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Impacts of L-Arginine on Haematological and Serum Biochemical Indices of Rats Exposed to Chlorpyrifos

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ABSTRACT

Chlorpyrifos is an organophosphorus insecticide that is applied expansively for pest control and its usage has been linked to several cases of poisoning. L-arginine is an α-amino acid that is crucial in protein biosynthesis and it has been reported to exert bioprotective effects in the body. The research was conducted in order to find out the impacts of L-arginine (AG) on haematological and serum biochemical indices in male Wistar rats exposed to chlorpyrifos. Thirty five rats were distributed into five groups. They received the following treatments by oral gavage for 28 days: distilled water [DT group], olive oil [LV; 1 ml/kg], chlorpyrifos (CF group; 8.5 mg/kg), L-arginine (AG; 100 mg/kg), chlorpyrifos (8.5 mg/kg)+L-arginine (100 mg/kg). The rats were sacrificed after the termination of the research. Subsequently, haematological and serum biochemical parameters were assessed. A significant ($p < 0.05$) reduction in the MCV of the CF group compared to the LV group was observed. Additionally, a substantial ($p < 0.05$) elevation was recorded in the MCHC of the CF group relative to the AG group. There were significant reductions in the calcium levels, while the magnesium levels were remarkably elevated in the CF and CF+AG groups compared to the DT and LV groups respectively. However, no significant alteration was noticed in the serum oxidative stress parameters (malondialdehyde, catalase and superoxide dismutase) that were analyzed. In this study, CF disrupted some haemato-biochemical parameters while AG minimally suppressed its effects. Further studies are warranted to expound the mechanisms of toxicity of CF, and the bioprotective propensity of AG.

Keywords: L-arginine, chlorpyrifos, haematology, serum biochemistry, *rats*

INTRODUCTION

Chlorpyrifos (CF) is an organophosphorus insecticide and acetylcholinesterase inhibitor that evokes severe cholinergic toxicity through the integumentary, respiratory or oral routes (Dawson *et al*., 2010). It is applied for pest management in agricultural, veterinary and residential settings (Singh *et al*., 2018). CF application is linked with disorders in the nervous, cardiovascular, respiratory, immunological, and reproductive systems (Sepand *et al*., 2020; Wang and Steinberg, 2022). Apart from cholinesterase inhibition, other identified mechanisms of CF toxicity include inflammation, endocrine disruption, oxidative and nitrosative stress, as well as apoptosis (Albasher *et al*., 2019; Küçükler *et al*., 2021; Nandi *et al*., 2022).

A disruption between the levels of antioxidants and pro-oxidants could evoke oxidative stress in biological systems (Qiu *et al*., 2019). CF has been shown to elicit aberrations in the haematological and biochemical indices of laboratory animals through the induction of oxidative stress (Aung *et al*., 2020; Kunnaja *et al*., 2021).

L-arginine is a conditionally essential amino acid and an antioxidant that is capable of alleviating oxidative stress (Zhang *et al*., 2019; Akinrinde *et al*., 2021). It is a crucial precursor for proline, polyamines, glutamate and nitric oxide synthesis (Shaki *et al*., 2021).

The aim of the proposed research was to find out if L-arginine, the amino acid, bioprotective agent and antioxidant, could counteract the subacute toxic effects of chlorpyrifos, a broadly used insecticide by farmers in Nigeria, on haemato-biochemical indices in male Wistar rats.

MATERIALS AND METHODS

The research was conducted at the Experimental Animal House, Faculty of Veterinary Medicine, University of Abuja Main Campus, Federal Capital Territory, Abuja, Nigeria. Thirty five (35) male rats were used and procured from the National Veterinary Research Institute (NVRI) Vom, Plateau State, Nigeria. They were accommodated in suitable cages at 23–25 ºC, 12 hours/12 hours light/dark cycle at the Experimental Animal House, Faculty of Veterinary Medicine, University of Abuja. The rats had free access to chow and water.

The investigation was approved by the University of Abuja Research Ethics Committee (UAV-23-146). The animals were catered for in harmony with the guiding principles of the National Institute of Health Guide for Care and Use of Laboratory animals (Garber *et al*., 2011).

Chemicals

A commercial grade of chlorpyrifos (Chloview®, 20 % emulsifiable concentrate) was procured from an agrochemical company in Abuja, Nigeria, and it was reconstituted in olive oil before administration to the rats. An analytical grade of L-arginine was purchased from Sigma Aldrich®, Germany. L-arginine was reconstituted in distilled water to obtain a 100 mg/ml solution before it was given to the rats on a daily basis.

The Subacute Toxicological Study

The rats were weighed and assigned randomly to five groups (n = 7). The experimental groups and the treatments administered to them were as follows: Distilled water (DT) group, olive oil

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(LV) group at 1 ml/kg, chlorpyrifos [CF, 8.5 mg/kg, 0.1LD_{50}, LD_{50} = 85 mg/kg, Akande et al. (2014)]. L-arginine (AG) at 100 mg/kg, and chlorpyrifos (8.5 mg/kg) and L-arginine (100 mg/kg) (CF+AG).

The treatments were administered to the rats once daily by oral gavage for 28 days and they were inspected for clinical signs of intoxication. After the study ended, blood samples were collected through cardiac puncture following chloroform anaesthesia.

Laboratory Investigations

Evaluation of Haematological Parameters:

Three millilitres of the rats' blood samples were dispensed in ethylene diamine tetraacetic acid sample bottles for the evaluation of haematological parameters. The erythrocyte indices were computed. The evaluation was conducted with the use of an automatic haematology analyzer (Mythic 18® Orphée, Geneva, Switzerland).

Assessment of Serum Biochemical Parameters:

Moreover, the rats' blood specimens (three millilitres) were placed in anticoagulant-free tubes. The blood specimens clotted and were incubated for 30 minutes. Subsequently, they were centrifuged at 1000 x g for 5 minutes to obtain clear straw coloured serum specimens for the estimation of biochemical parameters.

Assessment of Serum Electrolytes Levels:

Blood samples were collected from the rats and analyzed for levels of serum electrolytes (sodium, potassium, calcium, magnesium and chloride). The electrolytes were evaluated with a Clinical Chemistry Analyzer (Erba Diagnostics, Mannheim, Germany).

Determination of Malondialdehyde Concentration in the Serum of the Experimental Animals:

The malondialdehyde (MDA) levels were estimated in the serum samples by using an MDA assay kit (Elabscience Biotechnology Incorporation, Texas, USA). The method described by Draper and Hadley (1990) was applied. The absorbance was measured with an ultraviolet spectrophotometer at 532 nm. The MDA level in the samples was computed with the absorbance coefficient of MDA-TBA complex 1.56 x 10^5/cm/M.

Assays of Antioxidant Enzymes Activities:

Superoxide dismutase (SOD) activity was measured in the serum samples of the rats with an SOD assay kit (Elabscience Biotechnology Incorporation, Texas, USA). The method was predicated on the autoxidation of haematoxylin (Martin *et al*., 1987). Catalase (CAT) activity was estimated in the serum samples with a CAT assay kit (Elabscience Biotechnology Incorporation, Texas, USA). The procedure was based on the consumption of hydrogen peroxide substrate (Beers and Sizer, 1952). Glutathione peroxidase (GPx) level was appraised with the NWLSS™ activity assay kit. The assay was based on the oxidation of reduced glutathione to produce oxidized glutathione (Paglia and Valentine, 1967).

Data Analysis

The data derived from the research were stated as mean ± standard error of the mean. The data were scrutinized with one-way analysis of variance combined with Tukey's post hoc test

[GraphPad Prism version 4.00 for Windows, California, USA). Values of $P < 0.05$ were regarded as substantial.

RESULTS

Clinical Observations

The rats in the CF group manifested some signs of intoxication transiently such as anorexia, hypersalivation, hyperactivity and muscle tremor. However, these toxic manifestations were not detected in the animals in the other experimental groups.

Effects of the Treatments on the Haematological Indices of the Rats

There was no remarkable modification in the values of RBC, Hb, PCV, MCH, PLT, WBC, NEUT, LQ, MONO, EOS, BASO (Table 1). However, a significant ($P < 0.05$) diminution was noticed in the MCV of the CF group relative to the LV group. A substantial ($p < 0.05$) elevation was observed in the MCHC of the CF group relative to the AG group (Table 1).

Table 1: Effects of DT (distilled water), LV (olive oil), chlorpyrifos (CF) and/or L-arginine (AG) on the haematological parameters of male Wistar rats

PARAMETERS	DT	LV	AG	CF	CF+AG
RBC (x 10^{12}/L)	8.92±0.13	8.16±0.25	8.62±0.28	8.29±0.45	8.73±0.48
Hb (g/dl)	14.84±0.23	13.53±0.34	13.97±0.34	13.72±0.74	13.97±0.72
PCV (%)	46.00±0.89	43.00±1.08	44.67±1.52	41.60±2.36	44.00±2.31
MCV (fl)	51.58±0.45	52.73±0.37	52.10±0.63	**50.26±0.53***	50.80±0.23
MCH (pg)	16.62±0.15	16.58±0.11	16.15±0.27	16.54±0.16	16.03±0.09
MCHC (g/dl)	32.22±0.23	31.45±0.13	31.20±0.66	**32.98±0.07****	31.53±0.03
PLT (x 10^9/L)	850.40±35.28	645.30±43.08	717.20±93.06	511.40±134.60	784.70±88.88
WBC (x 10^9/L)	11.35±3.26	11.07±1.91	9.65±1.92	6.12±1.57	10.20±0.68
NEUT (x 10^9/L)	14.40±4.89	11.50±3.80	13.83±1.87	13.00±3.16	14.33±1.86
LQ (x 10^9/L)	78.40±4.03	76.25±3.75	72.83±4.67	71.20±6.18	76.00±2.65
MONO (x 10^9/L)	2.60±1.36	8.25±2.50	6.17±3.08	11.20±6.41	4.00±2.52
EOS (x 10^9/L)	3.60±0.60	2.50±0.65	5.33±1.09	2.60±1.21	4.33±0.88
BASO (x 10^9/L)	1.00±0.55	1.50±0.65	1.83±1.25	2.00±0.89	1.00±0

*$p < 0.05$ LV group versus CF group, **$p < 0.05$ AG group versus CF group, RBC (Red Blood Cell), Hb (Haemoglobin), PCV (Packed Cell Volume), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Haemoglobin), MCHC (Mean Corpuscular Haemoglobin Concentration), PLT (Platelet), WBC (White Blood Cell), NEUT (Neutrophil), LQ (Lymphocyte), MONO (Monocyte), EOS (Eosinophil), BASO (Basophil)

Effects of the Treatments on the Concentrations of Serum Electrolytes

There were significant ($P < 0.05$) reductions in the concentrations of calcium in the CF and CF+AG groups compared to the DT and LV groups respectively (Figure 1).

Additionally, the magnesium level was remarkably ($P < 0.05$) elevated in the CF and CF+AG groups relative to the DT and LV groups correspondingly (Figure 1).

Impacts of the Treatments on The Serum Oxidative Stress Parameters of The Rats

No noteworthy alteration was noticed in the serum MDA, serum SOD and serum CAT concentrations (Table 2).

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Table 2: Effects of DT (distilled water), LV (olive oil), chlorpyrifos (CF) and/or L-arginine (AG) on the levels of serum oxidative stress parameters of the rats

PARAMETERS	DT	LV	AG	CF	CF+AG
Serum MDA (nmol/ml)	6.62±0.28	9.55±0.81	9.25±2.62	13.81±3.82	8.64±1.26
Serum SOD (IU/L)	81.11±1.46	80.78±1.45	82.08±0.92	83.02±1.13	80.67±1.39
Serum CAT (IU/L)	12.44±1.35	10.02±0.71	8.97±0.61	9.48±0.45	9.78±0.95

MDA (malondialdehyde), SOD (superoxide dismutase) and CAT (catalase)

DISCUSSION

In the current investigation, there was no noteworthy alteration in the RBC, Hb, PCV, MCH, PLT, WBC, NEUT, LQ, MONO, EOS and BASO values among the experimental groups. However, a substantial diminution occurred in the MCV of the CF group, while a considerable elevation was recorded in the MCHC of the CF group. According to Ambali et al. (2011), CF exposure caused significant reductions in the PCV, Hb and RBC concentrations in rats, but evoked significant upsurges in the MCV and MCH, without a remarkable change in the MCHC among the treatment groups. Moreover, they documented a noteworthy decrease in the WBC, NEUT, lymphocyte and monocyte counts of the CF group. Kunnaja et al. (2021) affirmed that the values of MCV, MCH and MCHC were augmented in the group treated with CF at 16 mg/kg for 16 days, while the RBC count and PCV were decreased. Our results may have differed from those of other investigators because of biological variations among the rats used, differences in experimental designs and methodology, among others. In the present study, hypocalcaemia was observed in the CF-treated rats. This finding may be ascribed to impaired renal function. Tripathi *et al.* (2013) and Aung *et al*. (2020) reported that CF caused hypocalcemia in rats, and this is in agreement with the results of our research. Additionally, Aung et al. (2020) observed hyponatraemia, hypokalemia and hypochloraemia in rats exposed to CF and it was adduced that proximal tubular cell impairment evoked these findings. This is in contrast with our results in which there were no alterations in the levels of sodium, potassium and chloride ions. Hypermagnesaemia was recorded in the groups administered with CF in this research. However, Tripathi *et al.* (2013) stated that CF induced hypomagnesemia in rats. It is likely that we obtained a dissimilar outcome in this regard because of biological disparities among the rats used, variations in experimental designs and methodology, etc. Moreover, the levels of the serum electrolytes were normalized in the rats treated with AG in this investigation. AG has been shown to reverse electrolyte imbalances in male and female Wistar rats (Okon *et al*., 2022), thereby corroborating the results of our study. Furthermore, no significant modification was recorded in the serum MDA, SOD and CAT values in the CF group relative to the AG group. In contrast, Althagafy and Hassanein (2024) noticed that CF administered at 10 mg/kg orally for 28 days evoked a substantial amplification in the MDA concentration and reduced SOD activity in rats. Besides, AG has been shown to enhance the antioxidant enzymes concentrations in rats (SOD and CAT), while decreasing the MDA level (Pal *et al*., 2020). AG has been shown to evoke the antioxidant response through the triggering of glutathione synthesis and Nrf2 pathway (Liang *et al*., 2018). Our results regarding the serum oxidative stress parameters (MDA, SOD and CAT) may have deviated from those of other researchers because of our experimental approaches and some unknown factors.

CONCLUSION

In the current study, chlorpyrifos disrupted some haemato-biochemical parameters in the male Wistar rats, while L-arginine did not exert profound bioprotective effects at the dosage

administered to the male Wistar rats for 28 days. Additional research may expound the toxic mechanisms of chlorpyrifos, and the bioprotective property of L-arginine.

Conflict of Interest Statement

The authors assert that there is no conflict of interest.

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