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Research Article

Oxidative stress and neuronal dysfunction induced by combined low-dose exposure to abamectin and cypermethrin

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Abstract

Background : The increase in agricultural production has been accompanied by intensive pesticide use, leading to chronic environmental contamination. In Togo, residues exceeding regulatory limits have been detected in vegetable crops, particularly abamectin (ABM) and cypermethrin (CYP). ABM, derived from *Streptomyces avermitilis*, acts on GABA-gated chloride channels and crosses the blood–brain barrier, inducing oxidative stress and neurotoxic damage. CYP, a synthetic pyrethroid, targets voltage-gated sodium channels, resulting in abnormal neuronal discharges and excessive production of reactive oxygen species. While their acute effects are well known, the subchronic impacts of low-dose exposure, especially in combination, remain poorly understood. In this context, the present study aims to evaluate the subchronic neurotoxic effects of combined exposure to abamectin and cypermethrin, administered at realistic doses, in rats.

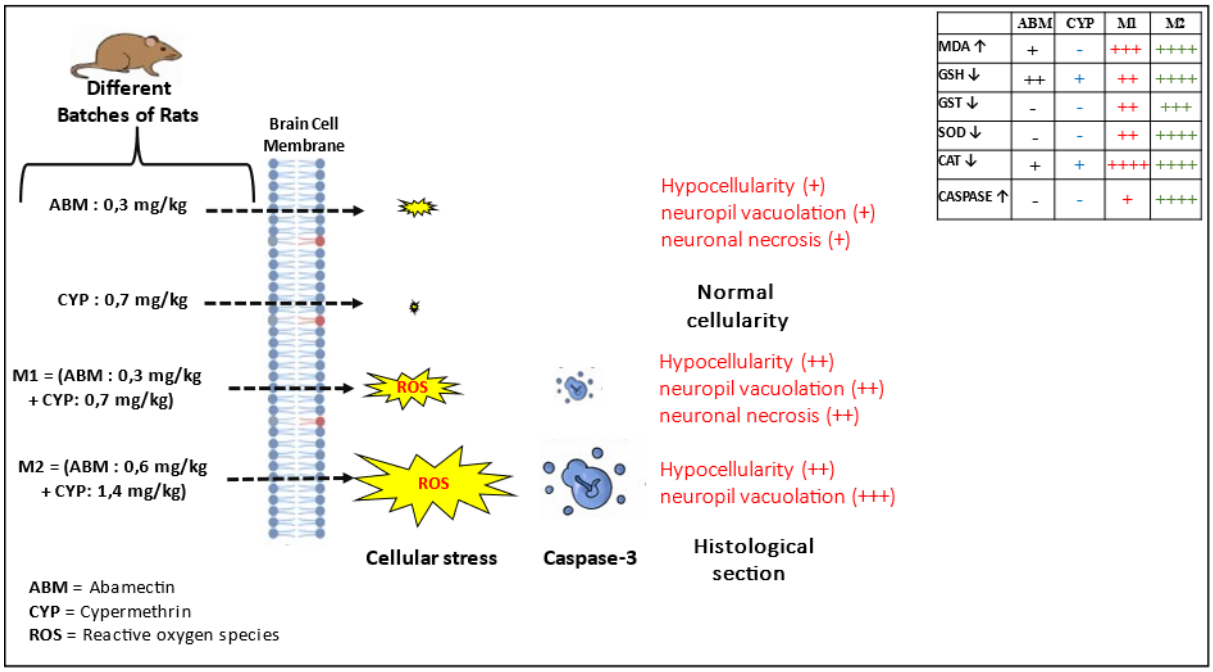
Methods : This study evaluated the subchronic neurotoxicity of ABM and CYP, administered individually or in combination for 90 days to 40 Wistar rats divided into five groups: control, ABM (0.3 mg/kg/day), CYP (0.7 mg/kg/day), mixture M1 (ABM 0.3 + CYP 0.7 mg/kg/day), and mixture M2 (ABM 0.6 + CYP 1.4 mg/kg/day).

Results : The results revealed that exposure, particularly to mixtures, decreased brain protein levels, significantly reduced glutathione, superoxide dismutase, and catalase, and markedly increased malondialdehyde levels compared to groups exposed to a single pesticide.. Glutathione S-transferase activity was less affected, but caspase-3 was activated in M1 and M2 groups, indicating apoptosis induction. Histological analyses in M1 and M2 groups showed pronounced hypocellularity associated with cellular hypertrophy and necrotic foci compared with controls.

Conclusions : The observed synergistic effect highlights an increased toxicological risk, underscoring the need for further mechanistic studies and appropriate regulatory measures. Under environmental conditions where combined exposures are frequent, these results highlight the importance of considering the impact of mixtures rather than isolated compounds.

Keywords: Abamectin, Cypermethrin, Oxidative stress, Pesticide mixture, low-dose

Graphical Abstract



	ABM	CYP	M1	M2
MDA ↑	+	-	+++	++++
GSH ↓	++	+	++	++++
GST ↓	-	-	++	+++
SOD ↓	-	-	++	++++
CAT ↓	+	+	++++	++++
CASPASE ↑	-	-	+	++++

INTRODUCTION

Global demographic expansion and the intensifying demand for agricultural productivity have driven a substantial escalation in pesticide use over the past decades. Insecticides, fungicides, and herbicides are now widely employed to maximize agricultural yields [1-3]. This massive use, although effective in the short term, is accompanied by a continuous release of residues into the environment [4-6]. These residues, present in soils, water, and crops, chronically expose human and animal populations to low doses of potentially toxic compounds [7-10].

In Togo, several studies have highlighted frequent, even inappropriate, pesticide use in agricultural practices [11, 12]. Pesticide residues have notably been detected in locally grown vegetables, sometimes at levels exceeding the maximum limits set by the Codex Alimentarius. A recent study conducted by Badjabaissi et *al*. (2024) revealed the presence of multiple pesticide residues in market gardening crops. Among these pesticides are abamectin and cypermethrin, two substances particularly widespread in Togolese agriculture [13].

Abamectin, derived from the metabolism of Streptomyces avermitilis, and cypermethrin, a synthetic pyrethroid, are both recognized for their effectiveness against a wide spectrum of parasites. However, beyond their usefulness in agriculture, these molecules present concerning toxicological profiles. Numerous studies have demonstrated their impact on various organs [14-20], with a predilection for the central nervous system [21-25]. Their mechanism of action relies mainly on the disruption of ion channels and the induction of oxidative stress, leading to neuronal alterations that are sometimes irreversible. Abamectin is one of the most widely used pesticides in the world due to its powerful insecticidal and vermicidal activity. It easily crosses the blood-brain barrier and activates GABA-dependent chloride channels, leading to inhibition of nerve influx and neurotoxic damage [26, 27]. It is also known to affect non-target species, including fish, beneficial insects, and mammals [28, 29]. Studies have shown that abamectin disrupts antioxidant activities and increases reactive oxygen species (ROS), impairing immune responses and causing neurotoxic and genotoxic damage [23, 30]. Cypermethrin, on the other hand, is a synthetic pyrethroid commonly used in agriculture, veterinary medicine, and in the control of domestic insects/parasites [31]. Although considered safe for domestic applications, some studies have reported adverse effects of cypermethrin on the brains of laboratory animals [32, 14]. Cypermethrin acts mainly on voltage-dependent sodium channels, keeping them open longer than normal, which provokes repetitive neuronal discharges and excessive production of reactive oxygen species (ROS) [32, 33]. These ROS are responsible for oxidative damage, including lipid peroxidation and cellular dysfunctions.

In laboratory animals, repeated oral exposures to these pesticides have led to the generation of reactive oxygen species (ROS) and nitrogen species, resulting in lipid peroxidation (LPO) [34, 35]. These data suggest that the brain, due to its low antioxidant capacity, high oxygen consumption, and abundance in polyunsaturated fatty acids, represents a preferred target of pesticide toxicity [36, 37].

Although the acute neurotoxic effects of abamectin and cypermethrin are well documented, the consequences of prolonged low-dose exposures, often more representative of real exposure conditions, remain less

studied. Moreover, the combined effects of these two pesticides, which may be synergistic or additive, have not been experimentally investigated. It is, however, well established that it is difficult to predict the toxicity of a mixture from the individual effects of its components [38], hence the importance of specific research on pesticide cocktails.

In this context, the present study aims to evaluate the subchronic neurotoxic effects of combined exposure to abamectin and cypermethrin, administered at realistic doses, in rats. The focus will be on the modulation of the brain antioxidant system, particularly on key oxidative stress enzymes, the apoptotic system, and the histology of the cerebral cortex, in order to better understand the mechanisms underlying this mixed neurotoxicity.

MATERIALS AND METHODS

1. Study framework and animal material

Male and female rats of the Wistar strain were provided by the animal facility of the Pharmaceutical Department of the Faculty of Health Sciences (FSS) of the University of Lome (Lome-Togo). A total of 20 male et 20 femele rats aged 5 to 6 weeks weighing approximately 150-180 g were used. They were fed and provided with water ad libitum under standard breeding conditions (temperature: 22±3°C, photoperiod 12/12H). The rats' urine and droppings collection trays were maintained once every three days until the end of the experiment. The work was carried out in the pharmacology and toxicology laboratory of the said department.

2. Chemicals

In this study, we used abamectin (Pestanal®, 31732) and cypermethrin (Pestanal®, 36128) both from Sigma-Aldrich. The products and reagents used for the evaluation of biological parameters were mainly from Sigma-Aldrich such as TRIS buffer (252859-100G), 5,5'-Dithiobis(2-Nitrobenzoic acid) (D8130-5G), glutathione (G4251-10G), pyrogallol (06931-50MG), 1-Chloro-2,4-dinitrobenzene (237329-50G) as well as the kits for the enzyme assay (Caspase-3, CASP3C-1KT).

3. Experimental

The rats were divided into five (05) groups, with eight (08) rats per group. Group T, the control group (T), received an acetone/distilled water solution (0.5%); group ABM, rats treated with abamectin (ABM) at a dose of 0.3 mg/kg/day; group CYP, rats treated with cypermethrin (CYP) at a dose of 0.7 mg/kg/day. Group M1, rats treated with ABM (0.3 mg/kg/day) and CYP (0.7 mg/kg/day) and Group M2, rats treated with ABM (0.6 mg/kg/day) and CYP (1.4 mg/kg/day).

They were subjected to a 10 day housing period in the animal facility of the Pharmaceutical Department of the Faculty of Health Sciences, University of Lomé. Two (02) pesticides (abamectin and cypermethrin) were used in this study, alone or in a mixture at consecutive doses of 0.3 mg/kg/day (1/30 of the LD50) and 0.7 mg/kg/day (1/250 of the LD50) for oral administration for 90 days. The choice of these doses was made on the basis of the results of pesticide dosage in vegetables reported by Badjabaissi et al. (2024) in Togo [13]. This study revealed that abamectin levels exceeded the maximum residue limit (MRL) in 7 out of 10 samples, while cypermethrin had the highest concentrations among all the substances analyzed, also exceeding the MRL. The pesticides were dissolved in acetone (0.5%) and then supplemented with distilled water to reach the required volume. The composition was prepared weekly throughout the experimental period.

4. Study of cellular and molecular integrity of neurocytes

Estimation of relative brain weight and preparation of cytosolic samples

Brains were collected the day after the 90th day of treatment, after a 12-hour fasting period. They were quickly rinsed with cold phosphate-buffered saline (PBS, 0.1 M, pH 7.4) and gently dried with semi-absorbent paper at 4°C. Each brain was weighed, and the relative weight (RP) was calculated using the following formula : RP = 100 x (organ weight/rat weight). For each experimental group, two brains (one male and one female) were randomly selected and fixed in 10% formalin for histopathological analysis. The remaining six brains (three males and three females) were used for biochemical analyses. Each brain intended for biochemical analysis was homogenized in cold phosphate-buffered saline (PBS, 0.1 M, pH 7.4) using a glass homogenizer. One (1) gram of total brain was diluted in 2 mL of PBS, and the resulting homogenate was centrifuged at 3000 rpm for 15 minutes at 4°C. The supernatant (cytosolic fraction) was collected and used for the determination of biochemical parameters. The cytosolic fractions were used to assess:

- oxidative stress biomarkers including reduced glutathione (GSH), glutathione S-transferase (GST), catalase (CAT), superoxide dismutase (SOD), and malondialdehyde (MDA) and
- the apoptotic marker, caspase-3 activity

Evaluation of biochemical parameter : Total protein determination at the tissue level

The total protein concentration in tissue homogenates was determined according to the Bradford method (1976), using bovine serum albumin (BSA) as the standard [39].

Evaluation of oxidative stress parameters

- **Malondialdehyde (MDA) determination**

The assay for malondialdehyde (MDA) was performed following the method described by Patlolla et al. (2009) [40]. Briefly, the reaction mixture contained 1-methyl-2-phenylindole (10.3 mM in acetonitrile, 650 µL), to which 250 µL of either MDA standard or tissue homogenate was added. The mixture was vortexed, and 150 µL of hydrochloric acid (12 N) and 10 µL of butylated hydroxytoluene (BHT, 0.1 M) were subsequently added.

The samples were incubated at 45 °C for 1 hour and then centrifuged at 3500 rpm for 10 minutes. The absorbance of the supernatant was measured at 586 nm. The MDA standard curve was prepared using concentrations of 0, 0.625, 1.25, 2.5, 5, 10, and 20 nM. A blank solution consisting of 75% acetonitrile, 25% ferric chloride, and 200 µL of Tris buffer (pH 7.4) was used as reference.

- **Reduced glutathione (GSH) determination**

The determination of reduced glutathione (GSH) levels was carried out using the modified method of Sedlak and Raymond (1968) [41]. In this procedure, tissue homogenates or standard GSH solutions were mixed with Tris buffer (0.2 M, pH 8.2) and 5,5'-dithiobis-2-nitrobenzoic acid (DTNB, 0.01 M). The reaction mixture was brought to a final volume of 1 mL with absolute methanol, sealed, and homogenized for 30 minutes at room temperature. After centrifugation at 3000 rpm for 15 minutes, the absorbance of the supernatant was measured at 412 nm following a 5-minute incubation. GSH concentrations were calculated from a standard calibration curve (10^{-6} to 10^{-2} mg/mL) and expressed as nanomoles per milligram of protein (nmol GSH/mg protein).

- **Glutathione S-transferase (GST) activity assay**

Glutathione S-transferase (GST) activity was determined according to the method of Habig et al. (1974) [42]. The reaction mixtures were prepared as follows: the blank contained 850 µL of phosphate-buffered saline (PBS, 0.1 M, pH 7.4), 55 µL of 1-chloro-2,4-dinitrobenzene (CDNB, 0.02 M), and 100 µL of reduced glutathione (GSH, 0.1 M). For the test samples, 830 µL of PBS, 50 µL of CDNB (0.02 M), 100 µL of GSH (0.1 M), and 20 µL of tissue homogenate were mixed. The formation of the conjugate, 1-S-glutathionyl-2,4-dinitrobenzene, was monitored spectrophotometrically at 340 nm. GST activity was expressed as nanomoles of CDNB conjugated per minute per milligram of protein (nmol CDNB/min/mg protein).

- **Catalase (CAT) activity assay**

Catalase (CAT) activity was determined according to the method of Aebi (1984) [43]. The reaction mixtures were prepared as follows: the blank contained 800 µL of phosphate-buffered saline (PBS, 0.1 M, pH 7.4) and 200 µL of hydrogen peroxide (H_2O_2, 0.5 M). For the test samples, 780 µL of PBS, 200 µL of H_2O_2 (0.5 M), and 20 µL of tissue homogenate were mixed. Enzymatic activity was measured spectrophotometrically by monitoring the decrease in absorbance at 240 nm, corresponding to the decomposition of H_2O_2. Absorbance readings were taken after a 15 second delay over a period of 60 seconds. Catalase activity was expressed as micromoles of H_2O_2 decomposed per minute per milligram of protein (µmol H_2O_2/min/mg protein).

- **Superoxide Dismutase (SOD) Enzyme Activity Assay**

Superoxide dismutase (SOD) activity was determined according to the method described by Marklund and Marklund (1974) [44] and modified by Hassan et al. (2014) [45]. The assay was based on the competition between the autoxidation of pyrogallol and the dismutation of superoxide radicals by SOD. Tissue homogenates or standards were incubated with Tris-succinate buffer (0.05 M, pH 8.2) and pyrogallol (8 mM) at 25 °C for 20 minutes. The rate of pyrogallol autoxidation was monitored spectrophotometrically at 412 nm over a 3minute period, with absorbance readings taken every 30 seconds.

- **Apoptosis biomarker assessment: Caspase 3 activity**

Caspase-3 activity was assessed in cytosolic extracts of brain tissue using a commercial colorimetric kit (Caspase-3 Activity Colorimetric Assay Kit, ref. APT131, Sigma®, Germany). The method was adapted for tissue analysis. The principle was based on the hydrolysis of the specific substrate Ac-DEVD-pNA, resulting in the release of the chromophore p-nitroaniline (pNA), whose absorbance at 405 nm is proportional to enzymatic activity. A standard curve was generated from pNA dilutions to establish the relationship between absorbance and concentration. Cytosolic extracts were incubated with the substrate at 37°C for 1 to 2 hours. After incubation, pNA absorbance was measured using a UV/Visible spectrophotometer. Caspase-3 activity was expressed in relative absorbance units (ΔDO) and compared between experimental groups. The increase in absorbance reflected increased caspase-3 activation, indicating an intensification of the apoptotic process in treated brain tissues.

5. Histological Tests

Histological examination was carried out in the cerebral cortex of rats from different batches. The number of tissue fragments, their appearance, size, and weight of each fragment were determined. Sections were then made, followed by systematic sampling. After dehydration in various ethyl alcohol baths of increasing strength (70%, 95%, and 100%), the samples were impregnated and embedded. Thin sections were then cut using a microtome and spread onto slides for hematoxylin-eosin staining. The slides were interpreted under a light microscope at various magnifications.

6. Statistical Analysis

The results were expressed as the mean of six replicates (mean ± standard deviation). Data visualization was performed using Microsoft Office Excel 2013 to generate graphs and histograms. Statistical analyses were conducted using GraphPad Prism version 8.4.3 (GraphPad Software, USA). The results were expressed as mean values ± standard error of the mean (M ± SEM). A p-value < 0.05 was considered statistically significant. Data were analyzed using one-way ANOVA, followed by

Tukey's multiple comparison test, according to the following significance levels : p > 0.05: not significant (ns) ; 0.05 > p > 0.01: significant (*) ; 0.01 > p > 0.001: highly significant (**) ; p < 0.001: very highly significant (***) ; p < 0.0001: extremely significant (****).

RESULTS

a. Effect of pesticides on relative brain weight (g) of rats

The results showed non-significant decreases in relative brain weight of pesticide-treated rats compared to the control group (Figure 1).

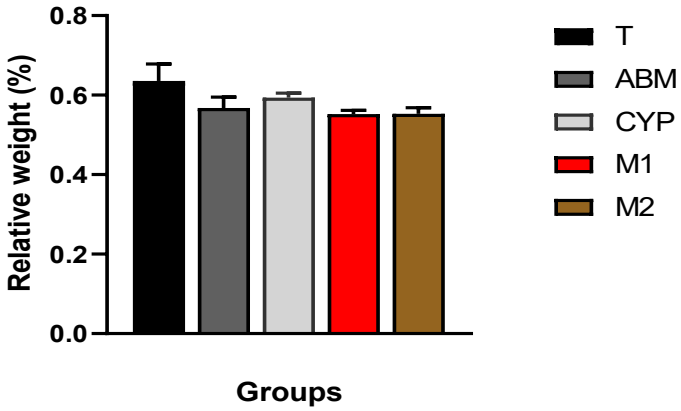


Figure 1 : Evolution of the relative weight (%) of the brains of treated rats after 90 days of treatment.

Abbreviations: T = Control; ABM = Abamectin (0.3 mg/kg); CYP = Cypermethrin (0.7 mg/kg); M1 = Abamectin (0.3 mg/kg) + Cypermethrin (0.7 mg/kg). M2 = Abamectin (0.6 mg/kg) + Cypermethrin (1.4 mg/kg). Each value represents Mean ± SEM. (n) number of animals per group = 8. (*) indicates a significant difference compared to the control group (T). Significance from p < 0.05.

b. Effects of pesticides on biochemical parameters

Protein Assays

The results of cytosolic protein assessment in the whole brain are summarized in Figure 2. A significant decrease in protein levels was observed in the ABM (p < 0.01), M1 (p < 0.001) and M2 (p < 0.0001) groups, compared to the control group. Treated rats in the M1 group showed a significant decrease in protein levels compared to the CYP group.

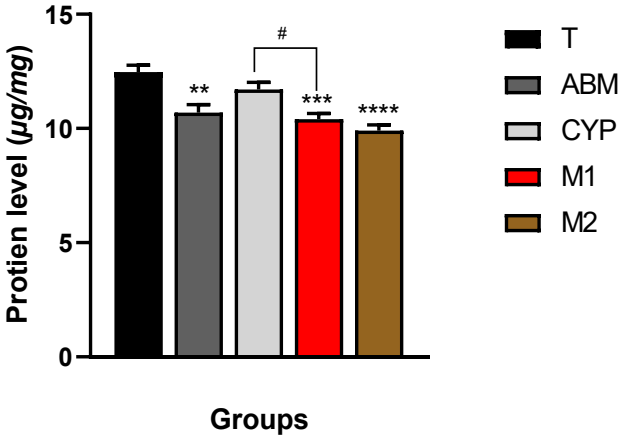


Figure 2: Effect of pesticides on the variation of protein levels in the total brain of rats after 90 days of treatment.

Abbreviations: T = Control; ABM = Abamectin (0.3 mg/kg); CYP = Cypermethrin (0.7 mg/kg); M1 = Abamectin (0.3 mg/kg) + Cypermethrin (0.7 mg/kg). M2 = Abamectin (0.6 mg/kg) + Cypermethrin (1.4 mg/kg). Each value represents Mean ± SEM. (n) number of animals per group = 6. (*) indicates a significant difference compared to the control group (T); (#) compared to the CYP group. Significance from p < 0.05.

c. Effects of Pesticides on Redox Status

Effets des radicaux libres

- **Malondialdehyde (MDA)**

Mixtures M1 ($p < 0.01$) and M2 ($p < 0.0001$) significantly increased MDA levels in the brain of rats compared to the control group. In this same figure, a highly significant increase in MDA levels in rats in group M2 ($p < 0.0001$) was reported compared to group M1. The addition of abamectin to cypermethrin (1.1 mg/kg/day) in rats (group M1) resulted in a significant increase ($p < 0.01$) in MDA levels compared to rats given only cypermethrin (group CYP). Furthermore, a significant increase was noted in group ABM ($p < 0.05$) compared to the control (Figure 3).

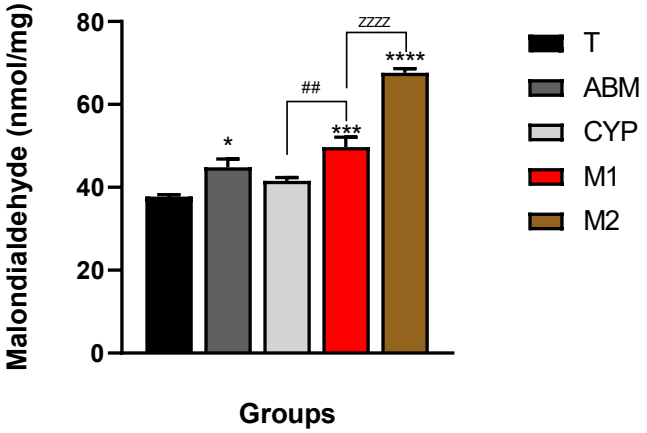


Figure 3: Effect of pesticides on the cytosolic variation of malondialdehyde levels in the whole brain of rats after 90 days of treatment.

Abbreviations: T = Control; ABM = Abamectin (0.3 mg/kg); CYP = Cypermethrin (0.7 mg/kg); M1 = Abamectin (0.3 mg/kg) + Cypermethrin (0.7 mg/kg). M2 = Abamectin (0.6 mg/kg) + Cypermethrin (1.4 mg/kg). Each value represents Mean ± SEM. (n) number of animals per group = 6. (*) indicates a significant difference compared to the control group (T); (#) compared to the CYP group and (z) compared to the M1 group. Significance from p < 0.05.

Effects on Non-Enzymatic Antioxidant System Parameters

- **Glutathione (GSH)**

The effects of abamectin and cypermethrin on GSH levels are shown in Figure 4. Exposure of rats to abamectin and cypermethrin resulted in a significant decrease in total brain glutathione (GSH) concentrations in groups ABM ($p < 0.01$); CYP ($p < 0.05$); M1 ($p < 0.01$); and M2 ($p < 0.0001$) compared to the control group (T). A significant decrease in glutathione levels was observed in rats from group M2 ($p < 0.0001$) compared to rats from group M1.

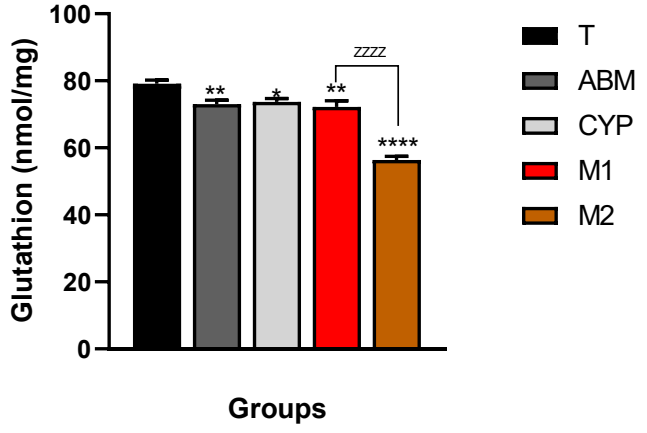


Figure 4: Effect of pesticides on cytosolic variation of glutathione levels in the whole brain of rats after 90 days of treatment.

Abbreviations: T = Control; ABM = Abamectin (0.3 mg/kg); CYP = Cypermethrin (0.7 mg/kg); M1 = Abamectin (0.3 mg/kg) + Cypermethrin (0.7 mg/kg). M2 = Abamectin (0.6 mg/kg) + Cypermethrin (1.4 mg/kg). Each value represents Mean ± SEM. (n) number of animals per group = 6. (*) indicates a significant difference compared to the control group, (z) compared to group M1. Significance from p < 0.05.

Effects on Enzymatic Antioxidant System Parameters

- **Glutathione S-Transferase (GST)**

Exposure of rats to abamectin and cypermethrin did not result in a significant decrease in total brain glutathione S-transferase (GST) levels in treated groups compared to the control group (T) (Figure 5-A). A significant decrease in glutathione levels was observed in rats in group M1 compared to rats in group T ($p < 0.001$) and in group CYP ($p < 0.01$).

- **Superoxide Dismutase (SOD)**

The effects of pesticides on rats were reflected in a significant decrease in SOD activity in groups M1 ($p < 0.01$) and M2 ($p < 0.0001$) compared to the control group. Compared to the groups treated with abamectin (ABM) and cypermethrin (CYP) alone, co-administration in group M1 resulted in a significant decrease in SOD activity in the total brain, $p < 0.05$ and $p < 0.001$, respectively (Figure 5-B).

- **Catalase (CAT)**

The study showed a significant decrease ($p < 0.05$) in the level of catalase activity in the brain tissues of rats treated with abamectin, cypermethrin, and mixtures of both pesticides M1 and M2 ($p < 0.0001$) compared to rats in the control group. Treatment of rats with the abamectin and cypermethrin mixture in batch M1 resulted in a significant decrease ($p < 0.05$) in catalase activity, compared to rats treated with only abamectin (batch ABM) and cypermethrin (batch CYP). A significant decrease ($p < 0.001$) in catalase activity was also observed in batch M2 compared to batch M1 (Figure 5-C).

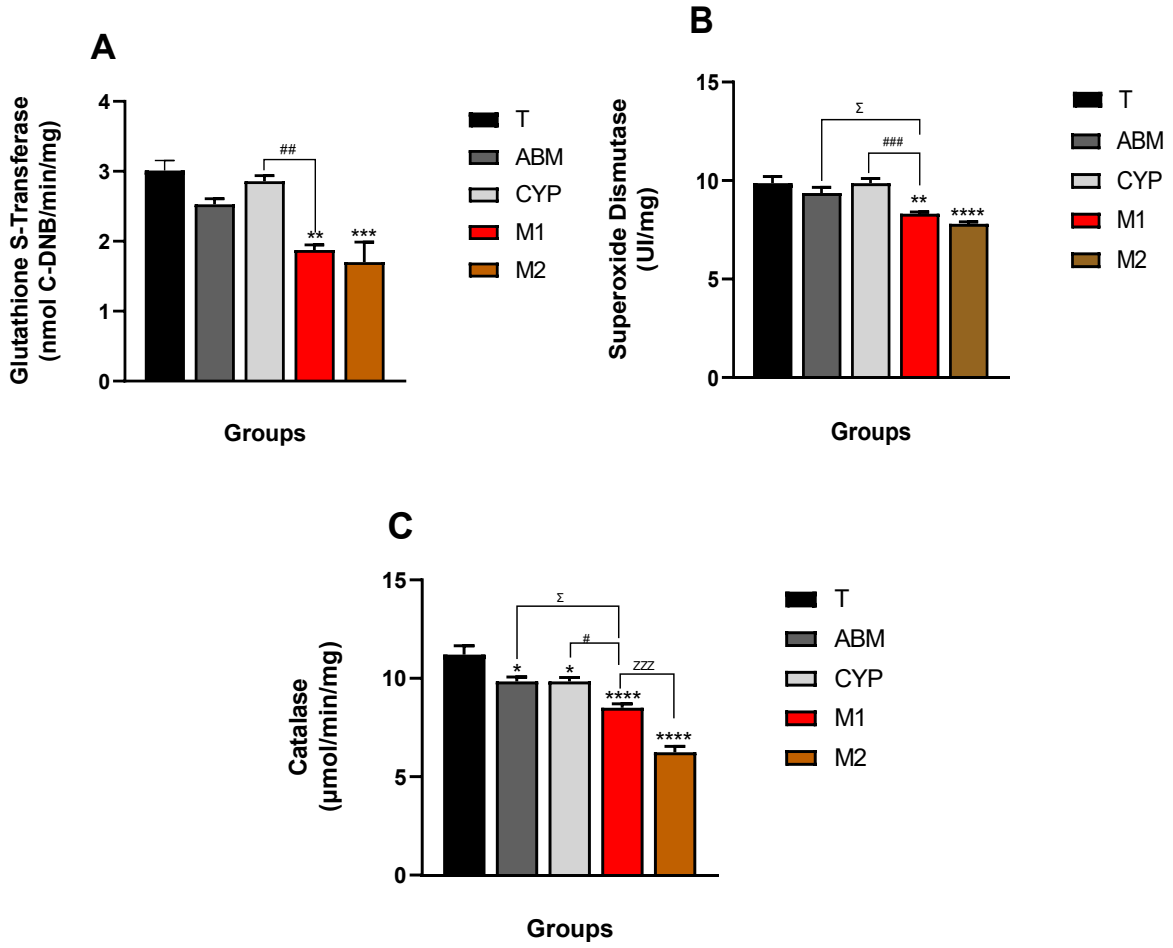


Figure 5: Effect of pesticides on the cytosolic variation of the parameters of the enzymatic antioxidant system in the whole brain of rats after 90 days of treatment. (A) Glutathione S-transferase levels; (B) Superoxide dismutase activity; (C) Catalase activity.

Abbreviations: T = Control; ABM = Abamectin (0.3 mg/kg); CYP = Cypermethrin (0.7 mg/kg); M1 = Abamectin (0.3 mg/kg) + Cypermethrin (0.7 mg/kg). M2 = Abamectin (0.6 mg/kg) + Cypermethrin (1.4 mg/kg). Each value represents Mean ± SEM. (n) number of animals per group = 6. (*) indicates a significant difference compared to the control group (T); (Σ) compared to the ABM group; (#) compared to the CYP group and (z) compared to the M1 group. Significance from p < 0.05.

d. Effects of pesticides on pro-apoptotic markers

- Caspase-3 activity

Statistical analysis of the results of the enzymatic assay of caspase-3 activity showed a significant increase in batches M1 ($p < 0.05$) and M2 ($p < 0.0001$) compared to the control batch. An increase in caspase-3 activity in batches M2 ($p < 0.05$) and M1 ($p < 0.05$) was obtained, respectively, compared to batches M1 and CYP. No statistically significant difference was observed in the other batches compared to the control (Figure 6).

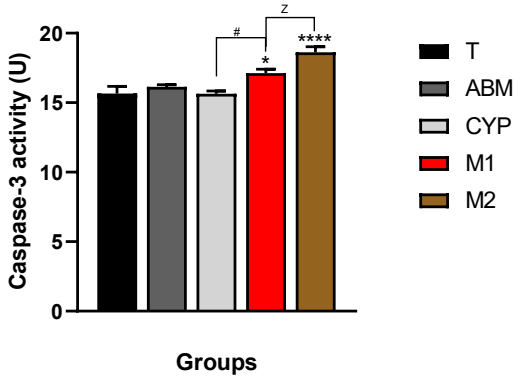


Figure 6: Effect of pesticides on the variation of caspase 3 activity in the total brain of rats after 90 days of treatment.

Abbreviations: T = Control; ABM = Abamectin (0.3 mg/kg); CYP = Cypermethrin (0.7 mg/kg); M1 = Abamectin (0.3 mg/kg) + Cypermethrin (0.7 mg/kg). M2 = Abamectin (0.6 mg/kg) + Cypermethrin (1.4 mg/kg). Each value represents Mean ± SEM. (n) number of animals per group = 6. (*) indicates a significant difference compared to the control group (T); (#) compared to the CYP group and (z) compared to the M1 group. Significance from p < 0.05

e. Effect of pesticides on the histology of the cerebral cortex of rats

Histological analysis of sections of the cerebral cortex of treated rats revealed abnormalities compared to controls (Figure 7). A slight decrease in cellularity, associated with necrosis and vacuolization of the neuropil, was observed in the cerebral cortex of rats in the ABM group compared to controls. Cellularity within normal limits was observed in the CYP group. Histological sections of the cerebral cortex of rats in groups M1 and M2 showed marked hypocellularity with the presence of neuropil vacuolization compared to the control group (Figure 7, D & E). Neuronal necrosis was observed in group M1 (Figure 7, D).

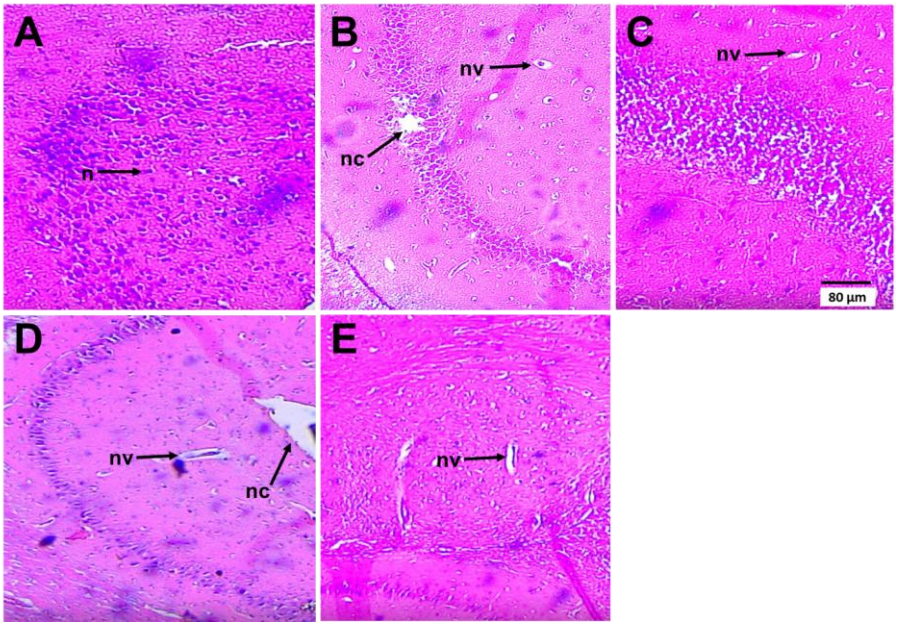


Figure 2 : Histological sections in the rat brain after 90 days of treatment. A = Control; B = Abamectin; C = Cypermethrin; D = M1 (Abamectin + Cypermethrin); E = M2 ((Abamectin + Cypermethrin) x 2). n = neurons with normal structures. nv = neuropils with vacuoles. nc = necrosis. Magnification: x100.

DISCUSSION

1. Pesticides and relative brain weight

Chronic exposure to low concentrations of abamectin, cypermethrin, or their combination did not result in any significant variation in relative brain weight between the treated groups and the control group. This stability could be explained by the fact that the administered doses were likely too low, or the exposure duration too short, to induce morphometric alterations.

Beyond the individual effects of each pesticide, the study also investigated the impact of their combination

in order to assess potential interactions (additive or synergistic) that could amplify neurotoxicity. In this context, groups M1 and M2 showed a significant decrease in body weight compared with the control group. However, no significant effect on brain weight was observed following combined exposure. This finding suggests that while co-exposure to abamectin and cypermethrin may disrupt certain physiological parameters such as body weight, it may not, under the experimental conditions of this study, be sufficient to cause detectable morphometric alterations in the brain. Nevertheless, the absence of changes in brain weight does not rule out possible underlying functional or biochemical effects. Indeed, previous studies have shown that low-dose pesticide exposure can affect neurophysiology without necessarily inducing changes in brain mass [7, 46, 47]. Thus, the impact of the mixture could manifest in a more subtle manner, particularly at the cellular or molecular level, which justifies the complementary analyses carried out in this study.

2. Pesticides and biochemical parameters

According to the results of our study, exposure of rats to pesticides alone (ABM) or in combination (M1 and M2) induced a disruption of the general metabolism of brain cells, particularly in protein profiles. This disruption is greater in batches exposed to the M1 mixture compared to ABM and CYP batches, suggesting an additive or synergistic toxic interaction. The measurement of total protein content is a classical indicator of stress in organisms [48, 49]. Under severe environmental constraints (oxidative, thermal, or water stress, pollution, infections...), proteins undergo denaturation processes [50], leading to a reduction in their concentration due to structural degradation and inhibition of synthesis mechanisms [51]. Furthermore, oxidative damage to proteins can compromise the integrity of cell membranes and disrupt key functions such as membrane fluidity, mitochondrial homeostasis, and regulation of oxidative stress [52].

3. Pesticides and redox status

The central nervous system (CNS), due to its intense activity, consumes a large proportion of the body's total oxygen approximately 20-25%. This high oxygen demand is accompanied by a moderate production of reactive oxygen species (ROS), which remains well regulated by endogenous antioxidant systems [53–55]. However, chronic exposure to certain pesticides may disrupt this balance by inducing significant oxidative stress, thereby placing the brain among the major targets of their toxicity [34, 56].

Overall, our results highlight an alteration of the cytosolic redox status in the brains of rats exposed to pesticides alone, suggesting a predominance of oxidative stress, characterized by a significant decrease in antioxidant potential. One of the alterations observed in our study was the decrease in GSH content in the cytosolic cells of rats treated with pesticides.

Glutathione (GSH) is an essential component that plays a central role in cellular defense against oxidative stress by scavenging free radicals [57]. It functions both as a non-enzymatic antioxidant and as a critical cofactor of enzymes involved in xenobiotic detoxification, particularly by catalyzing conjugation reactions [58, 59]. During its metabolic action, the sulfhydryl group of GSH is oxidized into disulfide compounds, and reduced glutathione (GSH) is conjugated for the elimination of xenobiotics [60]. Sule et al. (2022) demonstrated that the depletion of intracellular sulfhydryl groups by pesticides is a prerequisite for ROS generation [34]. Thus, the significant reduction in GSH content observed in rats exposed to abamectin and cypermethrin alone in this study, after chronic exposure, could lead to an increased susceptibility to free radical–induced damage.

In contrast to our findings, Bekkairi et al. (2024) [61], using a dose of 0.019 mg/kg for 21 days, and Radi et al. (2020) [25], using a dose of 2 mg/kg for 5 days, reported that abamectin increased GSH content. This discrepancy may be explained by the exposure duration. Acute or subacute exposure can trigger an initial adaptive response of the antioxidant system, resulting in elevated GSH levels to counteract oxidative aggression. Conversely, similar results to ours were reported by Sharma et al. (2014) after exposure to a higher dose of cypermethrin (3.83 mg/kg for 7 days) [**62**]. Our findings indicate that even at low doses, chronic exposure can induce continuous production of free radicals, leading to the progressive depletion of GSH and persistent impairment of the cellular redox defense system.

Beyond GSH, antioxidant enzymes such as GST, SOD, and CAT play crucial roles in the cellular antioxidant system. The conjugation of electrophilic substrates with the thiol group of GSH is catalyzed by glutathione S-transferases (GST), producing less harmful products for the organism [63]. GST is also involved in neutralizing lipid peroxides, thereby limiting ROS-induced damage in various cells. Located mainly in the cytosol, these enzymes participate in diverse intracellular transport and biosynthetic processes [64, 65]. Superoxide dismutase (SOD) and catalase (CAT) represent the main enzymatic defense mechanisms against the toxic effects of oxygen metabolism.

In the present study, GST and SOD activity was not significantly altered in rats exposed to abamectin or cypermethrin alone. This suggests that under the experimental conditions, these two antioxidant enzymes were able to maintain their function relatively stably, despite pesticide exposure. However, a downward trend was observed, possibly indicating the onset of redox imbalance, though not reaching statistical significance. In contrast, a significant inhibition of catalase (CAT) activity was observed in these groups. This enzyme plays a central role in the degradation of hydrogen peroxide (H_2O_2) into water (H_2O) and molecular oxygen (O_2), thereby preventing the accumulation of oxidant products harmful to cells [66–68]. Our results suggest that these pesticides increase H_2O_2 in the cytosol and

generate massive amounts of hydroxyl radicals °OH [25, 69, 70].

Because of the extremely reactive, unstable, and low-concentration nature of free radicals, indirect markers are generally measured [71]. Malondialdehyde (MDA) levels reflect the extent of lipid peroxidation and represent one of the fundamental mechanisms of free radical–induced cellular damage [72]. MDA is a product of oxidative degradation of unsaturated lipids in membranes [72, 73]. Thus, under stress induced by xenobiotics such as pesticides, when antioxidant systems become ineffective, cellular damage can be assessed through MDA levels, making it a reliable biomarker of oxidative stress.

Previous studies have reported elevated MDA levels in the brains of rats treated with abamectin [23, 61] and cypermethrin [62,74,75] at relatively high doses. In our study, a significant increase in MDA levels was observed in the ABM group compared to controls. This may be due to insufficient anti-ROS capacity, leading to hydroxyl anion generation that attacks membrane phospholipids. Unlike abamectin, cypermethrin did not induce a significant change in MDA levels. In the ABM group, inhibition of antioxidant enzymes SOD and CAT, responsible for eliminating free radicals, led to superoxide accumulation. This accumulation promoted lipid peroxidation, as revealed in our study. Previous research has reported that lipid peroxidation accumulation is accompanied by DNA damage, which can disrupt gene expression and lead to cell death [76–78]. This oxidative stress process also disrupts neuronal structure and reduces their capacity to produce intracellular ATP, essential for proper cellular functioning [79]. Such cellular damage leads to degeneration in key brain regions such as the hippocampus and striatum.

After characterizing the individual effects of each pesticide on oxidative stress, mixture analysis allows assessment of potential interactions whether additive, synergistic, or antagonistic. A significant accumulation of superoxide, reflected by marked inhibition of SOD, CAT, and GST activities, was observed in the M1 group compared to rats exposed to a single pesticide. Lipid peroxidation was also more pronounced in the M1 group. The strong inhibition of GST activity in M1 rats indicates insufficient conjugation of electrophiles and inadequate detoxification of these species. This inhibition is particularly concerning as it is accompanied by a significant reduction in CAT and SOD activity in the mixture group. The decline in these free radical–eliminating enzymes confirms the oxidative stress state induced by these pesticides in brain tissue during co-exposure. The simultaneous decrease of these enzymes likely promotes further accumulation of superoxide and other ROS, exacerbating oxidative stress in the brain. These results suggest the failure of the brain's antioxidant machinery to counteract ROS accumulation induced by these pesticides, likely due to the high oxidative metabolism in the brain [80].

Although other studies on abamectin and cypermethrin administered separately have reported similar effects at higher doses [30, 62, 81, 82], our study shows that comparable effects can occur at lower doses during chronic co-exposure to both pesticides. Since pesticides generate excess ROS, the compensatory effect of antioxidant enzymes may quickly become overwhelmed [34]. The significantly higher MDA increase in the M1 group compared to the ABM and CYP groups suggests altered neuronal lipid membrane integrity [83] and rapid depletion of intracellular ATP, compromising neuronal viability and leading to cell degeneration in the hippocampus, striatum, and whole brain. Such disturbances could have major impacts on the physiology and behavior of rats intoxicated by these pesticides [55, 84, 85]. Moreover, more significant changes in redox parameters were observed in the M2 group compared to the M1 group, suggesting a dose-dependent effect. These findings reveal that combined pesticide exposure exacerbates oxidative stress cumulatively or synergistically, leading to deeper impairment of antioxidant defense mechanisms.

The decrease in antioxidant enzyme activity was concomitant with a reduction in total protein content in the brains of treated rats. This reduction may be attributed to the inhibition of protein synthesis and reduced cell survival due to antioxidant enzyme deficiency observed in our study. In light of these imbalances, the possible involvement of apoptotic mechanisms warrants consideration.

4. Pesticides and the apoptotic signaling pathway

Reactive oxygen species (ROS) trigger fatal mitochondrial energy (ATP) depletion, proteolytic enzyme induction, and DNA fragmentation, ultimately leading to apoptotic cell death [33, 86]. Apoptosis is a programmed form of cell death, essential for cellular homeostasis, and is activated by various stimuli through caspases [87–89]. The accumulation of abnormal protein aggregates can also induce apoptosis, a mechanism implicated in several neurodegenerative diseases such as Alzheimer's and Parkinson's disease [90–93].

Oxidative stress induces the opening of mitochondrial pores, leading to the release of cytochrome c, activation of Apaf-1, and a cascade involving caspase-9 and caspase-3, the central proteins in apoptotic execution [94–96]. In this study, we investigated for the first time the expression of caspase-3 genes in rats exposed to abamectin, cypermethrin, and their mixture. However, no significant increase in caspase-3 activity was observed with abamectin or cypermethrin alone. In contrast, our findings differ from those of Ibrahim et al. (2022), who reported increased caspase-3 activity in the fetal brains of pregnant rats exposed to abamectin alone [23]. Moreover, previous studies have shown that brain apoptosis can result from oxidative stress induced by cypermethrin at high doses [70, 97]. Thus, the discrepancy between our results and the literature could be explained by differences in experimental conditions

(species, developmental stage, exposure duration, dose, or tissue analyzed).

Conversely, a significant increase in caspase-3 activity in the cytosol was observed in the mixture groups (M1 and M2), indicating enhanced activation of the apoptotic pathway. This activation may result from cumulative or synergistic toxic interactions between abamectin and cypermethrin, thereby amplifying pro-apoptotic mechanisms.

Indeed, individual exposure to abamectin or cypermethrin caused depletion of antioxidant enzymes such as catalase, superoxide dismutase (SOD), and glutathione (GSH), thereby weakening cellular antioxidant defenses. The combination of both substances could therefore intensify ROS production, leading to cytosolic stress disruption, DNA damage, and massive induction of neuronal apoptosis effects already reported at high doses for each pesticide when administered separately [30, 98, 99].

Although activation of this apoptotic mechanism indicates toxicity, it can also be interpreted as an adaptive response by the organism, aiming to eliminate severely damaged cells and thereby preventing deleterious genetic alterations that may lead to carcinogenesis [100, 101].

5. Pesticides and brain histology

Histological analysis remains an essential step in understanding the effects of toxic substances on the central nervous system. Unlike biochemical or behavioral analyses, it allows direct observation of tissue organization and integrity [102, 103]. In the case of the brain, histological sections provide precise insight into the state of cells, revealing neuronal loss, changes in cell density, or signs of degeneration. They thus establish a direct link between pesticide exposure and the observed structural alterations [104]. The distribution of antioxidant defense mechanisms in the brain varies across cell types and anatomical regions [105]. The cerebral cortex is particularly sensitive to oxidative stress due to its specific redox status, making it more vulnerable to ROS-induced damage [106].

In our study, histological examination of the cerebral cortex of rats chronically exposed to pesticides revealed a reduction in cell number compared with controls. In the ABM group, cortical sections showed necrosis and neuropil vacuolization compared with controls. These results suggest moderate neuronal damage, consistent with previous observations. Indeed, Bekkairi et al. (2024) reported in Algeria a reduction in brain size in rats treated with abamectin (0.0019 mg/kg for 21 days) compared with controls, due to cell destruction [61]. Moreover, these authors described advanced autolytic changes and the presence of dark spots in several regions. Radi et al. (2019) reported pyknosis and black-stained pyramidal neurons associated with degenerative changes in the pyramidal layer of hippocampal sections in rats following abamectin administration (2 mg/kg for five days) [25]. These data reinforce the idea that abamectin induces neurotoxicity marked by neuronal damage. Neuropil vacuolization, frequently associated with neurodegenerative diseases, reflects cellular degeneration and is a clear sign of brain injury.

In the CYP group, cortical cell density was within normal limits compared with controls. These results contrast with those of Ali et al. (2020), who reported shrunken and pale pyramidal cells with contracted cytoplasmic processes in the cerebral cortex of rats exposed to cypermethrin (1 mg/kg, three times per day for 21 days) [75]. This discrepancy may be related to the relatively lower dose and shorter exposure duration in our study. It suggests that, under certain experimental conditions, cypermethrin alone may not induce major histological lesions. By contrast, histological sections of the cerebral cortex of rats in the M1 and M2 groups revealed marked hypocellularity and neuropil vacuolization compared with controls, indicating more pronounced alterations in cell density than those induced by individual pesticides. Cellular necrosis was also observed in the M1 group, suggesting neuronal loss due to direct cytotoxicity [107, 108].

The combination of these pesticides potentiates their deleterious effects, causing more severe brain damage than each pesticide administered alone. These histological observations corroborate the biochemical results in the M1 groups, showing increased oxidative stress, activation of apoptotic pathways, and neurobehavioral alterations compared to individual exposures. The combination of abamectin and cypermethrin thus appears to amplify neurotoxicity by simultaneously engaging apoptotic and necrotic mechanisms [109, 110]. These results would support the hypothesis of additive or synergistic interactions between the two pesticides, making their combination more harmful than either pesticide alone. An increase in stress was noted in the M2 batch compared to the M1 batch, reflecting a dose-dependent effect. This toxicological potentiation more accurately reflects environmental and occupational exposure conditions, where individuals are rarely exposed to a single pesticide.

CONCLUSION

This study reveals that chronic low-dose exposure to abamectin or cypermethrin alone results in limited alterations in the rat brain, whereas their combination induces much more pronounced effects. Co-exposure disrupted protein metabolism and redox status, promoted lipid peroxidation, activated apoptotic pathways, and caused more severe histological damage. These findings suggest an additive or synergistic effect between the two pesticides, reflecting potentiation of their neurotoxicity. Under environmental conditions where combined exposures are frequent, these results highlight the importance of considering the impact of mixtures rather than isolated compounds. Further investigations, particularly on neurotransmitters and neurobehavioral functions, are necessary to better

characterize the neurological risks associated with such co-exposures.

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