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Rutin and Vitamin E Ameliorated Neuroinflammation and Liver Function Deficits in Male Wistar Rats Co-Exposed to Manganese and Vanadium

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ABSTRACT

Heavy metal exposure remains a rising concern for the environment and workers. This is mainly due to their contribution to systemic inflammation and their adverse effects on various body organs. Despite the trace elements vanadium and manganese being essential for the body, their excessive levels beyond the body's limits can trigger neuroinflammation and liver damage. This is mainly due to their activation of cytokines and disruption of the body's biochemical balance. This study evaluated the effects of vanadium and manganese, both separately and in combination, on selected neuroinflammatory markers and liver function in male Wistar rats. It also evaluated the protective effects of rutin and vitamin E. Forty male Wistar rats were randomly assigned into eight groups with five rats per group: a control group, a vanadium group (3mg/kg), a manganese group (100mg/kg), a vanadium-manganese group, a rutin group (100mg/kg), a vitamin E group, a vanadium-manganese-rutin group, and a vanadium-manganese-vitamin E group. The rats were exposed to the respective substances for 28 days. Blood samples were collected from the rats and tested for the levels of IL-1, IL-6, TNF, and routine liver function parameters using one-way ANOVA with a significance level at $p<0.05$. Vanadium treatment increased IL-6 (14.40 ± 0.79) and TNF (8.08 ± 1.32) levels compared with the controls ($p<0.05$), while manganese treatment caused a relatively small effect on the rats. However, the combined treatment with metals caused significant effects on the inflammatory parameters and liver enzyme and protein levels ($p<0.05$). The antioxidant treatment caused a significant reduction in the levels of IL-1, IL-6, and TNF and returned the liver enzyme and protein levels to normal ($p<0.05$). This study showed that vanadium and manganese exposure to the body can lead to significant neuroinflammatory and liver damage. Rutin and vitamin E can protect against such damage. Antioxidant therapy can thus be a potential therapy for people exposed to heavy metals

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1. INTRODUCTION

Heavy metal exposure is an ongoing global public health issue, affecting the environment and workers in many industries. Among heavy metals, vanadium and manganese are the most common in industrial environments, particularly given the rising incidence of systemic toxicity following long-term exposure (Dorman et al., 2025; Ngwa et al., 2024). These two heavy metals enter the body through contaminated air breathed into the body, particularly through the consumption of food and water, and are particularly prevalent in areas with heavy industries (Benedetto et al., 2020; Khoshakhlagh et al., 2025). Although they are essential in small quantities, an excess of either can upset the body's balance, affecting an individual's overall health.

Brain inflammation plays a key role in worsening conditions such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis (Khoury et al., 2024; Cantero Fortiz et al., 2024). Exposure to certain toxic metals, such as manganese or vanadium, triggers stronger immune reactions in the central nervous system, possibly harming nerve cells and reducing mental sharpness (Benedetto et al., 2020; Khoshakhlagh et al., 2025). The mechanism of the two heavy

metal-induced inflammatory responses is through oxidative stress, where the heavy metal-induces production of reactive oxygen species that triggers inflammatory responses, leading to the progression of the release of pro-inflammatory mediators such as IL-1β, TNF-α, IL-6, GFAP, and others (Bargues-Carot et al., 2026; Dorman et al., 2025). However, the risk may be heightened in the presence of both heavy metal species, as there is evidence of toxic interactions in brain tissue (Ngwa et al., 2024).

Heavy metals often harm the liver, given its key duties in processing toxins and foreign substances (Abbas, 2020). Instead of just filtering chemicals, it becomes a target - especially when vanadium triggers cell damage via reactive oxygen species (Chen et al., 2026). Oxidative manifest again with manganese, disrupting normal cellular chemical reactions and increasing the production of reactive oxygen species (Dorman et al., 2025). As the cell membranes become compromised, the function of the cell's key enzymes is altered, and the organs are impaired.

Despite common reliance on chelation for heavy metal poisoning, treatment paths are narrow. The side effects, cost, and limited access are challenges to the existing approaches. There is growing interest in natural antioxidants because they can inhibit oxidative stress and inflammation. Plant-derived antioxidants can complement or replace traditional approaches when these approaches are limited (Altanam et al., 2025; Sheweita et al., 2016).

Rutin is a flavonoid well known for its antioxidant and anti-inflammatory properties, which are beneficial in mitigating a variety of neurotoxic and oxidative tissue injuries (Kessas et al., 2024; De Araújo et al., 2023). It is also employed as a traditional medicine, with well-demonstrated efficacy attributed to its free radical-scavenging properties (Amini & Ahmad, 2025). Vitamin E is an antioxidant with lipid solubility; its role in protecting cell membranes from damage and the liver and brain from oxidative stress has been recognised (Kilicarslan You et al., 2024). Although studies indicate its potential benefits, there remains a gap in research on its overall effectiveness when organisms are exposed to manganese and vanadium, especially regarding neuroinflammatory and liver outcomes.

With this premise, this study investigates the effects of rutin and vitamin E on neuroinflammatory parameters and liver function parameters in male Wistar rats exposed to a combination of manganese and vanadium, with a view to understanding their therapeutic potential against heavy metal-induced neurotoxicity and hepatotoxicity.

2. MATERIALS AND METHODS

2.1 Experimental Animals

Forty (40) healthy Wistar rats (male), aged between 8–10 weeks and weighing 150g –160g, were obtained from the animal house of the Department of Pharmacology, University of Port Harcourt, Nigeria. The Animals were housed in cages with good ventilation and under standard laboratory conditions, including a 12-hour light/dark cycle, temperatures ranging from 22 to 25°C, and controlled humidity. The wister rats were provided with standard rat chow and water ad libitum. The rats were acclimatised for two weeks prior to the commencement of the experiment in accordance with internationally accepted principles for the use of laboratory animals.

2.2 Study Design and Grouping

A randomised controlled experimental design was employed. The animals were randomised into eight groups, each comprising 5 animals. The groups were as follows:

- Vanadium = 3 mg/kg
- Control = distilled water
- Vanadium + Manganese
- Manganese = 100 mg/kg
- Vitamin E
- Rutin = 100 mg/kg
- **Vanadium + Manganese + Vitamin E**
- **Vanadium + Manganese + Rutin**

All these were administered orally using a syringe once daily for 28 days. The body weight of the rats was recorded at the start and then weekly using an analogue automated scale.

2.3 Preparation of Treatments

Vanadium pentoxide and manganese sulfate ($MnSO_4 \cdot H_2O$) were freshly dissolved in distilled water. Rutin trihydrate (95%) was dissolved in distilled water at 100 mg/mL, and Vitamin E was prepared to a concentration of 100 IU/mL. Dosages were calculated based on each rat's body weight. For example, for a 150 g rat:

Vanadium dose per rat = 3mg/kg × 15kg = 0.45mg

The total volume required for group administration was adjusted according to the number of rats per group. Combination treatments were prepared by mixing the appropriate volumes of each solution for co-exposure groups.

2.4 Handling and Sacrifice of Experimental Animals

Rats were handled under controlled laboratory conditions. Twenty-four hours after the last treatment and any neurobehavioral assessments, animals were anaesthetized and sacrificed by cervical dislocation. Brains and livers were carefully dissected and collected for analysis. Blood samples were drawn via jugular puncture into EDTA and plain bottles for subsequent neuroinflammatory and liver function assays.

2.5 Biochemical Analysis

The serum was analysed for liver function parameters, including ALT, AST, and ALP. The wister rats' brain and liver tissues were prepared for oxidative stress and neuroinflammatory markers (IL-1β, IL-6, TNF-α, GFAP) using established laboratory methods

2.6 Statistical Analysis

Data are expressed as mean ± standard deviation (SD). A one-way ANOVA followed by Tukey's post-hoc test was performed using SPSS software. The Statistical significance was set at $p < 0.05$.

Materials Used: Rat cages, syringes, beakers, dissecting sets, cotton wool, EDTA and plain bottles, a light microscope, slides, gloves, sawdust, plastic buckets, rat chow, vanadium pentoxide, manganese sulfate, rutin trihydrate, and vitamin E.

3.0. RESULTS

3.1 Effects on Liver Function Markers

Table 1: Effects of Vanadium, Manganese, Rutin, and Vitamin E on Liver Function Markers in Male Wistar Rats

	Alb (g/dL)	TB (mg/dL)	CB (mg/dL)	TP (g/dL)	AST (U/L)	ALP (U/L)
Group1	46.33±1.53[a]	7.90±4.00[a]	5.27±0.45	58.33±2.52[a]	46.00±3.00[a]	30.67±4.04
Group 2	38.60±2.00[b]	9.50±0.2[b]	6.83±0.35	49.00±1.00[b]	63.50±2.00[a]	44.67±1.52
Group 3	40.67±3.06[b]	8.47±0.93[a]	5.07±0.25	46.00±1.00[a]	61.00±2.00[b]	34.67±6.51
Group 4	28.00±3.60[b]	10.17±0.99[b]	5.93±0.11	32.67±10.41[b]	68.00±4.58[b]	29.33±2.08
Group 5	45.00±2.00[b]	5.77±0.95[a]	18.03±25.09	62.33±12.22[b]	43.33±8.50[a]	37.67±7.02
Group 6	42.00±2.00[b]	7.60±2.001[a]	5.20±1.90	58.30±4.51[a]	48.00±6.00[a]	41.33±2.08
Group 7	42.00±2.08[b]	8.80±2.36[b]	6.27±1.45	57.33±7.51[b]	55.33±6.00[a]	43.33±1.53
Group 8	41.00±2.65[b]	6.07±0.25	4.33±0.57	52.33±2.51[a]	59.00±1.00[b]	28.33±6.11
p-value	0.005	0.031	0.630	0.02	0.003	0.11
F-value	4.689	3.03	0.756	5.930	5.369	1.333
Inference	S	S	NS	S	S	NS

Values with different superscripts are significantly different ($p<0.05$)

KEYS:
S = Significant,
NS = Non-significant

Table 1. The elevated ALB and TP levels, together with increased TBil and AST levels in vanadium- or manganese-injected rats, demonstrated liver dysfunction. Supplementation with rutin and vitamin E significantly modified these markers, returning albumin, protein, and enzyme levels to control values, especially in combination therapies.

3.2 Effects on Neuroinflammatory Markers

Table 2: Effects of Vanadium, Manganese, Rutin, and Vitamin E on Neuroinflammatory Markers

	IL-1	IL-6	TNF
Group1	2.95±0.19[a]	11.21±1.99[a]	4.76±1.39[a]
Group 2	5.45±0.62[b]	14.40±0.79[b]	8.08±1.32[b]
Group 3	4.32±0.44[b]	11.48±0.58[b]	4.29±1.30[a]
Group 4	3.77±0.53[b]	11.67±1.89[b]	5.26±1.18[b]
Group5	2.95±0.2[a]	8.47±0.77[a]	4.58±0.7[a]
Group 6	3.62±2.84[a]	7.54±1.49[a]	5.19±0.14[a]
Group 7	2.99±0.22[a]	7.15±1.01[a]	5.03±1.33[a]
Group 8	2.84±0.23[a]	7.59±0.62[a]	4.68±0.58[a]
p-value	<0.0001	<0.0001	0.02
F-value	15.888	12.076	5.467
Inference	S	S	S

Values with different superscripts are significantly different ($p<0.05$)

Keys
S = Significant

Table 2 shows that vanadium significantly increases IL-1, IL-6, and TNF levels, indicating high systemic inflammation. Manganese elicits a moderate inflammatory response, whereas mixed exposures elicit a medium inflammatory response. Rutin and vitamin E have effectively restored cytokine levels to near-normal levels when used individually or in combination with metals, indicating strong anti-inflammatory activity.

4. DISCUSSION

The current study shows that co-administration of vanadium and manganese causes significant liver impairment and systemic inflammation in male Wistar rats, as indicated by significant changes in liver function markers and protein and

inflammatory markers. The decrease in albumin and total protein concentrations following co-administration of vanadium and manganese in rats indicates liver impairment. This is because albumin, the main protein in plasma, is synthesised by the liver. It is essential for the transport of substances and the maintenance of oncotic pressure (Abbas, 2020). The significant increase in total bilirubin concentration following co-administration of the two metals indicates liver impairment. This is because the liver metabolises bilirubin. Impaired liver function, therefore, leads to the accumulation of bilirubin (Ramírez-Mejía et al., 2024). This is supported by the liver impairment observed after the exposure of rats to toxic metals (Moman, 2022; Daniels, 2022).

The enzymatic indicators of liver damage also support the earlier results. For instance, aspartate aminotransferase (AST) was found to increase significantly in groups exposed to vanadium and manganese, indicating liver cell damage and membrane instability (Daniels, 2022). The administration of rutin was found to reverse the effects of metal-induced increases in liver enzyme activity, returning AST to normal, while vitamin E partially normalised AST. This indicates that these antioxidants improve the resistance of liver cells to metal-induced toxicity.

The process of oxidative stress and inflammation is at the core of the observed liver toxicity in this experiment. Vanadium is particularly potent at inducing inflammation, as reflected by sharp increases in IL-1, IL-6, and TNF. Manganese produces smaller blips in the inflammatory markers, increasing IL-1 and IL-6. When the combination of the two metals is used, the profile changes, showing decreases in IL-1 and TNF compared to the profile observed with vanadium; however, IL-6 remains high, indicating low-grade inflammation.

The anti-inflammatory activity of Rutin was very potent, as were its protective actions on the liver. Rutin normalised the levels of IL-1, IL-6, and TNF to nearly baseline levels, as well as the abnormalities in albumin, total proteins, and bilirubin. Vitamin E also exhibited anti-inflammatory activity and improved biochemical markers of liver function, although its ability to normalise AST was slightly less clear-cut. This protective activity is consistent with previous studies showing that vitamin E reduces oxidative stress and inflammatory markers in metal toxicity models (Zhou et al., 2016). When used in combination, the two antioxidants appeared to have a synergistic effect on biochemical and inflammatory markers, returning them to nearly normal levels, indicating an improved capacity to combat vanadium- and manganese-induced toxicity.

The mechanisms of the protective effects are likely due to several factors, including the powerful antioxidant properties of rutin and vitamin E, which can counteract free radical activity, thereby stabilising liver cell membranes, reducing hepatocyte susceptibility to oxidative damage, and modulating the inflammatory response. Moreover, the improvement in albumin and protein synthesis reflects the return of liver metabolism to normal, indicating the return of liver homeostasis.

From the translational perspective, the takeaways would apply to people exposed to metals in the environment or at work. Rutin and vitamin E are interesting compounds because they are accessible, safe, and powerful antioxidants. They may represent opportunities for reducing liver toxicity and overall toxicity at an affordable cost, potentially as part of the diet or as an adjunct to current therapies for reducing the impact of long-term metal exposure.

5.1 CONCLUSION

This study demonstrated that co-exposure to vanadium and manganese induces significant liver dysfunction and systemic inflammation in male Wistar rats, as evidenced by altered albumin, total protein, total bilirubin, and AST levels, and elevated inflammatory markers IL-1, IL-6, and TNF. Both rutin and vitamin E effectively mitigated these toxic effects, restoring liver function markers and reducing pro-inflammatory cytokine levels toward baseline.

Rutin is highlighted in this study for its best liver-protective and anti-inflammatory properties, restoring liver function indicators and inflammatory cytokine levels to near-normal levels. Although vitamin E also reduces liver dysfunction and inflammation, particularly in IL-1, IL-6, and TNF levels, it is still inferior to rutin in reducing TNF levels. However, the combination of the two treatments increases liver-protective properties, demonstrating the potential of an antioxidant-based approach for preventing metal-induced toxicity.

The superior liver-protective properties of rutin and vitamin E may be attributed to their anti-inflammatory effects, which may have helped stabilize liver cell membranes, promote protein synthesis, and modulate the inflammatory cytokine response in the liver. These two compounds have the potential to prevent liver dysfunction in people exposed to vanadium and manganese, particularly in areas where such treatments are not available.

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