Histological and Biochemical Evaluation of the Protective Potential of Ascorbate and Alpha-Tocopherol against Cypermethrin-Induced Toxicity

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Abstract

The unrestricted and unsystematic use of cypermethrin pesticides has detrimental effects on the organs, ranging from short-term sickness to long-term effects. The ameliorating effect of alpha-tocopherol and ascorbate was investigated singly and in combination with cypermethrin-induced oxidative stress using murine models. Additionally, the livers and kidneys of rats were histologically evaluated. Twenty-five (25) adult male Wistar rats with an average weight of 190 g were allocated randomly into five groups consisting of five rats each. Group I consists of the unexposed control rats, while rats in groups II-V were the test group exposed to cypermethrin at standard doses of 10 $mg.kg^{-1}$ bw. While rats in group II were exposed and untreated, group III-V was administered with ascorbate (5000 $mg.kg^{-1}$ bw), alpha-tocopherol (3000 $mg.kg^{-1}$ bw), and co-administered with both vitamins at their standard doses, respectively. Regimen administration was by gavage for 28 days, and while the vitamins were administered daily, cypermethrin exposure was done twice a week. At the end of the experiment, rats were euthanized, and blood obtained via cardiac puncture was used for biochemical analysis, while the liver and kidneys excised were processed for histopathological evaluation. Results revealed elevated aspartate transferase (AST), alanine transferase (ALT), malondialdehyde (MDA), and creatinine levels. At the same time, a decrease in superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) activities was observed in the test group ($p<0.05$). Additionally, treatment with ascorbate and alpha-tocopherol co-administration reversed the biochemical parameters in the exposed rats. Conclusively, ascorbate and alpha-tocopherol ameliorate oxidative damage associated with cypermethrin exposure.

Keywords: Cypermethrin, Histopathology, Pesticides, Toxicity, Vitamins.

INTRODUCTION

Pesticides function by attracting, seducing, and then destroying pests and are commonly referred to as insecticides, fungicides, bactericides, herbicides, or rodenticides, which are chemical groups used to control weeds and populations of insects, fungi, or other harmful pests [1,2]. The uncontrolled usage of pesticides adversely impacts the environment and is also associated with a variety of health problems ranging from short-term illness to cancer. Reducing their use is difficult because intensive agriculture heavily relies on pesticides to maintain maximum yields [3]. Cypermethrin pesticides are broad-spectrum, less toxic, biodegradable, and highly effective synthetic pesticides used globally in agriculture, pest management, and households as mosquito repellents for about four decades [4,5]. Cypermethrin is based on pyrethrin, a natural compound extracted from Chrysanthemum plants, and is rapidly metabolized with metabolites that are easily excreted [6]. Although they do not severely bioaccumulate in humans, chronic exposure may result in poisoning symptoms or even death [4].

Cypermethrin's biological activity results from neuronal membrane depolarization, which allows more sodium ions to pass through voltage-gated sodium channels [7]. There is a paucity of information on the chronic health effects of repeated exposure to cypermethrin. However, epidemiological studies associated with environmental and occupational exposure have reported the presence of cypermethrin metabolites in urine [8]. Additionally, it has been established that cypermethrin is lipophilic and can be distributed to tissues with high lipid content, such as fat and nervous tissue, as well as the liver, kidney, and milk, with the liver being the most commonly affected target tissue because it is the primary site of metabolism for these chemicals as well as the first organ to be exposed to the chemical following cypermethrin absorption [9,10]. Hence, this study investigates the histopathological and biochemical changes in the studied organs of male rats sub-acutely exposed to cypermethrin, as well as the possible mitigating effects of ascorbate and alpha-tocopherol that could serve as a therapeutic relief in cypermethrin toxicity.

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MATERIAL AND METHOD

Experimental animals

Twenty-five (25) adult male Wistar rats purchased from the Animal Holding of the University of Medical Sciences Ondo State, Nigeria (UNIMED) were acclimatized for four weeks and fed with standard rat pellets obtained from Chikun farms and water ad-libitum. The rats were properly housed in a clean, well-ventilated space [11].

Experimental Design and Ethical approval

After four weeks of acclimatisation, the rats were divided into five groups, each with five rats, following the method of Adeniyi *et al.* [12]. The Ethical Committee of UNIMED approved the use of experimental animals and assigned the approval number NHREC/TR/UNIMED-HREC-Ondo St/22/06/21.

Specimen collection

After experimentation, all animals in the groups were euthanized, and blood samples were collected and transferred into a lithium heparinized anticoagulant bottle for biochemical analysis. The liver and kidneys were immediately excised, preserved, and processed for histopathological studies [13].

Histopathological and Biochemical studies

The prefixed liver and kidney samples were histologically processed as described by Moronkeji *et al.* [14]. Briefly, the tissues were dehydrated in graded alcohol solutions, followed by clearing in two changes of xylene, infiltrated in two changes of wax bath, and embedded using paraffin wax. The sections were hydrated and stained with Harris Haematoxylin for five minutes, rinsed in water, and differentiated with 1% acid alcohol for one minute. Sections were rinsed in water and blued in tap water for ten minutes, followed by counterstaining using 1% aqueous eosin, and dehydration in ascending grades of alcohol was ensured. The stained slides were cleared in two changes of xylene, mounted using dibutyl phthalate propylene xylene (DPX), and examined microscopically using x10 and x40 objective lenses. For the biochemical studies, the plasma from the euthanized rats was used to perform the liver and renal function tests described in the diagnostic kits obtained from Randox Laboratory, UK [14].

Oxidative Stress Assays

The supernatant obtained from each rat's homogenate samples of the liver and kidney was preserved at -70°C. For the assessment of superoxide dismutase (SOD), glutathione peroxidase (GPX), and Catalase activity (CAT), protocols from the ELISA kits obtained from Elabscience Biotechnology Inc USA were used. Additionally, Malondialdehyde (MDA) was spectrophotometrically analyzed as described by Oludare *et al.* [15].

Statistical analysis

The data obtained were analyzed using SPSS version 23. The chi-square and Fisher exact tests compared the categorical variables, and P-values < 0.05 were considered statistically significant.

RESULT AND DISCUSSION

Histopathological Findings

Liver of Rats

The histopathological findings in this study revealed that cypermethrin exposure had a deleterious impact on the livers of the exposed rats. While the unexposed control rats had normal liver histoarchitecture (Fig. 1a), the untreated cypermethrin-exposed rats had congested venules and sinusoidal spaces, as well as hepatic vacuolation and necrosis (Fig. 1b). Furthermore, when compared to the cypermethrin-exposed untreated rats, treatment with 5000 $mg.kg^{-1}$ bw of ascorbate showed reduced cytopathic changes typified by normal hepatocytes (Fig. 1c). In contrast, the alpha-tocopherol (3000 $mg.kg^{-1}$ bw) treated rats showed inflamed liver parenchyma (Fig. 1d). The cypermethrin-exposed rats treated with ascorbate and alpha-tocopherol at standard doses of 5000 $mg.kg^{-1}$ bw and 3000 $mg.kg^{-1}$ bw respectively had histoarchitecture similar to the unexposed control (Fig. 1e).

Kidney of Rats

The kidneys of the control rats showed no pathological lesions (Fig. 2a). In contrast, the cypermethrin-exposed untreated rats had a poor histoarchitectural structure characterized by periglomerular inflammation with degenerated renal tubules as well as congested and inflamed interstitial space (Fig. 2b).

The kidneys of the ascorbate-treated rats had a normal glomerulus and no congested or inflamed interstitial space (Fig. 2c), whereas the interstitial space of the alpha-tocopherol-treated rats was mildly inflamed (Fig. 2d). The co-administration with ascorbate and alpha-tocopherol revealed a normal glomerulus with a mildly congested and infiltrated interstitial space (Fig. 2e).

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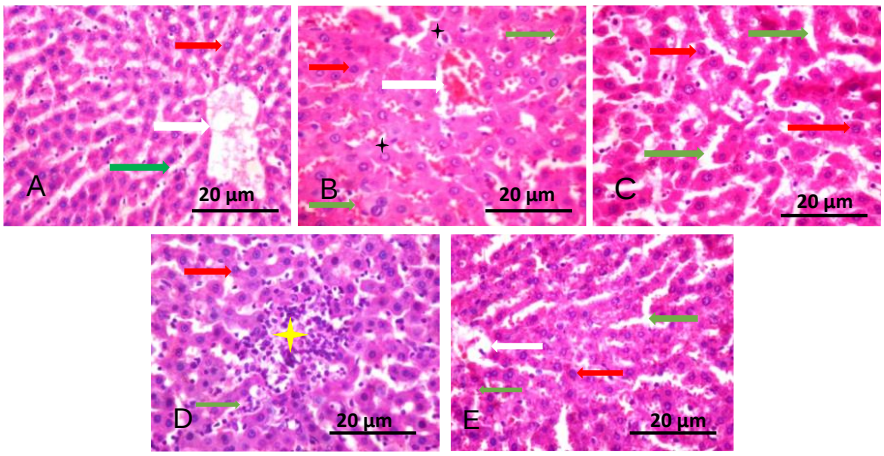

Figure 1. H and E-stained section of the liver of rats, with magnification of 400x

Description:

The central venules
Sinusoid
The hepatocytes
Vacuolation and necrosis
Mononuclear inflammatory cellular aggregate

A. Unexposed control rats: normal liver histoarchitecture devoid of lesions, the central venules, the sinusoid spaces and the hepatocytes appear normal.
B. Cypermethrin-exposed untreated rats: mildly congested central venules, vacuolation and necrosis is also evident in some of the hepatocytes while the morphology of other hepatocytes appears normal, the sinusoids are mildly dilated and congested.
C. Cypermethrin-exposed rats + 5000 mg.kg^{-1} bw ascorbate: hepatocytes with normal morphology, and mildly dilated sinusoid space evident.
D. Cypermethrin-exposed rats + 3000 mg.kg^{-1} bw alpha tocopherol: the liver parenchyma with focal area of mononuclear inflammatory cellular aggregate, the morphology of the hepatocytes appears normal, the sinusoids are dilated and mildly infiltrated by inflammatory cells.
E. Cypermethrin-exposed rats + 5000 mg.kg^{-1} bw ascorbate + 3000 mg.kg^{-1} bw alpha tocopherol: normal central venules, the morphology of the hepatocytes appears normal, the sinusoids appear normal and not infiltrated.

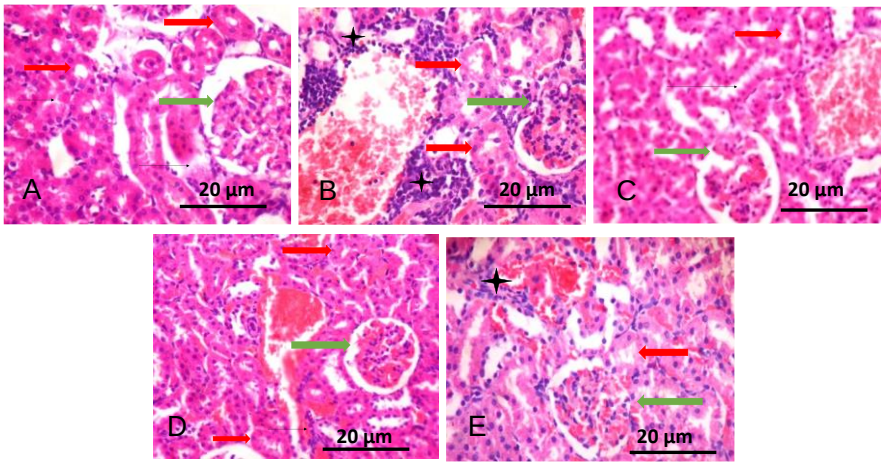

Figure 2. H and E-stained kidney sections with magnification of 400x

Description:

Normal glomeruli
Renal tubules
Mononuclear inflammatory cells
Interstium

A. Unexposed control rats: appeared normal, the renal cortex shows normal glomeruli, mesengial cells, and capsular spaces, with the renal tubules appearing normal, while the interstium are devoid of inflammation.
B. Cypermethrin exposed untreated rats: poor histoarchitecture (periglomerular inflammation with degenerated renal tubules); interstitium are congested and infiltrated with mononuclear inflammatory calls.
C. Cypermethrin-exposed rats + 5000 mg.kg^{-1} bw ascobate: the renal cortex consisting of a normal glomeruli, the renal tubules are normal, with the interstitium devoid of congestion or inflammation.
D. Cypermethrin-exposed rats + 3000 mg.kg^{-1} bw alpha-tocolpherol treated rats: moderate architecture with a normal glomerulus, the renal tubules are normal, while some regions of the interstitium are mildly inflammed.
E. Cypermethrin-exposed rats + 5000 mg.kg^{-1} bw ascorbate + 3000 mg.kg^{-1} bw alpha tocopherol: a normal glomeruli, the renal tubules and the interstitium are mildly congested and infiltrated with mononuclear inflammatory cells.

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Biochemical Findings

Aspartate Transferase and Alanine Transferase

The biochemical findings in this study revealed that cypermethrin-exposed untreated rats had elevated AST and ALT levels. Meanwhile, rats administered with ascorbate, alpha-tocopherol, or the combinative with both vitamins had reduced AST and ALT levels ($p<0.05$) (Table 1).

Creatinine

The creatinine values in the Cypermethrin-exposed, alpha-tocopherol, or co-administrative treatment groups were statistically insignificant ($p>0.05$). In contrast, rats treated with ascorbate had a significantly lower creatinine value ($p<0.05$) compared to the Cypermethrin-exposed untreated rats and other treatment groups (Table 2).

Oxidative stress markers in the liver samples

The oxidative stress parameters in the liver tissue homogenate samples revealed a disruption in the oxidant-antioxidant homeostasis as a result of cypermethrin exposure. While MDA levels were significantly elevated in the untreated cypermethrin-exposed rats, SOD, GPX, and CAT levels were significantly reduced ($p<0.05$). However, treatment with ascorbate, alpha-tocopherol, or co-administrative treatment with both vitamins alleviated the deleterious impact of cypermethrin by lowering MDA levels while increasing SOD, GPX, and CAT levels ($p<0.05$) (Table 3).

Oxidative Stress Markers in the Kidney Samples.

The oxidative stress parameters in the kidney homogenate samples revealed elevated MDA levels in the untreated cypermethrin-exposed rats, while SOD, GPX, and CAT values were significantly reduced ($p<0.05$). Furthermore, vitamin treatment mitigated the negative impact of cypermethrin by lowering MDA levels while increasing SOD, GPX, and CAT levels in the treated rats ($p<0.05$) (Table 4).

Table 1. Mean and standard deviation values of aspartate transferase and alanine transferase across all groups

Parameter(s)	Group 1	Group 2	Group 3	Group 4	Group 5
AST (mmol.L^{-1})	0.0752±0.046^{b}	0.1598±0.0228^{a}	0.1032±0.01994^{b}	0.1098±0.02168^{b}	0.0978±0.03339^{b}
ALT (mmol.L^{-1})	0.0628±0.057^{b}	0.3006±0.1144^{a}	0.1236±0.04403^{b}	0.114±0.05787^{b}	0.0674±0.04466^{b}

Notes: Group 1: control, Group 2: exposed untreated, group 3: ascorbate treated, group 4: alpha-tocopherol treated, group 5: ascorbate and alpha-tocopherol co-administered treated rats. a>b. ^{a} = (p = 0.000) ^{b} = (p = 0.012).

Table 2. Mean and standard deviation of Creatinine values across all groups

Parameter (s)	Group 1	Group 2	Group 3	Group 4	Group 5
Creatinine (µmol.L^{-1})	51.924±48.7243^{b}	95.48±8.31607^{a}	76.41±10.00598^{ab}	90.132±12.40513^{a}	89.626±19.41008^{a}

Notes: Group 1: control, Group 2: exposed untreated, group 3: ascorbate treated, group 4: alpha-tocopherol treated, group 5: ascorbate and alpha-tocopherol co-administered treated rats. a>ab>b. ^{a} = (p = 0.011), ^{ab} = (p = 0.019), ^{b} = (p = 0.027).

Table 3. Mean and standard deviation values of oxidative stress parameters in the liver homogenate samples across all groups

Parameter(s)	Group 1	Group 2	Group 3	Group 4	Group 5
MDA (µmol.L^{-1})	0.33±0.052^{c}	7.793±1.122^{a}	1.879±0.373^{b}	1.564±0.637^{b}	0.668±0.182^{c}
SOD (µmol.mL^{-1})	6.815±0.407^{b}	2.864±0.754^{d}	4.89±0.35^{c}	5.586±0.718^{c}	12.577±1.395^{a}
GPx (µmol.L^{-1})	84.741±2.782^{b}	45.589±2.612^{d}	56.683±3.02^{c}	58.33±2.536^{c}	113.735±8.892^{a}
CAT (µmol.L^{-1})	15.196±0.645^{b}	8.135±0.756^{d}	9.909±1.189^{cd}	11.48±1.225^{c}	28.168±4.065^{a}

Notes: Group 1: control, Group 2: exposed untreated, group 3: ascorbate treated, group 4: alpha-tocopherol treated, group 5: ascorbate and alpha-tocopherol co-administered treated rats a>b>c>cd>d. ^{a} = (p = 0.000), ^{b} = (p = 0.019), ^{c} = (p = 0.027), ^{cd} = (p = 0.032), ^{d} = (p = 0.042).

Table 4. Mean and standard deviation values of oxidative stress parameters in the kidney homogenate samples across all groups

Parameter(s)	Group 1	Group 2	Group 3	Group 4	Group 5
MDA (µmol.L^{-1})	0.211±0.051^{c}	5.315±0.765^{a}	0.905±0.339^{b}	0.867±0.164^{b}	0.664±0.354^{bc}
SOD (µmol.mL^{-1})	14.184±1.646^{a}	3.841±1.525^{d}	8.116±0.935^{c}	8.571±0.647^{c}	12.333±1.543^{b}
GPx (µmol.L^{-1})	64.522±6.737^{a}	21.767±1.2^{d}	30.638±2.729^{c}	32.448±2.229^{c}	46.322±2.143^{b}
CAT (µmol.L^{-1})	12.772±1.071^{a}	4.785±0.795^{c}	7.871±0.736^{b}	8.595±0.829^{b}	12.248±0.892^{a}

Notes: Group 1: control, Group 2: exposed untreated, group 3: ascorbate treated, group 4: alpha-tocopherol treated, group 5: ascorbate and alpha-tocopherol co-administered treated rats. a>b>bc>c>d. ^{a} = (p = 0.002), ^{b} = (p = 0.021), ^{bc} = (p = 0.029), ^{c} = (p = 0.035), ^{d} = (p = 0.045).

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DISCUSSION

Cypermethrin is a class II pyrethroid widely used in agriculture due to its efficacy. However, it is considered moderately toxic [16]. We investigated the histopathological, biochemical, and oxidative stress responses to cypermethrin exposure using murine models and the ameliorative potential of ascorbate and alpha-tocopherol when singly administered or in combination. The liver, being the most commonly targeted organ exposed to chemicals following absorption as well as the major site of metabolism, plays an integral role in the biotransformation and detoxification of chemicals [10]. This integral metabolic function played by the liver predisposes it to constantly coming into contact with these toxic chemicals, and long-term exposure could lead to derangement and predispose it to the development of several diseases.

The liver section of the unexposed control rats was normal, evidenced by an unaltered histoarchitecture with a non-congested central vein and hepatocytes with normal sinusoids, which is consistent with the findings of Soliman *et al.* [17]. Conversely, the cypermethrin-exposed untreated rats showed hepatocyte vacuolation and necrosis, additionally, the sinusoids were mildly dilated and congested [18].

The ascorbate-treated cypermethrin-exposed rats had better liver histoarchitecture than the untreated group, as evidenced by normal-appearing hepatocytes and sinusoidal spaces devoid of congestion or inflammation. In contrast, the alpha-tocopherol-treated group showed a focal area of mononuclear inflammatory cellular infiltration in the liver parenchyma with mildly inflamed sinusoidal space. Furthermore, the co-administered group had normal central veins and sinusoids devoid of inflammation and congestion.

Our findings align with Abdellatif *et al.* [19], who documented the beneficial impact of co-administration of ascorbate and alpha-tocopherol. Furthermore, as observed in our studies, cypermethrin can accumulate in the kidneys due to the lipophilic nature of the organ, resulting in severe renal damage such as tubular cell toxicity, inflammation, and nephrotoxicity [20]. While the kidney histoarchitecture of the unexposed control rats was devoid of lesions, the exposed untreated rats had poor kidney histoarchitecture as evidenced by periglomerular inflammation and degenerated renal tubule with congested and inflamed interstitial space [17].

The histoarchitecture of the ascorbate-treated rats was better relative to the cypermethrin-exposed untreated rats with a normal appearing glomerulus and interstitial space devoid of inflammation or congestion. Adikwu and Deo [18] previously reported on the hepatoprotective property of ascorbate, which has been linked to its antioxidant properties. The alpha-tocopherol treatment group had a moderate histoarchitecture, with some regions within the interstitial space inflamed. However, the renal tubules and the renal cortex appeared. The kidneys of the rats co-administered with the vitamins had a mildly congested and inflamed interstitial space, with the renal tubules and renal cortex appearing normal, which aligns with the observations of Abdellatif et al. [19].

When compared to the unexposed negative control rats, biochemical studies revealed elevated AST and ALT levels in the cypermethrin-exposed untreated group; however, single or co-administration of the vitamins reverted the enzyme activities in the rats, with the most significant reduction observed with the co-administration of ascorbate and alpha-tocopherol at standard doses of 5000 mg.kg-1 bw and 3000 mg.kg-1 bw. Studies by Mossa *et al.* [16] reported elevated liver AST and ALT in cypermethrin-exposed male mice, thus indicating the cytopathic effect of this type II cypermethrin. Additionally, elevated creatinine levels were observed in all exposed groups. However, vitamin administration reversed the creatinine values in the treatment group, with the most significant reduction observed in rats treated with ascorbate at 5000 mg.kg-1 bw, supporting ascorbate's mitigating potential in pyrethroid-induced toxicity [18,21].

The analysis of the oxidant-antioxidant levels in the liver homogenate samples from all groups revealed a derangement in the cypermethrin-exposed group. Significantly elevated MDA levels were observed in the untreated exposed rats, whereas co-administrative treatment with both vitamins reversed the MDA levels better than single administration. According to Chrustek *et al.* [6], cypermethrin exposure elevates MDA while decreasing antioxidant levels. A finding consistent with our findings confirms that cypermethrin can cause oxidative stress, corroborating the findings of Ullah et al. [22]. We observed that the SOD, GPX, and CAT values were better reversed in rats co-administered with the vitamins when compared to the other tests group (Table 3).

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The evaluation of oxidative stress parameters in kidney homogenate samples revealed elevated MDA levels in untreated exposed rats, with the most significant mitigating effect observed in rats co-administered with both vitamins. Furthermore, the GPX, SOD, and CAT values were elevated compared to the other test groups, supporting the beneficial effects of ascorbate and alpha-tocopherol previously reported [18].

CONCLUSION

Ascorbate and alpha-tocopherol co-administration mitigates cypermethrin-induced toxicity better. It also ameliorates the cytopathic effects on liver and kidney histoarchitecture and aids in reversing oxidant-antioxidant disruption in rats that are exposed to cypermethrin.

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