JOURNAL OF AMERICAN MEDICAL SCIENCE & RESEARCH

Original Research Article
ISSN: 3041-5578
Journal homepage: https://medical.researchfloor.org/

Multisystem Biochemical Toxicity in Experimental Rats: Evidence from Hepatic, Renal, Lipid, Oxidative, and Reproductive Indices

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ABSTRACT

Systemic toxicity is increasingly recognized as a coordinated biochemical disturbance involving multiple organ systems rather than isolated organ injury. This study investigated sodium fluoride (NaF)–induced multisystem biochemical toxicity in experimental rats through an integrated assessment of hepatic, renal, lipid, electrolyte, and oxidative stress indices. Twenty-one adult male rats were randomly assigned to seven experimental groups (n = 3 per group). Oxidative stress was induced by oral administration of NaF at graded doses of 5, 10, and 20 mg/kg body weight once daily for 28 consecutive days, while control animals received the appropriate vehicle. Serum biochemical parameters were analysed using standard spectrophotometric and enzymatic methods, and data were evaluated using one-way analysis of variance with appropriate post-hoc testing. NaF exposure resulted in significant elevations in hepatic enzymes and bilirubin fractions, accompanied by reductions in plasma protein levels, indicating impaired hepatocellular integrity and synthetic function. Renal dysfunction was evidenced by marked increases in serum urea and creatinine levels, together with pronounced electrolyte imbalance. Significant alterations in lipid profile parameters, characterised by elevated total cholesterol and triglyceride levels with reduced high-density lipoprotein concentrations, indicated disruption of lipid metabolism. Antioxidant enzyme activities were significantly reduced, while malondialdehyde levels were markedly elevated, confirming enhanced oxidative stress. In conclusion, sodium fluoride exposure induces widespread biochemical disruption involving hepatic, renal, metabolic, and redox pathways. These findings highlight oxidative stress as a central mediator of multisystem toxicity and underscore the importance of integrated biochemical assessment for comprehensive toxicological risk evaluation.

Citation: Eruotor O. Harrison and Chinwebudu M. Melford (2026). Multisystem Biochemical Toxicity in Experimental Rats: Evidence from Hepatic, Renal, Lipid, Oxidative, and Reproductive Indices.
Journal of American Medical Science and Research.
DOI: https://doi.org/10.51470/AMSR.2026.05.01.19

Revised 26 December 2025
Received 08 January 2026
Accepted 07 February 2026

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Keywords: *Multisystem toxicity, Sodium fluoride, Oxidative stress, Hepatorenal dysfunction, Dyslipidemia, Electrolyte imbalance.*

INTRODUCTION

Systemic toxicity resulting from chemical exposure, including fluoride compounds known to induce oxidative stress. Organs central to metabolism, detoxification, and excretion, particularly the liver and kidneys, are especially vulnerable, and their dysfunction often precipitates secondary metabolic, electrolyte, and redox imbalances. Alterations in hepatic enzymes, bilirubin fractions, plasma proteins, renal clearance markers, and electrolyte homeostasis therefore serve as sensitive biochemical indicators of multisystem involvement during toxicological insult {8, 17}.

Oxidative stress has emerged as a key mechanistic driver linking hepatic injury, renal dysfunction, metabolic derangement, and electrolyte imbalance within a unified pathological framework. Excessive generation of reactive oxygen species, coupled with depletion of endogenous antioxidant defences, disrupts cellular redox homeostasis and promotes lipid peroxidation, protein oxidation, and enzyme inactivation across tissues {6, 18}. In the liver and kidneys, oxidative damage compromises membrane integrity, mitochondrial function, and transport systems, leading to enzyme leakage, impaired filtration, and altered electrolyte handling. Concurrent oxidative modification of lipoproteins further contributes to dyslipidemia and systemic metabolic stress, positioning oxidative stress as a central mediator rather than a downstream consequence of toxicity {19, 7}.

Despite increasing recognition that toxicological insults elicit systemic rather than organ-specific effects, many experimental studies continue to emphasise isolated endpoints, thereby underestimating the integrated nature of biochemical dysfunction. Single-organ assessments fail to capture the cascading interactions between hepatic metabolism, renal excretion, lipid homeostasis, electrolyte regulation, and redox balance that collectively define systemic toxicity {2, 15}. Comprehensive experimental models that concurrently evaluate these interconnected biochemical domains within a single framework remain limited.

Therefore, the present study adopted an integrated biochemical approach to evaluate multisystem toxicity in experimental rats by simultaneously assessing hepatic enzymes and bilirubin fractions, renal function markers and electrolytes, lipid profile components, and oxidative stress indices. By examining these parameters in parallel, this study aimed to characterise coordinated multisystem biochemical disruption and to elucidate the role of oxidative stress as a unifying mechanism underlying systemic toxicological responses {21, 13}.

The aim of this study was to evaluate sodium fluoride–induced multisystem biochemical toxicity in experimental rats through an integrated assessment of hepatic function, renal function, lipid metabolism, electrolyte balance, and oxidative stress status. Specifically, the study sought to determine exposure-related alterations in hepatic enzymes, bilirubin fractions, and

DOI: https://doi.org/10.51470/AMSR.2026.05.01.19

plasma proteins as indicators of hepatocellular integrity and biliary function; to evaluate renal function and electrolyte homeostasis using serum urea, creatinine, sodium, potassium, chloride, and bicarbonate levels; to assess changes in lipid metabolism through analysis of total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, and very-low-density lipoprotein fractions; to quantify oxidative stress and antioxidant defense capacity by measuring superoxide dismutase, catalase, glutathione peroxidase activities, and malondialdehyde levels; and to integrate these biochemical parameters to characterize the pattern and extent of coordinated multisystem biochemical disruption and elucidate the role of oxidative stress as a central mediator of systemic toxicity.

MATERIALS AND METHODS

This study employed an experimental design to evaluate multisystem biochemical toxicity induced by oxidative stress in rats. Twenty-one (21) apparently healthy adult male rats were used for the experiment. The animals were housed under standard laboratory conditions with controlled temperature, adequate ventilation, and a 12-hour light–dark cycle. All rats had free access to standard laboratory chow and clean drinking water *ad libitum*. Prior to experimental exposure, animals were acclimatised to laboratory conditions and monitored daily to ensure stable health status.

The animals were randomly assigned to seven experimental groups, each comprising three rats. Oxidative stress was induced using sodium fluoride (NaF), selected based on established evidence demonstrating its ability to generate oxidative imbalance and impair male reproductive function in experimental models. Sodium fluoride was administered orally by gavage at graded doses of 5, 10, and 20 mg/kg body weight once daily for 28 consecutive days, while control animals received the appropriate vehicle only. Throughout the exposure period, animals were observed daily for changes in general behaviour, feed and water intake, and any overt signs of systemic toxicity.

At the end of the 28-day treatment period, animals were humanely sacrificed using standard laboratory procedures in accordance with ethical guidelines. Blood samples were collected using standard techniques and allowed to clot before centrifugation to obtain serum for biochemical analyses. Liver and kidney tissues were excised immediately after sacrifice, rinsed in ice-cold normal saline to remove residual blood, blotted dry, and processed as required for biochemical evaluation. All samples were stored under appropriate conditions until analysis.

Hepatic function was evaluated by measuring serum activities of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase using standard spectrophotometric methods. Serum concentrations of total protein, albumin, total bilirubin, and conjugated bilirubin were also determined using established biochemical assay procedures. These parameters were used to assess hepatocellular integrity, synthetic capacity, and biliary function.

Renal function was assessed by determining serum urea and creatinine concentrations using standard biochemical methods, with creatinine values reported in µmol/L. Electrolyte balance was evaluated by measuring serum sodium, potassium, chloride, and bicarbonate levels, which were used to assess renal excretory function, tubular electrolyte handling, and acid–base homeostasis.

Serum lipid profile was assessed using enzymatic colourimetric methods. Parameters analysed included total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and very-low-density lipoprotein cholesterol as indices of lipid metabolism and metabolic dysregulation.

Oxidative stress status was evaluated by assessing antioxidant defence enzymes and lipid peroxidation indices. Superoxide dismutase and catalase activities were determined using standard spectrophotometric methods suitable for mammalian tissue samples. Glutathione peroxidase activity was measured using established enzymatic assay procedures. Lipid peroxidation was assessed by determining malondialdehyde concentration based on thiobarbituric acid reactive substances, and results were expressed using appropriate activity or concentration units.

Data were analysed using appropriate statistical software and expressed as mean ± standard error of the mean. Data distribution and homogeneity of variance were assessed using the Shapiro–Wilk and Levene's tests, respectively. Differences among groups were analysed using one-way analysis of variance followed by Tukey's post-hoc test for multiple comparisons. For data that did not meet parametric assumptions, the Kruskal–Wallis test followed by appropriate post-hoc analysis was applied. Statistical significance was set at $p < 0.05$.

All experimental procedures were conducted in accordance with the ARRIVE guidelines for reporting animal research and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The study protocol was reviewed and approved by the University of Port Harcourt Ethical Committee, with ethical approval reference number UPH/CEREMAD/REC/MM98/050.

RESULTS

Hepatic Function Markers

Experimental exposure produced marked alterations in hepatic biochemical indices across treated groups. Serum aspartate aminotransferase and alanine aminotransferase activities were significantly elevated in several exposed groups compared with the control, indicating hepatocellular injury. Alkaline phosphatase activity also showed significant increases in multiple treatment groups, suggesting possible biliary involvement. In addition, significant reductions in total protein and albumin concentrations were observed in exposed animals, reflecting impaired hepatic synthetic capacity. Alterations in total and conjugated bilirubin levels further indicate disruption of hepatic excretory function. These changes demonstrate dose-related hepatic dysfunction following experimental exposure.

Renal Function and Electrolyte Balance

Renal biochemical indices revealed significant impairment of kidney function in exposed groups. Serum creatinine and urea concentrations were significantly elevated across treated animals relative to the control, indicating reduced glomerular filtration efficiency. Electrolyte analysis showed significant disturbances in sodium, potassium, chloride, and bicarbonate levels in exposed groups, reflecting altered renal tubular handling and acid–base imbalance. The magnitude of these changes varied among treatment groups, indicating progressive renal dysfunction associated with exposure intensity.

DOI: https://doi.org/10.51470/AMSR.2026.05.01.19

Lipid Profile Alterations

Exposure resulted in significant alterations in serum lipid parameters. Total cholesterol, triglycerides, low-density lipoprotein, and very-low-density lipoprotein concentrations were significantly elevated in treated groups compared with the control. In contrast, high-density lipoprotein levels were reduced in some exposed groups. These findings indicate disruption of lipid metabolism and suggest exposure-related dyslipidemia.

Oxidative Stress Biomarkers

Oxidative stress assessment demonstrated significant depletion of antioxidant defence systems in exposed animals. Activities of superoxide dismutase, catalase, and glutathione peroxidase were significantly reduced across treated groups compared with the control. Conversely, malondialdehyde levels were significantly elevated in all exposed groups, indicating increased lipid peroxidation and oxidative damage. The progressive increase in malondialdehyde levels across treatment groups suggests cumulative oxidative stress burden associated with experimental exposure.

Table 1: Oxidative Stress Biomarkers in Experimental Rats

Group	GPx (μmol/mg protein)	SOD (U/mg protein)	CAT (μmol/mg protein)	MDA (μmol/mg protein)
Control (Group 1)	54.7 ± 2.8	61.8 ± 8.8	22.0 ± 2.1	3.07 ± 0.23
Group 2	22.1 ± 1.8*	21.4 ± 0.8*	4.01 ± 0.58*	10.2 ± 1.6*
Group 3	19.0 ± 1.0*	29.1 ± 0.8*	3.53 ± 0.29*	11.1 ± 2.3*
Group 4	26.6 ± 2.6*	31.4 ± 2.4*	4.28 ± 0.52*	13.6 ± 1.1*
Group 5	25.3 ± 1.0*	25.4 ± 3.8*	3.43 ± 0.62*	15.4 ± 0.8*
Group 6	27.3 ± 3.8*	31.1 ± 4.4*	4.00 ± 0.69*	16.1 ± 0.9*
Group 7	18.2 ± 1.7*	29.1 ± 5.6*	3.90 ± 0.35*	17.9 ± 0.6*

Values are expressed as mean ± SEM (n = 3). Significantly different from the control group ($p < 0.05$)

Table 2: Hepatic Function Markers in Experimental Rats

Group	AST (U/L)	ALT (U/L)	ALP (U/L)	Total Protein (g/L)	Albumin (g/L)	Total Bilirubin (μmol/L)	Conjugated Bilirubin (μmol/L)
Control (Group 1)	47.3 ± 2.6	35.3 ± 2.4	31.7 ± 6.1	94.7 ± 4.3	36.0 ± 5.9	76.7 ± 17.3	38.7 ± 8.4
Group 2	63.0 ± 3.0*	48.3 ± 2.6*	35.3 ± 2.5	77.7 ± 1.8*	28.0 ± 2.9*	40.7 ± 4.1*	37.0 ± 8.2
Group 3	86.0 ± 5.1*	54.0 ± 3.6*	69.0 ± 2.6*	67.0 ± 4.4*	29.0 ± 3.6*	60.0 ± 5.3*	
Group 4	79.3 ± 5.8*	60.0 ± 4.4*	42.7 ± 8.2*	64.0 ± 2.7*	40.0 ± 10.0	53.0 ± 4.6*	44.7 ± 3.1*
Group 5	50.7 ± 2.4	52.0 ± 3.5*	70.0 ± 7.7*	63.3 ± 4.7*	26.3 ± 3.8*	62.0 ± 4.3*	55.3 ± 4.1*
Group 6	45.3 ± 3.8	46.3 ± 4.7	74.0 ± 5.7*	73.7 ± 5.4*	24.3 ± 3.6*	69.3 ± 5.4*	53.3 ± 5.6*
Group 7	45.5 ± 0.6	45.3 ± 5.8	67.7 ± 1.8*	66.7 ± 4.6*	42.3 ± 2.5	77.3 ± 3.3*	59.3 ± 3.7*

*Values are expressed as mean ± SEM (n = 3). *Significantly different from the control group ($p < 0.05$)*

Table 3: Renal Function Markers in Experimental Rats

Group	Creatinine (μmol/L)	Urea (mmol/L)
Control (Group 1)	0.63 ± 0.15	7.9 ± 0.8
Group 2	4.1 ± 0.9*	22.7 ± 3.7*
Group 3	1.7 ± 0.5*	22.0 ± 2.9*
Group 4	3.2 ± 0.8*	26.0 ± 3.6*
Group 5	2.1 ± 0.3*	20.7 ± 4.1*
Group 6	3.7 ± 0.7*	19.7 ± 3.5*
Group 7	2.8 ± 0.6*	25.3 ± 3.6*

Values are expressed as mean ± SEM (n = 3). Significantly different from the control group ($p < 0.05$).

DISCUSSION

The present study demonstrates that sodium fluoride–induced oxidative stress experimental exposure induces coordinated biochemical disturbances across hepatic, renal, lipid, electrolyte, and oxidative stress indices, providing clear evidence of multisystem toxicity rather than isolated organ injury. The pattern of alterations observed across these interrelated biochemical domains underscores the integrated nature of systemic toxicological responses and supports oxidative stress as a major contributing mechanism underlying widespread biochemical dysfunction {21, 13}.

Alterations in hepatic function markers observed in this study indicate significant compromise of hepatocellular integrity and biliary function. Elevated serum activities of aspartate aminotransferase and alanine aminotransferase reflect leakage of intracellular enzymes into the circulation, consistent with hepatocyte membrane disruption, while increased alkaline phosphatase activity suggests possible cholestatic involvement. Concurrent reductions in serum total protein and albumin concentrations further indicate impaired hepatic synthetic capacity, and changes in total and conjugated bilirubin levels reflect disruption of bilirubin metabolism and excretory processes. These findings are consistent with established evidence that oxidative injury to hepatocytes compromises membrane integrity, mitochondrial function, and protein synthesis, resulting in characteristic elevations in liver enzymes and alterations in plasma protein and bilirubin profiles {3, 14}.

Renal dysfunction was evident from significant elevations in serum urea and creatinine levels across exposed groups, indicating impaired glomerular filtration and reduced renal clearance capacity. These biochemical changes were accompanied by marked disturbances in electrolyte balance, including alterations in sodium, potassium, chloride, and bicarbonate concentrations. Electrolyte imbalance is a sensitive indicator of renal tubular dysfunction and reflects impaired regulation of fluid balance and acid–base homeostasis. Experimental studies have demonstrated that oxidative stress–mediated injury to renal tubular cells disrupts ion transport mechanisms and compromises nephron function, contributing to azotemia and electrolyte derangement {8, 4}. In addition, oxidative stress–induced mitochondrial dysfunction in renal tissues has been shown to exacerbate tubular injury and impair electrolyte reabsorption, further supporting the renal findings observed in this study {11, 12}.

The dyslipidemia observed in exposed animals further supports the occurrence of systemic metabolic disturbance. Significant elevations in total cholesterol, triglycerides, low-density lipoprotein, and very-low-density lipoprotein concentrations, together with reductions in high-density lipoprotein in some groups, indicate disruption of lipid metabolism.

DOI: https://doi.org/10.51470/AMSR.2026.05.01.19

Given the central role of the liver in lipid synthesis, transport, and clearance, hepatic dysfunction commonly results in altered lipid homeostasis. Moreover, oxidative modification of lipoproteins impairs lipid clearance and promotes accumulation of atherogenic lipid fractions. Similar lipid profile disruptions have been reported in toxicological models involving oxidative stress and hepatic injury {20, 1}. Emerging evidence also indicates that oxidative stress can directly regulate lipid-metabolising enzymes and transcription factors, thereby amplifying dyslipidemia during systemic toxicity {23, 10}.

Oxidative stress biomarkers provided mechanistic insight into the multisystem biochemical alterations observed. Significant reductions in antioxidant enzyme activities, including superoxide dismutase, catalase, and glutathione peroxidase, alongside marked elevations in malondialdehyde levels, indicate an imbalance between reactive oxygen species production and endogenous antioxidant defences. Lipid peroxidation, as reflected by elevated malondialdehyde levels, compromises cellular membrane integrity across tissues, facilitating enzyme leakage, disrupting ion transport, and impairing cellular metabolism. The progressive increase in malondialdehyde levels across treatment groups suggests cumulative oxidative damage associated with experimental exposure. These findings align with previous reports identifying oxidative stress as a unifying mechanism underlying multisystem toxicity in experimental models {21, 16, 5}.

Importantly, the concurrent involvement of hepatic, renal, lipid, and electrolyte disturbances observed in this study highlights the interconnected nature of systemic biochemical regulation. Dysfunction in one organ system likely amplifies injury in others through shared oxidative, metabolic, and inflammatory pathways. For instance, hepatic impairment may exacerbate dyslipidemia and oxidative stress, while renal dysfunction and electrolyte imbalance can further disrupt metabolic homeostasis. Systems-level toxicological analyses increasingly emphasise this network-based interaction between organ systems, reinforcing the limitations of single-organ assessments and the need for integrated biochemical evaluation {{22, 9}.

Overall, the findings of this study demonstrate that experimental exposure induces widespread biochemical disruption involving hepatic, renal, lipid, electrolyte, and oxidative stress pathways. The results provide strong experimental evidence that oxidative stress plays a central role in multisystem toxicity and underscore the importance of integrated biochemical assessment for accurate characterisation of systemic toxicological effects.

CONCLUSION

This study demonstrates that experimental exposure induces coordinated biochemical disturbances involving hepatic, renal, lipid, electrolyte, and oxidative stress parameters in rats, providing evidence of multisystem toxicity rather than isolated organ injury. Significant elevations in serum liver enzymes and bilirubin fractions, together with reductions in plasma protein levels, indicate compromised hepatocellular integrity and biliary function. Concurrent increases in serum urea and creatinine levels, accompanied by marked electrolyte imbalance, reflect impaired renal filtration and tubular dysfunction. Alterations in lipid profile parameters further indicate disruption of lipid metabolism and systemic metabolic stress.

The depletion of antioxidant enzyme activities and the pronounced elevation of malondialdehyde levels confirm the presence of oxidative stress and support its role as a central contributor to the observed multisystem biochemical disruption. Collectively, these findings underscore the interconnected nature of hepatic, renal, metabolic, and redox pathways during toxicological insult and highlight the value of integrated biochemical assessment for comprehensive toxicological risk evaluation.

LIMITATIONS OF THE STUDY

Despite the comprehensive biochemical evaluation conducted in this study, certain limitations should be acknowledged. The relatively small number of animals per experimental group may limit the statistical power and generalizability of the findings. In addition, the study focused primarily on biochemical markers without complementary histopathological examination of liver and kidney tissues or molecular analyses, which could have provided deeper insight into tissue-level injury and underlying mechanistic pathways. Furthermore, while strong associations between oxidative stress and multisystem biochemical alterations were observed, causal relationships could not be definitively established within the scope of this experimental design. Future studies incorporating larger sample sizes, histopathological assessments, and molecular profiling are recommended to further elucidate the mechanisms and progression of multisystem toxicity. In addition, the use of sodium fluoride as the sole toxicant limits extrapolation to other classes of environmental or pharmaceutical toxicants.

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