed group compared with the group administered with both chlorpyrifos and cypermethrin. Analysis of ALT also revealed a significant ($p< 0.05$) elevation of the enzyme in the combined insecticide treatment group compared with the control and cypermethrin exposed groups.

KEYWORDS: cypermethrin, chlorpyrifos , oxidative stress, malondialdehyde, reproductive, male rats

INTRODUCTION

Pesticides are ubiquitous chemicals based on their widespread use in the control of pests on farms in homes and on animal bodies. The benefits of their usage in increasing farm crop yields leading to enhanced food production, and their efficacy in the control of disease vectors make them very valuable despite the risk of health hazards and environmental pollution which are concomitant to their widespread use, particularly in developing countries (Ikpeme *et al*, 2016).

Pesticides are considered potent toxicants for reproductive health in humans and animals

which may induce male infertility (Ezeji et.al., 2015). Exposure of pregnant animals have been shown to result in deleterious consequences such as increased foetal resorption and decreased litter size (Ramon-Yusuf et. al., 2017).

Among the various pesticides, insecticides are the most used with cypermethrin (CY) and chlorpyrifos (CPF) being the most preponderantly applied (Mansour et. al., 2018) Synthetic pyrethroids and their metabolites have been found in varying concentrations in virtually all environmental compartments (air, soil and water) and their widespread use in agriculture and residential areas has bolstered their presence in the environment and human exposure (Liu et. al 2009). These compounds have been detected in human samples such as breast milk and urine Saillenfa et. al, 2015) and have been implicated in the causation of deleterious effects such as induction and / inhibition of cytochrome P450 which may lead to their increased toxicity and interaction with other drugs (Anadon et. al, 2009). Also some pyrethroids including cypermethrin, have been identified as direct and indirect endocrine disruptors (Brander et. al, 2016),

Some of these pyrethroids have been shown to have disruptive effects on multiple nuclear hormone receptors and thus have the propensity to influence endocrine and reproductive functions (Bretveld et. al, 2006). Others have been identified as endocrine disrupting chemicals (EDCs) which have been incriminated in male reproductive impairments causing substantial male reproductive damage. They exert their toxic effects on male reproductive systems through diverse and complex mechanisms including antagonising androgen receptors, inhibiting steroid synthesis, affecting the hypothalamic-pituitary-gonadal axis, acting as estrogen receptors and inducing oxidative stress (Qi Wang et. al., 2020)

Cypermethrin is a type II pyrethroid since it has α- cyano group at the α-carbon of ester linkage and like all type II pyrethroids, it is a more potent neurotoxin than type I pyrethroids . It is an effective type II synthetic pyrethroid which is widely used in the control of agricultural pests such as those affecting cotton, vegetables and fruits (Sharma et. al, 2014). CY exerts its effect by prolonging the closure of voltage-gated sodium channels (VGSCs) thus increasing the influx of Na^+ with the consequence of depolarization leading to overexcitation of the cell membrane. (Soderland, 2012).

The literature is replete with evidence of the deleterious toxic effects occasioned by exposure to CY on the reproductive system such as alterations in the weight of reproductive organs, depletion of viable sperm and levels of sex hormones. In addition, remarkable changes have been reported in the testicular architecture of exposed animals through the instrumentality of oxidative stress (Alaa-Eldin et. al, 2017; Noashi et. al. ,2012).

Chlorpyrifos (CPF), an organophosphate insecticide is efficacious as a broad spectrum insecticide hence its widespread use in agricultural, domestic and industrial settings (Heikel et. al., 2014). It is a moderately hazardous class II insecticide (WHO, 2010) with an oral LD50 of 200 mg/kg body weight in adult male rats (Savithri et. al., 2016). Like its organophosphate counterparts, CPF exerts its toxicity through the inhibition of acetylcholinesterase enzyme and the consequent accumulation of acetylcholine at the synapses with concomitant hyperexcitability of the cholinergic receptors. In addition, CPF can achieve the causation of deleterious effects through the induction of oxidative stress (Heikal et.al., 2013), Slotkin

(2004) Yu et.al, 2008) and endocrine disruption (Nandi et. al., 2022), Montanari et. al., (2024).
Despite the well acknowledged toxic consequences of exposure to pyrethroid and organophosphorus insecticides these compounds have become ubiquitous in various environmental settings and are often used in combination. For instance, Chlorpyrifos and cypermethrin are pesticides widely used by cocoa farmers in Nigeria (Ikpeme et. al., 2016).
The fact that the irreversible inhibition of esterases by organophosphates leads to inhibition of activity of carboxylase enzymes responsible for hydrolysis of pyrethroids and consequently slows down their biotransformation and excretion, is a solid basis for the anticipation of a synergistic effect between chlorpyrifos and cypermethrin when used in combination and has been shown to elicit potent danger to male reproductive functions including significant reduction in sperm parameters with significant increase in sperm head abnormalities. (Ikpeme, 2016, Elnamaky et. al., 2018).

Materials and Methods

Chemicals and preparations

Commercial grade cypermethrin (Cypeforce®) (10% EC, Nagarjuna Agrochemicals limited Pujguta, Hyderabad, India) and commercial grade chlorpyrifos 20% EC (Rocket®) Jibali Agrotec Nigeria) were obtained from a reputable Agrochemical store in Abuja. The pesticides were dissolved in water to prepare the required concentrations used to dose animals in the various treatment groups. (OECD, 2025).

Animals and design:

Twenty mature male albino rats obtained from the animal breeding facilities of the National Institute for Pharmaceutical Research (NIPRD), Idu-Abuja, Nigeria were used for the study. The animals which were clinically healthy were housed in groups of five in plastic cages with wood shavings as bedding. All animals in the study were fed rodent diet compounded using chick mash. Tap water was made available to them *ad libitum.*

The handling and maintenance of all animals followed the National Institutes of Health Guide for care and use of Laboratory Animals (Garber, et. al, 2011). Ethical clearance was obtained from the University research Ethics Committee. After 2 weeks of acclimation, animals were distributed into four groups (n=5). The first group used as control received 0.5 ml distilled water orally. The second, third and fourth groups received Cypermethrin (19 mg/kg/day), Chlorpyrifos (25 mg/kg/day) and Cypermethrin (19.0mg/kg) + Chlorpyrifos (25.0mg/kg) , orally by gavage daily for 28 days. All animals were kept under daily observation until the end of the study period.

Sample Collection and Tissue preparation

At the end of the experimental period, the animals were sacrificed under anaesthesia and fresh blood was immediately collected by cardiac puncture. Blood for haematological analysis was collected into ethylenediaminetetraacetic acid (EDTA)-coated tubes while blood for biochemical analysis was collected and centrifuged at 4,500 rpm for 20 minutes and serum was extracted and stored at -20°C until the biochemical analyses were undertaken.

Specimen of reproductive organs (testes, epididymis) brain, liver and kidney were collected and preserved for morphometric analysis.

Statistical Analysis

Data obtained from this study were analysed

and presented as mean ± standard error of the mean (Mean±SEM).

Statistical significance among the various groups was subjected to a One-way analysis of variance (ANOVA), and the test of significance between treated groups and control group were evaluated using Tukey's multiple post hoc test. All statistical analyses were performed using GraphPad Prism version 7 software (GraphPad Prism Inc., San Diego, CA, USA) and P<0.05 values were considered significant.

Results

Effects of separate and combined exposure to cypermethrin and chlorpyrifos on some morphometric parameters in male albino rats

The results of the organosomatic indices revealed a significant (p< 0.05) decrease in the weight of both the right and left epididymis in the combined chemical treatment group compared to the control, chlorpyrifos and cypermethrin exposed groups respectively (Table 1). The weight of the brain of the combined treatment group was significantly (p< 0.05) lower compared with the chlorpyrifos exposed group, however, there were no significant changes in the other groups.

Furthermore, the volume of the testis measure was significantly (p< 0.05) lower in the cypermethrin exposed group compared with the control (Table 1). However, there were no significant changes recorded in the other parameters evaluated.

Table 1: Morphometric parameters of male rats following single and combined treatment with cypermethrin, chlorpyrifos and chlorpyrifos + cypermethrin (Mean±SE)

parameter	Control	Chlorpyrifos	Cypermethrin	Chlorpyrifos + Cypermethrin
Kidney weight (g)	1.59±0.13	1.965±0.118	1.586±0.059	1.444±0.088
Liver weight (g)	9.352±0.53	10.50±0.768	9.214±0.540	8.388±0.781
R.Testis weight (g)	1.500±0.077	1.58±0.07	1.401±0.047	1.35±0.058
L. Testis weight (g)	1.452±0.0629	1.566±0.0373	1.404±0.0398	1.376±0.050
R. Epididymis wt (g)	0.518±0.043[a]	0.5775±0.018[*]	0.512±0.010[a]	0.378±0.033[a]
L. Epididymis wt (g)	0.528±0.038	0.559±0.030	0.468±0.022[*]	0.398±0.042[a]
Brain weight (g)	1.81±0.042	1.928±0.06[*]	1.782±0.018	1.658±0.07[a]
Testis Vol. (ml)	1.50±0.158[a]	1.25±0.25	0.800±0.122[*]	1.12±0.102
Testis Diameter (m)	1.40±0.109	1.325±0.025	1.24±0.024	2.38±1.40
R. Epi. Length (cm)	4.78±0.153	4.65±0.05	4.52±0.10	4.32±0.20
L. Epi. Length (cm)	4.88±0.208	4.475±0.225	4.600±0.14	4.360±0.285
Body weight (g)	293.9±12.30	329.0±13.15	280.1±8.15	232.2±17.85

Data were presented as Mean ±SEM, N=5. Different superscripts are statistically significant (p<0.05) when compared to the control and treatment groups after Tukey's multiple comparison post hoc test.

Effects of separate and combined exposure to cypermethrin and chlorpyrifos on Haematological parameters in male albino rats.

The results of the hematological parameters are presented in Table 2. It was observed that exposure of the rats to the different individual chemicals and in combination did not yield any significant change in the haematological indices analyzed.

Table 2: Haematological parameters of male rats exposed to cypermethrin, chlorpyrifos and their combination (Mean ±SE)

Parameters	Control	Chlorpyrifos	Cypermethrin	Chlorpyrifos + Cypermethrin.
RBC (10^{12}/L)	7.516±0.16	7.645±0.39	7.64±0.76	6.786±0.67
Hb (g/L)	15.08±0.33	15.68±0.94	15.92±1.43	13.78±1.42
PCV (%)	44.80±1.16	37.40±6.40	46.34±4.00	39.28±3.84
MCV (fl)	59.62±0.82	60.30±0.70	61.08±1.65	57.90±0.96
MCH (pg)	20.06±0.16	20.50±0.19	21.00±0.69	20.28±0.76
MCHC (g/l)	33.62±0.22	33.98±0.18	34.38±0.85	35.06±1.58
WBC (10^9/L)	3.89±0.57	4.978±0.96	3.52±0.37	3.81±0.55
Lymph (%)	91.78±1.68	85.70±3.05	82.52±4.86	89.26±1.36
Platelet (10^9/L)	794.0±38.19	811.0±26.24	707.8±74.14	711.4±95.17
Granulated(10^9/L) WBC	2.72±0.76	4.575±1.07	8.54±3.88	3.42±0.52

Data were presented as Mean ±SEM, N=5. ($p<0.05$)

Effects of separate and combined exposure tocypermethrin and chlorpyrifos on selected biochemical parameters in male albino rats.

Regarding biochemical parameters, the study revealed a significant increase in the serum albumin concentration in the group treated with chlorpyrifos and cypermethrin compared with the control group. Similarly, the value of the group exposed to a combination of both chemicals was significantly ($p< 0.05$) higher than the cypermethrin exposed group.

The concentration of serum urea in the combined chlorpyrifos and cypermethrin group was significantly ($p< 0.05$) increased compared to the control and chlorpyrifos only groups. Whereas the concentration in the chlorpyrifos exposed group was significant when compared with cypermethrin administered group. Furthermore, creatinine level was significantly ($p< 0.05$) lowered in the combined treatment compared with both the control, chlorpyrifos and cypermethrin exposed groups.

Again, a significant difference ($p< 0.05$) in urea concentration was also observed between chlorpyrifos and cypermethrin treatment and the control.

Markers of liver function enzymes such as ALP, ALT and AST evaluated in this study shows a significant ($p< 0.05$) elevation in the chlorpyrifos exposed group compared with the group administered with both chlorpyrifos and cypermethrin. Analysis of ALT also shows a significant ($p< 0.05$) elevation of the enzyme in the combined chemical treatment group compared with the control and cypermethrin exposed group.

Table 3: Profiles of liver function enzymes in male rats exposed to single treatment with cypermethrin , and chlorpyrifos and their combination.

Parameters	Control	Chlorpyrifos	Cypermethrin	Chlorpyrifos + Cypermethrin.
Total Protein (g/dl)	4.99±0.166	5.24±0.32	4.90±0.18	5.60±0.30
Albumin (g/dl)	2.65±0.19	3.19±0.06	2.69±0.13[a]	3.43±0.09[*]
Globulin (g/dl)	2.34±0.32	2.04±0.32	2.22±0.11	2.17±0.27
Urea (g/dl)	25.58±1.26	32.30±3.24[a]	21.57±2.39	16.80±1.55[*]
Creatinine(g/dl)	4.68±0.42	6.93±0.49[ab]	4.33±0.29[ab]	1.17±0.16
ALP (U/L)	264.4±37.88	276.1±28.62[a]	204.2±20.61	161.4±16.34[*]
ALT (U/L)	8.95±0.74	11.24±1.56	8.22±1.95[a]	21.00±3.69[a]
AST (U/L)	45.25±8.47	35.99±12.83	55.72±15.87	16.84±6.73

Data were presented as Mean ±SEM, N=5. Different superscripts are statistically significant ($p<0.05$) when compared to the control and treatment groups after post hoc Tukey's multiple comparison

Oxidative stress markers.

The results of the oxidative stress and antioxidant parameters revealed a significant ($p< 0.05$) decrease in MDA, a measure of lipid peroxidation in the chlorpyrifos plus cypermethrin exposed group compared with the control rats which received only distilled water.. While a significant ($p< 0.05$) decrease was also observed between cypermethrin exposed group and the group administered with the combination of cypermethrin and chlorpyrifos. However, no significant changes were seen in the results of the antioxidant enzymes evaluated.

Table 4: Oxidative stress markers in rats exposed to chlorpyrifos and cypermethrin individually and in combination

Parameters	Control	Chlorpyrifos	Cypermethrin	Chlorpy + Cyperm
SOD (U/L)	74.75±9.78	92.52±3.40	90.00±4.64	81.52±13.72
GPx (mU/L)	6.69±0.63	6.68±0.61	5.33±0.55	7.47±0.68
NO (µM)	0.72±0.05	0.88±0.06	0.84±0.08	0.80±0.20
MDA(mmol/ml)	4.16±0.96[a]	3.29±0.71	3.78±0.44[a]	1.23±0.21

Data were presented as Mean ±SEM, N=5. Different superscripts are statistically significant ($p<0.05$) when compared to the control and treatment groups after post hoc Tukey's multiple comparison post hoc test.

Discussion

This study investigated the individual and combined effects of cypermethrin and chlorpyrifos on reproductive parameters, haematological and biochemical profiles, as well as oxidative stress markers in male albino rats. Findings indicated that both insecticides possess toxic potential when administered separately and a synergistic or additive effect with more profound toxicity when used in combination.

Morphometric analysis revealed a significant reduction in the weight of the epididymis and brain in the group exposed to the combination of cypermethrin and chlorpyrifos. The testicular volume was significantly lower in the cypermethrin-treated group, suggesting detrimental effects on testicular integrity. These findings are consistent with recent studies linking cypermethrin and chlorpyrifos exposure with testicular degeneration, reduced reproductive organ weight, and impaired sperm quality (El-Namaky et al., 2018; Suresh et al., 2021).

Biochemical markers showed significant ($p< 0.05$) increases in serum albumin and urea levels, with a notable decrease in creatinine in the combined treatment group. Similar renal and hepatic toxicity effects following pesticide exposure have been reported by Liang et al, (2024) who reported a significant decrease in creatinine level which was attributed to a dysfunction of the liver and kidneys following combined exposure to pesticides The results again, suggest an increase potential for nephrotoxicity in the administration of single pesticide compared to the coadministration of both chemicals as evident in the significant reduction in serum creatinine level in combined pesticides administration compared to the increase observed in individually administered groups.

Elevated ALT levels in the chlorpyrifos and combination groups point to hepatocellular damage, in line with previously reported organophosphate- and pyrethroid-induced hepatotoxicity (Saleh & Abbas, 2020). The observed reduction in MDA levels, despite exposure to oxidative stress-inducing pesticides, may reflect a compensatory antioxidant response or altered lipid metabolism (Yang et al., 2021).

Overall, the results support the hypothesis that combined exposure to cypermethrin and chlorpyrifos exerts a synergistic toxicological burden on reproductive tissues, liver, and kidneys of male rats. These findings agree with recent literature indicating that even sub-lethal doses of these pesticides can significantly impair reproductive and endocrine function (El-Namaky et al., 2018; Yang et al., 2021).

Conclusion

This study demonstrates that oral exposure to cypermethrin and chlorpyrifos, individually and in combination, induces significant alterations in reproductive morphometry, liver and kidney function, and oxidative stress markers in male albino rats. While haematological parameters remained unaffected, the combined exposure group showed the most severe impairments. These findings are supported by recent evidence suggesting that pesticide mixtures may have additive or synergistic effects on male reproductive health through endocrine disruption and oxidative damage

Given the widespread agricultural use of these compounds, this study highlights the importance of evaluating combined pesticide exposures and reinforces the need for stricter regulation and monitoring to prevent reproductive health risks.

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