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Copper sulphate and its implications on lipid profile, serum electrolytes and cerebellar histology

Christopher Chiedozie Mbadugha[1]*, Michael Ebe Nandi[2], Ikechukwu Ezeah[3], Akpanabasi Alexis Malachy[1], Ernest Aniefiok Daniel[1]

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Author Affiliation:
[1]Department of Human Anatomy, Faculty of Basic Medical Sciences, University of Uyo, Nigeria
[2]Department of Human Anatomy, Faculty of Basic Medical Sciences, Cross River State University, Nigeria
[3]Department of Surgery. University of Medical Sciences, Ondo State, Nigeria

***Corresponding Author:**
Christopher Chiedozie Mbadugha,
Department of Human Anatomy, Faculty of Basic Medical Sciences,
University of Uyo, Nigeria,
Email: christophermbadugha@uniuyo.edu.ng

Contact list:

Christopher Chiedozie Mbadugha:	christophermbadugha@uniuyo.edu.ng
Michael Ebe Nandi:	enandi15@gmail.com
Ikechukwu Ezeah:	eikechukwu@unimed.edu.ng
Akpanabasi Alexis	Malachy: akpanabasimalachy@gmail.com

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ABSTRACT

Copper is essential in tiny amounts, but animal and cell studies show that excess copper sulphate is directly toxic to the body, mainly through oxidative stress, inflammation, and cell death. This study explored the effect of copper sulphate on the body weight, lipid profile, serum-electrolyte and cerebellar histology of adult Wistar rats. Twenty-five (25) adult male Wistar rats were divided into five groups of five animals each (n = 5). Group A served as the normal control group. Group B received 5 mg/kg body weight of copper sulphate while Group C received 10 mg/kg body weight of copper sulphate. Group D and Group E was administered copper sulphate at 100 mg/kg body weight and 200 mg/kg body weight respectively. The experiment lasted for 28 days. This study evaluated body weight changes, lipid profile assay, serum-electrolyte analysis and histological analysis of the cerebellar tissues. After three weeks of the experiment, significant weight loss was noted in Group 2 when compared to the control group. There was no significant difference between all the groups in the lipid profile assay. Also, results from the serum-electrolyte analysis showed no significant difference between all the groups in this experiment. However, histological alterations, in form of prominent glomeruli and vacuolations, were noticed at 10 mg/kg b.w., 100 mg/kg b.w. and 200 mg/kg b.w. of copper sulphate administration. In conclusion, high doses of copper sulphate can harm cerebellar tissue.

Keywords: Copper sulphate, lipid profile, electrolytes, Wistar rat, cerebellum.

1. INTRODUCTION

Copper is an essential trace element, but copper sulfate ($CuSO_4$) is toxic when exposure is high, causing damage to multiple organs. Exposure can occur by ingestion, skin contact (especially on burns), or inhalation (Park *et al.*, 2018; Khan *et al.*, 2024). Ingested copper sulphate, probably in drinking water or food (including supplements containing copper sulfate), is absorbed mainly in the upper small intestine (duodenum) via specific transporters such as Copper Transporter 1 (Ctr1) and ATPase Copper Transporting Alpha Polypeptide (ATP7A) (Taylor *et al.*, 2019; Chen *et al.*, 2020). Copper sulphate generates reactive oxygen species, causing lipid peroxidation, DNA damage, and cell death in many tissues (Naz *et al.*, 2025). In the liver cells, $CuSO_4$ triggers ER-stress pathways (PERK/ATF4, CHOP, JNK, caspase-12), mitochondrial dysfunction, and apoptosis (Wu *et al*., 2020; Li *et al*., 2024).

Significant exposure to $CuSO_4$ has been linked to multiple organ-system dysfunction including acute kidney injury, which may progress to chronic kidney disease (Perestrelo *et al*., 2021); acute hepatitis, cytolysis, long-term hepatotoxicity via oxidative and ER stress (Perestrelo *et al*., 2021); seizures (Lahir *et al*., 2024). Animal studies also show neurobehavioral changes, growth impairment, and widespread oxidative damage at subtoxic or environmental doses (Kumar *et al*., 2015; Wu *et al*., 2020).

Elevated pro-inflammatory cytokines (TNF-α, IL-6) and activation of caspase-3, Bax, p53, with loss of anti-apoptotic Bcl-2 due to high exposure to copper sulphate indicate inflammatory cell death in multiple brain regions (Arowoogun *et al*., 2020; Adeleke *et al*., 2023). A study in 2023 showed that $CuSO_4$ disrupts mitochondrial dynamics and triggers ROS-driven mitophagy in hypothalamic neurons (Zhu *et al*., 2023). In animal experiment, $CuSO_4$ accumulation resulted in impaired memory, poor motor coordination, depression-like behavior, oxidative DNA damage and neuronal loss (Kumar *et al*., 2015; Erfanizadeh *et al*., 2021). Reduced movement, prolonged immobility; severe cortical gliosis, edema and neuronal necrosis were recorded at higher doses (Alnuaimi and Alabdaly, 2022). The pattern across many species supports that excess copper sulphate is strongly neurotoxic and could contribute to neurodegenerative or mood disorders when brain copper is chronically elevated (Erfanizadeh *et al*., 2021; Zhang *et al*., 2023).

2. MATERIALS AND METHODS

Materials

Twenty five (25) adult male albino Wistar rats, rat cages, saw dust, weighing balance, Agro feed, feeding plates, water bottles, gavage oral syringe, beakers, spatula, masking tape, latter gloves, cotton wool, water bath, syringes, sample bottles, markers, dissecting set, dissecting board, Ketamine hydrochloride, Copper (II) sulfate, marker, surgical gloves, slides, cover slide, cotton wool, forceps, staining racks, rotary microtome, oven, hematoxylin and eosin staining materials and light microscope were used in the course of this study.

Animal Care and Handling

The rats were housed in wooden cages. The rats were fed with standard rat chow and water given ad libitum. They were kept to acclimatize for two weeks before initiation of experiment. They were kept under room temperature of 27°C to 30°C. Daily cleaning was done and the animals were taken care of according to the applicable guideline for the care and use of laboratory animals.

Preparation of Copper Sulphate

Copper sulphate was purchased from a local chemical shop in Uyo, Akwa Ibom State. The chemical was dissolved in distilled water and the animals were weighed and given specific quantity (doses) of the chemical. The administration was done orally using oral gavage.

Experimental Protocol

Twenty-five (25) rats were divided into five (5) groups designated as A, B, C, D and E consisting five (5) rats. Group 1 (control group) was given distilled water. Group 2 was given 5 mg/kg body weight of $CuSO_4$. Group 3 was given 10 mg/kg body weight of $CuSO_4$. Group 4 was given 100 mg/kg body weight of $CuSO_4$. Group 5 received 200 mg/kg body weight of $CuSO_4$. The experiment lasted for 28 days (Table 1).

Table 1. Experimental Design

Group	Number	Treatment	Dosage
A (Control group)	5 rats	Distilled water	*ad libitum*
B (Test group)	5 rats	Copper sulphate	5 mg/kg body weight
C (Test group)	5 rats	Copper sulphate	10 mg/kg body weight
D (Test group)	5 rats	Copper sulphate	100 mg/kg body weight
E (Test group)	5 rats	Copper sulphate	200 mg/kg body weight

Determination of Changes in Body Weight

The body weight of the animals was measured prior to administration and subsequently at weekly intervals on days 8, 15, 21, and 28 using an electronic weighing balance. Weight change was calculated by subtracting the initial body weight from the final body weight recorded on day 28. Changes in body weight were analyzed using Student's paired T-test.

Termination of Experiment

On the 29th day, the animals were sacrificed. The animals were anaesthetized through injection of 50 mg/kg of ketamine intraperitoneally, after which blood samples were collected via cardiac puncture into plain bottles for analysis. The serum was separated by centrifuging for 20 minutes at 3500 rpm, then kept in plastic vials and immediately stored for biochemical studies. The brain was then placed in a petri dish with saline solution to remove any blood or other biological fluid and debris. The brain was preserved in 10 % buffered formalin for 48 hours. The tissue was promptly processed for paraffin wax embedding and stained with hematoxylin and eosin.

3. RESULTS

Changes in body weight following the administration of Calcium Carbide

Findings from this study show that copper sulphate has varying effect on body weight (Table 2). At week 1, Group C had a significantly lower body weight compared to Group D. This was also the case at week 2. After three weeks, the average body weight of Group B was significantly lesser that the Control group (Group 1).

Effect of Copper Sulphate on the Lipid Profile of Wistar rats

Findings from this study shows varying result for the effect of copper sulphate on the lipid profile of experimental rats. This result, however, showed no significant difference between the different experimental groups (Table 3).

Effect of Copper Sulphate on Serum-Electrolyte level of Wistar rats

Analysis of serum-electrolyte levels of Wistar rats exposed to copper sulphate showed varying result. However, there were no significant differences between the different experimental groups (Table 4).

Effect of Copper Sulphate on the histology of the cerebellum of Wistar rats using hematoxylin and eosin staining method

Histological analysis of the cerebellar tissue showed normal histological features in control group and Group B (5 mg/kg b.w of copper sulphate) rats. Group C (10 mg/kg b.w of $CuSO_4$), Group D (100 mg/kg b.w of $CuSO_4$), and Group E (200 mg/kg b.w of $CuSO_4$) showed altered histological features in form of abnormal prominence of glomeruli and presence of vacuolations in the cerebellar tissue (Figure 1).

Table 2. Effect of calcium carbide on the body weight of Wistar rats

Groups	Week 1	Week 2	Week 3
A	199.75±6.70	200.25±6.80	235.00±10.47*
B	183.75±10.38	195.50±10.62	217.25±11.92*
C	155.66±4.70*	157.33±6.57*	168.00±8.14
D	206.20±7.74*	204.60±10.75*	223.60±13.00
E	165.66±13.53	181.66±14.31	186.33±13.28

Key: Values are expressed as mean ± standard error of mean (Mean±SEM) at 95% level of significance ($P < 0.05$)
* = significant difference when compared between groups
A = rats given distilled water Group A (Control).
B = rats given 5 mg/kg body weight of Copper Sulphate
C = rats given 10 mg/kg body weight of Copper Sulphate
D = rats given 100 mg/kg body weight of Copper Sulphate
E = rats given 200 mg/kg body weight of Copper Sulphate

Table 3. Comparison of Changes in Lipid Profile of Adult Male Albino Rats Administered Copper Sulphate

Groups	Total cholesterol (TC) mmol/l	Triglyceride mmol/l	VLDL mmol/l	HDL mmol/l	LDL mmol/l
A	4.665	1.219	0.554	1.171	2.940
B	3.7105	1.223	0.556	1.286	1.869
C	3.505	1.202	0.546	1.227	1.732
D	3.995	1.346	0.612	1.216	2.167
E	3.426	1.181	0.537	1.055	1.834

Key: Values are expressed as mean ± standard error of mean (Mean±SEM) at 95% level of significance ($P < 0.05$)

A = rats given distilled water Group A (Control).

B = rats given 5 mg/kg body weight of Copper Sulphate

C = rats given 10 mg/kg body weight of Copper Sulphate

D = rats given 100 mg/kg body weight of Copper Sulphate

E = rats given 200 mg/kg body weight of Copper Sulphate

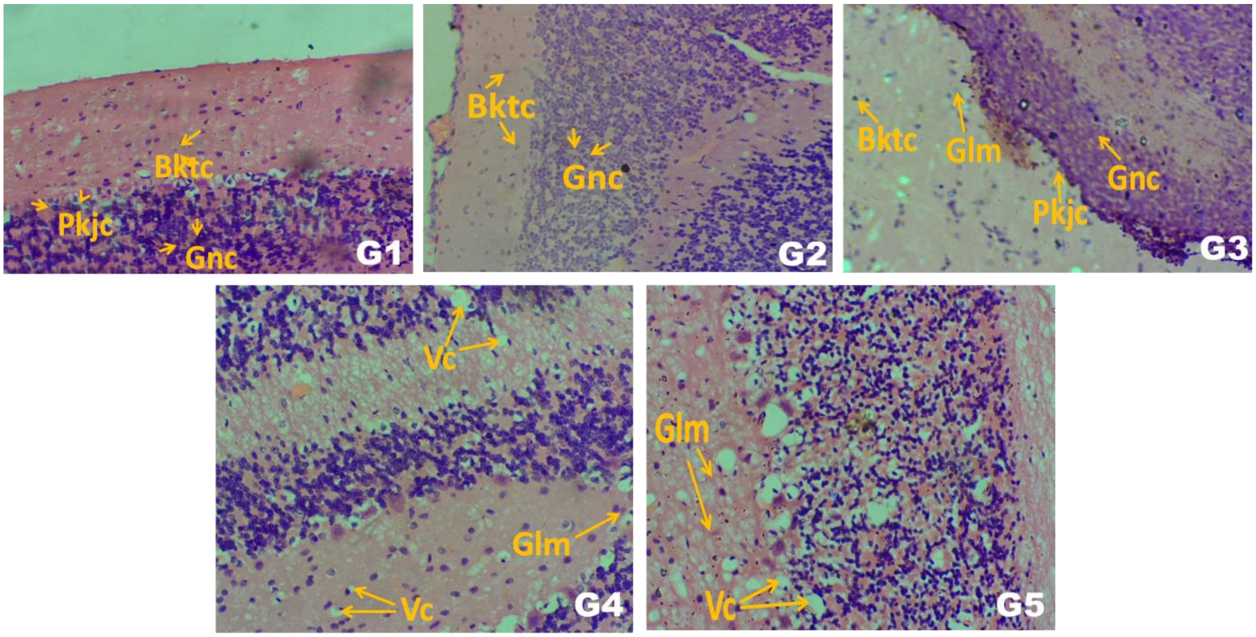

Figure 1. Photomicrograph of the cerebellum of adult Wistar rats (X400).

Legend:

G1 = Control Group. Section revealed normal features: basket cells of the molecular layer (**Bktc**), Granule cells (**Gn**c) of the granule layer and Purkinje cells (**Pkjc**). Inference: Unaffected.

G2 = Group 2 rats orally administered 5 mg/kg b.w. of Copper Sulphate. Section revealed normal features: basket cells of the molecular layer (**Bktc**), Granule cells (**Gnc**) of the granule layer. **Inference**: 5 mg/kg b.w. of copper sulphate has no effect on the cerebellar cortex.

G3 = Group 3 rats orally administered 20 mg/kg b.w. of Copper Sulphate. Section revealed basket cells of the molecular layer (**Bktc**), Granule cells (**Gnc**) of the granule layer and Purkinje cells (**Pkjc**), and Glomeruli (**Glm**) in the granule cell layer. **Inference:** Presence of the Glomeruli indicates slight disruptive effect by 20 mg/kg b.w. of copper sulphate.

G4 = Group 4 rats orally administered 100 mg/kg b.w. of Copper Sulphate. Section revealed Glomeruli (**Glm**) in the granule cell layer and vacuolation (**Vc**) in both the granule and molecular layers. **Inference:** Presence of the Glomeruli and Vacuolation indicates severe disruptive effect by 100 mg/kg b.w. of copper sulphate.

G5 = Group 5 rats orally administered 200 mg/kg b.w., of Copper Sulphate. Section revealed Glomeruli (**Glm**) in the granule cell layer and vacuolation (**Vc**) in both the granule and molecular layers. **Inference:** Presence of the Glomeruli and Vacuolation indicates severe disruptive effect by 200 mg/kg b.w. of copper sulphate.

Table 4. Comparison of Changes in Electrolyte Level of Adult Male Albino Rats Administered Copper Sulphate

Groups	HCO_2 (mmol/l)	Na^+ (mmol/l)	K^+ (mmol/l)	Cl^- (mmol/l)
A	21.00	139.00	3.300	100.00
B	21.00	140.00	3.400	96.00
C	22.00	141.00	3.300	98.00
D	21.00	137.00	3.200	97.00
E	19.00	136.00	3.300	98.00

Key: Values are expressed as mean ± standard error of mean (Mean±SEM) at 95% level of significance ($P < 0.05$)
A = rats given distilled water Group A (Control).
B = rats given 5 mg/kg body weight of Copper Sulphate
C = rats given 10 mg/kg body weight of Copper Sulphate
D = rats given 100 mg/kg body weight of Copper Sulphate
E = rats given 200 mg/kg body weight of Copper Sulphate

4. DISCUSSION

Copper plays a critical role in maintaining enzymatic and metabolic homeostasis; however, excessive exposure can destabilize multiple regulatory pathways (Dunn and Evans, 2023). The toxic effects of copper sulphate are largely attributed to its ability to generate reactive oxygen species and impair cellular membranes (Sarawi *et al*., 2021 and Fawzy *et al*., 2021). This study evaluated the effect of copper sulphate on the body weight, lipid profile, serum-electrolyte level and histology of the cerebellum of adult male Wistar rats. This study showed a variable effect of $CuSO_4$ on body weight. While the rats exposed to 5 mg/kg b.w. of copper sulphate showed a significantly lesser body weight compared to the control, the higher doses of copper sulphate did not cause significant difference in body weight changes when compared to the control group. Earlier researchers have made contradictory report on the effect of copper sulphate on body weight. While Blavi *et al*., (2021) and Forouzandeh *et al*., (2022) recorded that $CuSO_4$ administration led to increase in body weight, Aldulaimi *et al*., (2021) and Huang *et al*., (2021) reported significant weight loss following copper sulphate administration for 30 and 90 days respectively. This variation may be because copper influences enzymes, oxidative stress, appetite regulation, and lipid metabolism, and these pathways can push weight either up or down (Wang *et al*., 2022).

In this study, there was no significant effect of $CuSO_4$ on the lipid profile of the experimental animals. This finding aligns with earlier reports by previous researchers. A meta-analysis of five randomized trials (Cu supplements, various salts including copper sulfate) in 2020, found no significant effect on total cholesterol, LDL C, or HDL C (Wang *et al*., 2020). Rojas-Sobarzo *et al*., (2013) had earlier reported that 8 mg/day copper sulphate supplementation in healthy Chilean men for 6 months had no significant effect on their lipid profiles. Copper sulphate does not always change lipid profile parameters in experimental or clinical studies probably because lipid metabolism appears to be maintained within homeostatic limits under certain exposure conditions (Wang *et al*., 2021).

The neutral effect of $CuSO_4$ on the electrolyte balance seen in this study may also be linked to the tightly-controlled copper homeostasis of the body. People exposed to elevated copper intake can show increases in serum copper/substrates, yet still maintain electrolyte balance because the excess is buffered by binding proteins and efficient excretory pathways (Araya *et al*., 2006).

In this study higher doses (10 mg/kg b.w., 100 mg/kg b.w. and 200 mg/kg b.w.) of copper sulphate caused alterations in the cerebellar tissue. This is due to the neurotoxic potential of copper sulphate (Saied *et al*., 2022). This was also earlier reported by Grintsova *et al*., (2017) who recorded marked nuclear changes in Purkinje (ganglion) neurons, progressing from reversible polymorphic changes to necrobiotic lesions (chromatolysis, pyknosis, karyorrhexis) with prolonged exposure to copper sulphate.

5. CONCLUSION

In conclusion, the findings of this study demonstrate that exposure to copper sulphate produces biological effects selectively depending on the physiological system involved. While copper sulphate did not significantly alter the lipid profile or serum electrolyte levels, likely due to the presence of effective homeostatic and regulatory mechanisms, it produced dose-dependent structural alterations in the cerebellum, showing its ability to cause neurotoxicity. In general, these findings show that copper sulphate toxicity may be observed more prominently at the tissue level, particularly within the central nervous system, even in the absence of marked systemic biochemical changes.

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Author Contributions:

Christopher Chiedozie Mbadugha: Proposed the idea, supervised the research work, and edited the manuscript.
Michael Ebe Nandi: Collected the data and drafted the manuscript.
Ikechukwu Ezeah: Designed the research and supervised the experiment
Akpanabasi Alexis Malachy: Reported the research and developed the manuscript.
Ernest Aniefiok Daniel: Carried out the research and analyzed the data obtained
All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Ethical Approval

In this article, the animal regulations are followed as per the ethical committee guidelines of Department of Human Anatomy, Faculty of Basic Medical Sciences, University of Uyo, Nigeria; the authors observed the Copper sulphate implications on lipid profile, serum electrolytes and cerebellar histology in Wistar rats. The Animal ethical guidelines are followed in the study for observation, identification & experimentation.

Informed Consent

Not applicable.

Conflicts of interests

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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