

# Mechanistic Insights into Sodium Fluoride-Induced Oxidative Stress and Glucose Homeostasis Imbalance in Albino Rats

Ankul Singh<sup>1</sup>, Vivek Pratap Singh<sup>2</sup>, Devesh Kumar Joshi<sup>3\*</sup>

<sup>1</sup>Research Scholar, Department of Biochemistry, Nims Institute of Allied Medical Science and Technology, Nims University Rajasthan, Jaipur – 303121 (India).

<sup>2</sup>Assistant Professor, Department of Biotechnology, Nims Institute of Allied Medical Science and Technology, Nims University Rajasthan, Jaipur - 303121(India).

<sup>3</sup>Assistant Professor, Department of Biochemistry, Nims Institute of Allied Medical Science and Technology, Nims University Rajasthan, Jaipur - 303121(India).

**\*Corresponding Author:**

Email ID : [deveshkumar.joshi@nimsuniversity.org](mailto:deveshkumar.joshi@nimsuniversity.org)

## ABSTRACT:

Sodium fluoride (NaF), a widespread environmental contaminant, has been implicated in metabolic disturbances and oxidative stress. This study aimed to evaluate the impact of NaF exposure on glucose homeostasis and oxidative stress biomarkers in albino rats. Animals were divided into four groups and administered NaF at concentrations of 0, 0.5, 10, and 20 ppm for a defined experimental period. Key biochemical parameters, including malondialdehyde (MDA), reactive oxygen species (ROS), superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH), were analysed. Results demonstrated a significant dose-dependent increase in oxidative stress markers (MDA, ROS) and a concomitant decrease in antioxidant enzyme activities (SOD, CAT, GSH). These findings indicate that NaF exposure disrupts redox homeostasis and may impair glucose regulation through oxidative damage to metabolic tissues. The study highlights oxidative stress as a central mechanism in fluoride-induced metabolic dysfunction and suggests potential therapeutic targets for mitigating fluoride toxicity.

**How to cite this article:** A. Singh, V. P. Singh, D. K. Joshi. Mechanistic Insights into Sodium Fluoride-Induced Oxidative Stress and Glucose Homeostasis Imbalance in Albino Rats. *Int J Drug Deliv Technol.* 2026;16(22s): 663-673. DOI: 10.25258/ijddt.16.22s.80.

## Introduction:

Fluorosis is a public health concern, endemic in 25 countries worldwide. Chronic fluoride (F<sup>-</sup>) toxicity is caused by exposure to excessive F<sup>-</sup> >1.5 parts per million (ppm) (WHO 2003) primarily through water. According to Saravanan et al. (Saravanan et al. 2008), fluorosis is endemic in over two-thirds of the states of India. According to Majumdar (2011), fluorosis affects about 25 million individuals worldwide, and 66 million people, including children under the age of 14 years, are at risk of developing fluorosis. Chronic F<sup>-</sup> toxicity is classified as dental, skeletal and non-skeletal fluorosis on the basis of tissues affected. The earliest sign of chronic F<sup>-</sup> toxicity is expressed as dental fluorosis (Krishnamachari 1986). Fluoride in drinking water has a profound effect on teeth and bones (Razbe et al. 2013). In the areas with naturally high F<sup>-</sup> levels in water, the prevalence of dental fluorosis was significantly higher than in areas with lower levels (Gamarra et al. 2024). Long-term F<sup>-</sup> exposure results in skeletal fluorosis, forming bone deformities, calcification of ligaments, resulting in restricted movements (Vieira et al. 2005). The communities with high F<sup>-</sup> exposure, particularly those

dependent on groundwater with naturally high F<sup>-</sup> concentrations, showed an increased risk of skeletal fluorosis (Shaji et al. 2024). The chronic F<sup>-</sup> exposure reduced the IQ in children, especially in areas with high levels of F<sup>-</sup> in drinking water (Saxena et al. 2012). The F<sup>-</sup> exposure might also be associated with thyroid problems, including hypothyroidism, risk of kidney and liver damage, especially in areas with high levels of F<sup>-</sup> in the water (Iamandii et al. 2024; Khandare et al. 2017). Fluoride displaces hydroxide ions from hydroxyapatite, Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>OH, the principal mineral constituent of teeth (in particular the enamel) and bones, to form the harder and tougher fluorapatite, Ca<sub>5</sub>(PO<sub>4</sub>)<sub>3</sub>F (Razbe et al. 2013). In non-skeletal fluorosis, soft tissues such as gastrointestinal tract, brain, liver and kidney etc., are affected. Residents in fluorotic locations may exhibit any type of symptom in these organs that could be a sign of non-skeletal fluorosis (Krishnamachari 1986). Fluoride is transported in the form of ionic and nonionic F<sup>-</sup> in the plasma, where ionic F<sup>-</sup> does not tend to bind with plasma protein and is readily eliminated through urine. 35–45% of F<sup>-</sup> is reabsorbed from renal filtration and returned to the circulatory

\*Author for Correspondence: [deveshkumar.joshi@nimsuniversity.org](mailto:deveshkumar.joshi@nimsuniversity.org)

system when it is in the form of hydrogen fluoride. The course of reabsorption of F<sup>-</sup> is highly influenced by the pH of tubular fluid and urinary flow (Whitford 1996). Hence, the concentration of F<sup>-</sup> in kidney tubules is considerably high and it is even higher than the concentration in plasma (WHO 2002). Fluoride toxicity is markedly influenced by the co-presence of any other xenobiotics. Although, fluoride and ethanol are two well documented neurotoxicants co-exposing alcoholic population residing in high fluoride endemic areas, little is known about their combined effects 10-13. Previously, we reported for the first time that female rats co-exposed to fluoride and ethanol exhibit compromised antioxidant defense in brain 7. To better understand fluoride-alcohol interactions, we designed the present investigation to assess oxidative stress, mitochondrial dysfunctions, AChE activity, neurotransmitter functions and morphology in rat brain co-exposed to fluoride and ethanol. The situation of serious imbalance between oxidant and antioxidant is referred to as oxidative damage. In many diseases, tissue damage is often accompanied by an imbalance in the oxidant/antioxidant status. Previous studies have shown that fluoride exposure can increase the lipid peroxidation levels, and reduce the activities of glutathione peroxidase (GSH-Px), catalase (CAT) and superoxide dismutase (SOD) in the rat kidney. Guan et al [30] has also found that the lipid peroxidation levels of kidney are markedly increased in rats treated with high levels of fluoride, and speculated that the oxidative damage and modification of membrane lipids may be implicated in the pathogenesis of fluorosis. However, the exact mechanism of fluoride-induced renal oxidative damage is unclear at present.

**Materials & Methods Experimental design/Animal:**

Male albino rats weighing between 10 and 11 weeks, 280g, were used as subjects throughout this study. The

Animal Ethical Committee oversaw the acquisition and care of male albino rats (*Rattus norvegicus* L.) weighing between 175 and 200g, by CPCSEA guidelines. After being acclimated to the laboratory environment, they were fed pelleted chow and libitum and water. In India, the animals were housed in four-animal polypropylene cages (Animal House, NIMS University) with bedding made entirely of dust-free rice husk. From February to June 2025, the rats were kept in plastic cages in a climate-controlled setting (23–25°C). Prior to the studies, they were housed at the NIMS University's animal husbandry department in Rajasthan for ten days to acclimate. The rats were given a typical pellet meal and constant access to water during the experiment. For thirty (90) days, a total of thirty-six (36) albino rats were split up into four equal groups and given various treatments every day. The rats were randomly assigned to four groups of nine under the same conditions, and they were positioned as follows:

**Dose:** In the proposed study, we will administer Sodium Fluoride in different concentrations (0.5, 5, or 20 ppm/1 ml/day/rat, respectively) for 90 days. The rats will be divided into 4 Groups, and 9 rats in each group. The Sodium Fluoride will be given to the rats as per the following groups. For the present study, the experiment will be designed as per the following schedule. The rats were split up at random into four groups of 6 animals each, all of which were kept in the same conditions.

**Experimental Design and Treatment Protocol:** There were 36 albino rats of the male gender, and they were randomly separated into four experimental groups with nine animals in each (n = 9). Sodium fluoride was given orally in gavage/cannula, on a 90-day schedule in a single daily dose (Table 1).

**Table 1: Experimental design and sodium fluoride dosage in albino rats for 90 days.**

GROUP	TREATMENT DESCRIPTION	DOSAGE (PPM)	VOLUME/DURATION	VOLUME/DURATION
Group-I (Control)	Distilled water	0	1 ml/90 days/rat	Oral (gavage/cannula)

<b>Group -II</b>	Sodium fluoride (NaF) dissolved in distilled water, after induction via cannula	0.5	1 ml/90 days/rat	Cannula induction + Oral
<b>Group -III</b>	Sodium fluoride (NaF) dissolved in distilled water, after induction via cannula	10	1 ml/90 days/rat	Cannula induction + Oral
<b>Group- IV</b>	Sodium fluoride (NaF) dissolved in distilled water, after induction via cannula	20	1 ml/90 days/rat	Cannula induction + Oral

**Monitoring of Body Weight:**

All animals were also weighed at baseline (day 0) and then at irregular time intervals (once a week) during the experiment period of 90 days, using a digital balance. The changes in body weight were evaluated as a universal measure of systemic toxicity and metabolic change. Serum was kept at the relevant temperatures until biochemical analyses were performed. To isolate serum in blood, the blood was centrifuged at 3000 rpm for 15 minutes.

**Blood Collection and Serum Preparation:**

Blood samples were collected following an overnight fasting period, at two time points: the first sample was baseline (day 0), and the second sample was at the end of the experimental period (day 90). Chloroform was used as an anaesthetic on animals, and blood was taken by cardiac puncture under aseptic conditions.

**Collected blood samples were divided into:**


EDTA vials - in case of haematological analysis, Plain vials - to estimate serum insulin and Fluoride vials- glucose, liver function test (LFT), and renal function test (RFT)


**Glucose Homeostasis:**

Glucose homeostasis refers to the hormonal and neural regulatory mechanisms that maintain blood glucose levels within a very narrow range. In healthy individuals, the body regulates glucose release and production in order to ensure sufficient glucose flux to meet the body's demands. The proper control of glucose homeostasis requires the synchronised actions of several organ systems, including but not

limited to the brain, liver, skeletal muscle, and adipose tissue. The multiple mechanisms regulating glucose metabolism are complex and tightly regulated by hormones, like insulin and leptin, and their impact on glucose homeostasis is detailed elsewhere. Interestingly, blood glucose levels are highly influenced by GCs, the main hormones released after a stressful event. For instance, GCs increase glucose production in the liver by stimulating hepatic gluconeogenesis. Additionally, GCs decrease glucose utilisation and uptake in skeletal muscle and WAT. Indeed, energy and glucose homeostasis are intimately connected since both systems respond to changes in energy stores and availability. Accordingly, they share many common regulatory pathways. Glucose homeostasis is the physiological process of maintaining blood glucose levels within a narrow, stable range. It is primarily regulated by the pancreatic hormones insulin (lowers blood sugar) and glucagon (raises blood sugar) to ensure a steady energy supply. Disruption of this balance leads to hypo- or hyperglycaemia and diseases like diabetes.

**Key Components of Glucose Regulation:**

 **Insulin:** Released by pancreatic beta-cells when blood glucose is high (e.g., after eating), promoting glucose uptake into cells and storage as glycogen in the liver.

 **Glucagon:** Released by pancreatic Alpha-cells when blood glucose is low (e.g., fasting), stimulating

the liver to produce glucose through glycogenolysis and gluconeogenesis.

**Organs Involved:** The liver acts as a buffer for glucose, while muscle and adipose tissue are key sites for insulin-dependent glucose uptake.

**Supporting Hormones:** Other hormones like cortisol, adrenaline, and growth hormone can act to increase blood glucose levels during stress or fasting.

**Key Processes:**

**Glycogenesis:** Conversion of glucose into glycogen for storage (triggered by insulin).

**Glycogenolysis:** Breakdown of stored glycogen into glucose (triggered by glucagon).

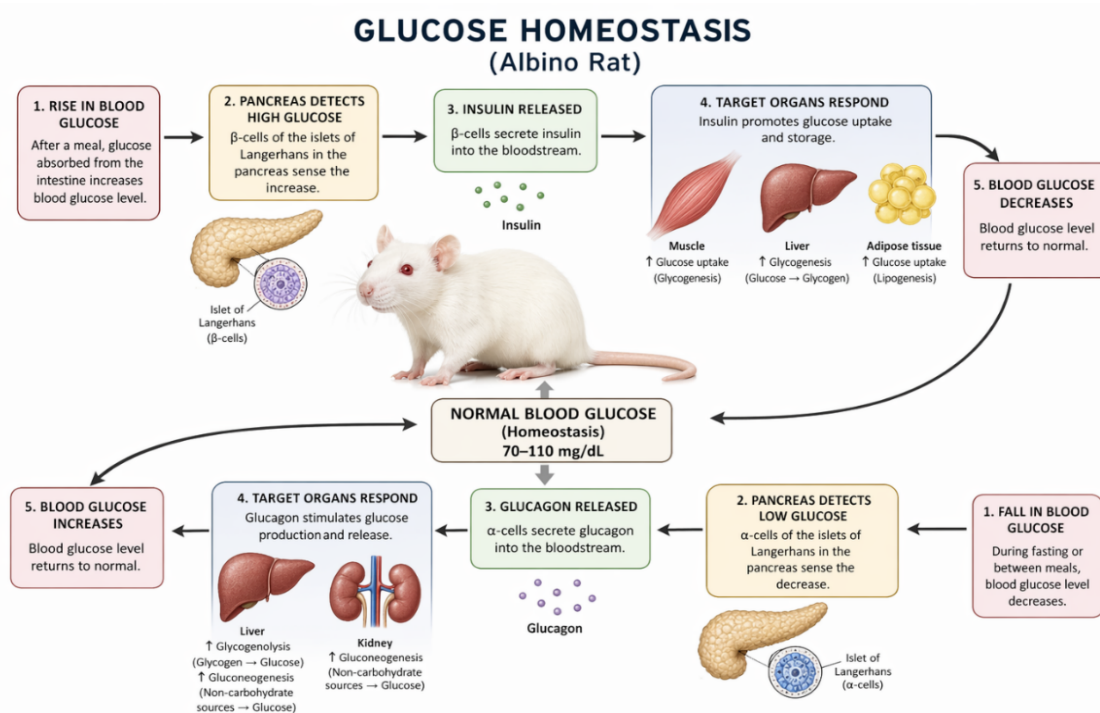
**Gluconeogenesis:** Production of glucose from non-carbohydrate sources (e.g., amino acids) in the liver.

### Disruptions in Glucose Homeostasis:

**Diabetes Mellitus:** A chronic failure to maintain homeostasis, categorised by high blood sugar (hyperglycemia) due to lack of insulin (Type 1) or reduced insulin sensitivity (Type 2).

**Hypoglycemia:** Abnormally low blood sugar, which can lead to fatigue, dizziness, or unconsciousness.

**Metabolic Syndrome:** Linked to obesity and dysfunction in glucose regulation. Proper glucose homeostasis is critical for brain function and overall energy metabolism, requiring the coordinated action of the endocrine system and liver to prevent organ damage.



Finger No. 1 Glucose Homeostasis Albino Rat

### Effect of Sodium Fluoride on Glucose Homeostasis:

#### Alteration in Insulin Secretion

- NaF exposure reduces insulin expression and secretion, leading to impaired glucose regulation.
- Chronic fluoride intake may cause:
- Insulin resistance
- Hyperglycemia or glucose intolerance

#### Changes in Glucose Uptake:

#### Studies in Wistar/albino rats show:

- Increased fluoride (50 ppm) → elevated insulin levels but altered glucose utilisation

- Increased glucose uptake in brain regions (cortex, hippocampus)

#### Mechanistic Pathways:

- NaF disrupts glucose homeostasis via:
- Pancreatic β-cell damage
- Interference with GLUT transporters
- Mitochondrial dysfunction
- Increased oxidative stress (key link)

#### Sodium Fluoride-Induced Oxidative Stress: Reactive Oxygen Species (ROS) Generation

- NaF significantly increases
- ROS production

- Lipid peroxidation (↑ MDA levels)
- Cellular oxidative damage

**Antioxidant Enzyme Suppression:**

**Key antioxidant enzymes are reduced**

- Superoxide dismutase (SOD)
- Catalase (CAT)

**Result:**

- Glutathione (GSH)

**Chronic exposure decreases overall antioxidant defence capacity:**

**Tissue Damage Oxidative stress leads to:**

- Liver damage (↑ ALT, AST)
- Apoptosis (cell death)

**Table-2. Body and organ weight of control and experimental rats.**

	Control	NaF-treated
Body Weight	174.4 ± 2.7	158.6 ± 2.2*
Liver Weight	26.7 ± 0.62	24.7 ± 0.58 <sup>ns</sup>
Kidney Weight	3.87 ± 0.05	3.04 ± 0.04*
Brain Weight	1.28 ± 0.01	1.03 ± 0.01*
Testes Weight	0.39 ± 0.01	0.30 ± 0.01 <sup>ns</sup>

**Table-3. Effect of Sodium Fluoride on ALP, SGOT and SGPT in control and experimental rats**

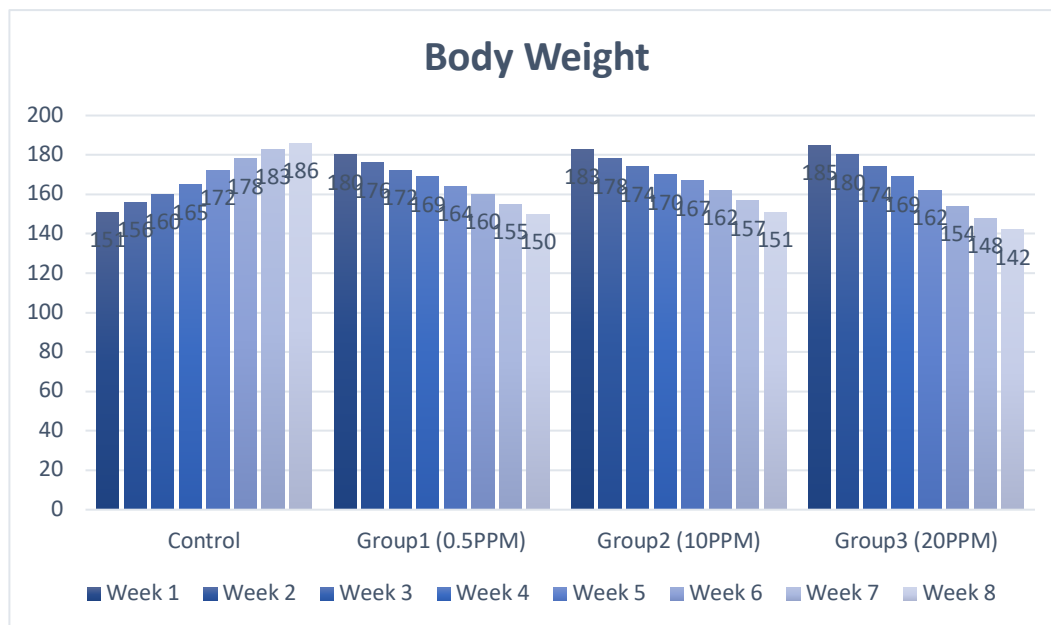
	07 days Control	Exp	20 days Control	Exp	40 days Control	Exp
ALP	29.3 ± 3.9	34.8 ± 3.9*	26.4 ± 4.9	35.5 ± 7.8*	28.5 ± 4.1	57.1 ± 4.5*
SGOT	17.5 ± 2.7	20.4 ± 1.9 <sup>ns</sup>	16.7 ± 3.5	23.4 ± 5.6*	17.6 ± 2.3	36.4 ± 3.8*
SGPT	13.8 ± 2.8	15.3 ± 11.4 <sup>ns</sup>	14.2 ± 2.8	21.5 ± 11.7*	14.0 ± 3.2	31.1 ± 11.6*

**Haematological parameters**

**Table 4– Haematological parameters in blood include RBC, WBC, Hb, MCH (mean cellular haemoglobin concentration), MCV (mean cellular volume), PCV (packed cell volume), and MCH (mean cellular haemoglobin)**

PARAMETER	WBC	RBC	Hb	PCV	MCV	MCH	MCHC	PLATELET
	(10 <sup>3</sup> /μl)	(10 <sup>6</sup> μl)	(g/dl)	%	(fL)	(pg)	(g/dl)	(10 <sup>5</sup> /mm <sup>3</sup> )
<b>Control</b>	<b>12.51</b>	<b>6.71</b>	<b>14.12</b>	<b>35.32</b>	<b>45.81</b>	<b>15.81</b>	<b>32.12</b>	<b>8.96</b>
	±	±	±	±	±	±	±	±
	1.24	0.74	1.35	2.25	2.14	1.06	1.64	0.68
<b>Group-1</b>	<b>5.83</b>	<b>4.11</b>	<b>8.21</b>	<b>23.43</b>	<b>52.61</b>	<b>19.32</b>	<b>32.12</b>	<b>5.34</b>
	±	±	±	±	±	±	±	±
	0.61	0.46	0.59	1.59	3.41	1.02	1.57	0.59
<b>Group-2</b>	<b>7.11</b>	<b>5.21</b>	<b>9.19</b>	<b>28.19</b>	<b>53.91</b>	<b>19.65</b>	<b>33.01</b>	<b>5.91</b>
	±	±	±	±	±	±	±	±
	0.97	0.48	1.02	1.84	3.32	1.02	1.57	0.54
<b>Group-3</b>	<b>12.46</b>	<b>7.37</b>	<b>13.89</b>	<b>35.68</b>	<b>41.56</b>	<b>11.61</b>	<b>26.15</b>	<b>802</b>
	±	±	±	±	±	±	±	±
	1.22	0.70	1.30	2.21	2.11	1.01	1.56	0.8

**Body Weight Albino Rats:**



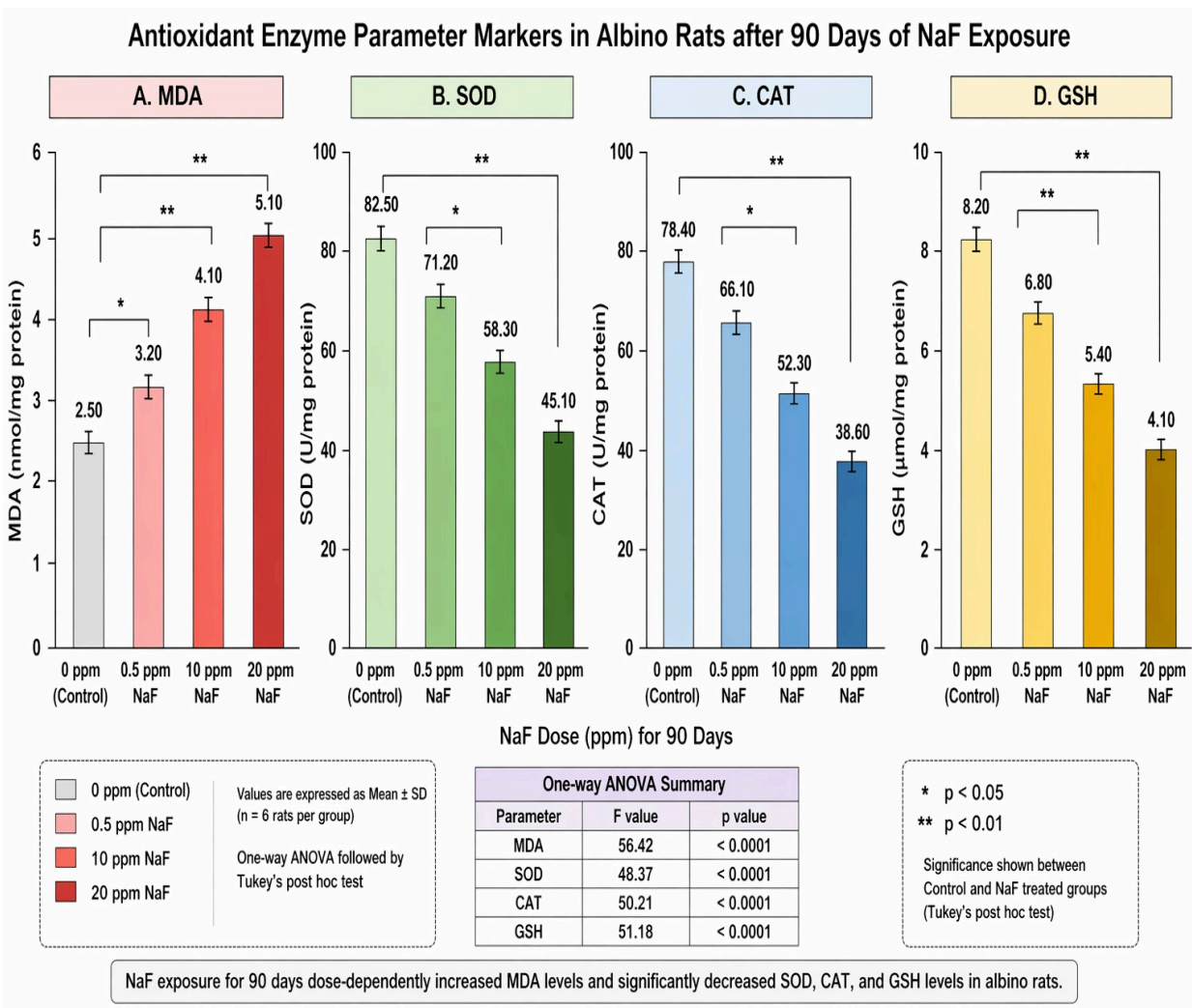
**Figure 2: The bar graph you shared represents Body Weight changes across 8 weeks in different groups exposed to varying concentrations of sodium fluoride**

**Result Statement: in Oxidative Stress:**

Fluoride exposure induced dose-dependent oxidative stress in albino rats. Rats treated with 0.5 ppm fluoride showed mild oxidative changes, while 10 ppm fluoride produced moderate oxidative damage. The highest dose, 30 ppm, caused marked oxidative stress, indicated by increased MDA and ROS levels and decreased antioxidant enzymes such as SOD, CAT, and GSH. These findings suggest that fluoride toxicity increases free radical production and reduces antioxidant defence in albino rats.

**Oxidative Stress:**

NaF Dose (ppm)	MDA	SOD	CAT	GSH	ROS
0	2.5	8.5	50	7.2	100
0.5	3.2	7.2	45	6.5	130
10	4.8	5.5	35	4.5	180
20	5.9	4.2	27	3.1	215



**Table 5– Oxidative Stress Parameter Markers**

**Antioxidant enzymes:**

Antioxidant enzymes are the primary defence against reactive oxygen species (ROS), neutralising free radicals to prevent oxidative damage. Key enzymes include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR). Activity is highly adaptable, often increasing in response to stress (e.g., exercise, pesticide exposure) but decreasing

**Key Antioxidant Enzymes & Functions:**

- **Superoxide Dismutase (SOD):** Converts harmful superoxide radicals into hydrogen peroxide, acting as

a crucial first line of defence in the cytosol and mitochondria.

- **Catalase (CAT):** Efficiently breaks down hydrogen peroxide into water and oxygen, protecting cells from damage, particularly in the liver and red blood cells.
- **Glutathione Peroxidase (GPx):** Reduces hydrogen peroxide and lipid peroxides to alcohols using glutathione, often relying on selenium as a cofactor.
- **Glutathione-S-transferase (GST):** Detoxifies various electrophilic compounds, playing a key role in reducing cellular oxidative stress. with ageing or chronic illnesses.

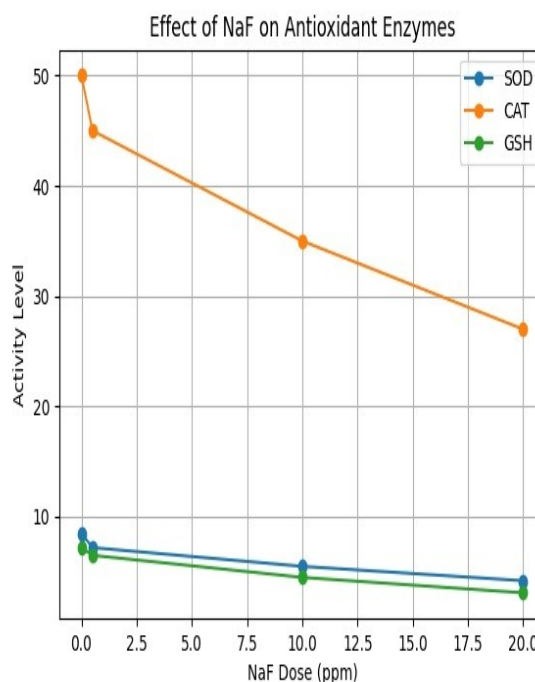
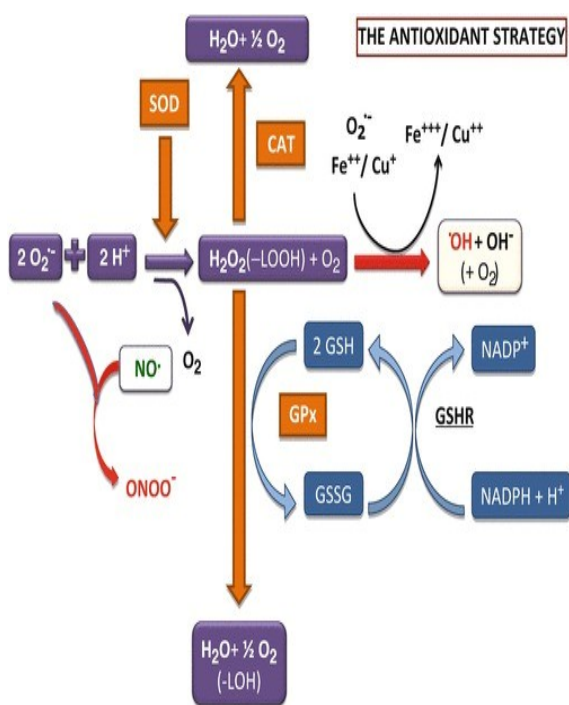


Figure 3: Antioxidant Enzyme Parameter Markers Bar Graph

**DISCUSSION:**

The present study investigated the impact of sodium fluoride (NaF) exposure on glucose homeostasis and oxidative stress in albino rats, revealing a clear dose-dependent alteration in biochemical parameters. The findings demonstrate that NaF administration significantly enhances oxidative stress while simultaneously suppressing antioxidant defence mechanisms, thereby contributing to metabolic dysregulation.

A key observation in this study is the progressive increase in malondialdehyde (MDA) and reactive oxygen species (ROS) levels with increasing NaF concentrations. MDA is a well-established marker of lipid peroxidation, and its elevation indicates enhanced membrane damage due to free radical attack. The concurrent rise in ROS further confirms that NaF exposure induces a pro-oxidant state. These results are consistent with previous experimental reports suggesting that fluoride toxicity leads to excessive generation of reactive oxygen intermediates, overwhelming cellular redox balance and initiating oxidative damage in vital tissues such as the liver, pancreas, and brain.

In contrast, the study recorded a significant decline in antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH), across NaF-treated groups. SOD serves as the first line of defence against superoxide radicals, while CAT and GSH are critical for detoxifying hydrogen peroxide and maintaining intracellular redox homeostasis. The observed reduction in these enzymes suggests that NaF not only increases ROS production but also impairs the enzymatic machinery responsible for neutralising oxidative stress. This dual effect exacerbates cellular damage and contributes to functional impairment of metabolic organs.

**CONCLUSION:**

The present study demonstrates that exposure to sodium fluoride (NaF) induces significant metabolic and biochemical alterations in albino rats, primarily through the disruption of glucose homeostasis and induction of oxidative stress. A clear dose-dependent relationship was observed, where increasing concentrations of NaF led to a marked elevation in oxidative stress markers, including malondialdehyde (MDA) and reactive oxygen species (ROS), alongside a significant decline in key antioxidant enzymes such

as superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH). These findings confirm that NaF toxicity impairs the antioxidant defence system, leading to excessive free radical generation and cellular damage. The imbalance between oxidants and antioxidants appears to play a crucial role in altering metabolic pathways, potentially leading to insulin dysfunction and impaired glucose regulation. Statistical analysis (ANOVA) further validated that these changes were highly significant, reinforcing the conclusion that sodium fluoride exposure has a profound impact on redox balance and metabolic health.

#### REFERENCES:

1. Vuong, A. M., Yolton, K., Xie, C., Dietrich, K. N., Braun, J. M., Webster, G. M., ... & Chen, A. (2021). Childhood exposure to per-and polyfluoroalkyl substances (PFAS) and neurobehavioral domains in children at age 8 years. *Neurotoxicology and teratology*, *88*, 107022.
2. Tang, Z., Lai, C. C., Luo, J., Ding, Y. T., Chen, Q., & Guan, Z. Z. (2021). Mangiferin prevents the impairment of mitochondrial dynamics and an increase in oxidative stress caused by excessive fluoride in SH-SY5Y cells. *Journal of biochemical and molecular toxicology*, *35*(4), e22705
3. Gao, Y., Liang, C., Zhang, J., Ma, J., Wang, J., Niu, R., ... & Wang, J. (2018). Combination of fluoride and SO<sub>2</sub> induce DNA damage and morphological alterations in the male rat kidney. *Cellular Physiology and Biochemistry*, *50*(2), 734-744.
4. Mittal, M., Chatterjee, S., & Flora, S. J. S. (2018). Combination therapy with vitamin C and DMSA for arsenic-fluoride co-exposure in rats. *Metallomics*, *10*(9), 1291-1306.
5. Perera, T., Ranasinghe, S., Alles, N., & Waduge, R. (2020). Experimental rat model for acute tubular injury induced by high water hardness and high water fluoride: efficacy of primary preventive intervention by distilled water administration. *BMC nephrology*, *21*, 1-16.
6. Dec, K., Łukomska, A., Baranowska-Bosiacka, I., Pilutin, A., Maciejewska, D., Skonieczna-Żydecka, K., ... & Gutowska, I. (2018). Pre-and postnatal exposition to fluorides induce changes in rats liver morphology by impairment of antioxidant defense mechanisms and COX induction. *Chemosphere*, *211*, 112-119.
7. Choubisa, S. L., Choubisa, D., & Choubisa, A. (2023). Fluoride contamination of groundwater and its threat to health of villagers and their domestic animals and agriculture crops in rural Rajasthan, India. *Environmental geochemistry and health*, *45*(3), 607-628.
8. Choubisa, S. L. (2018). A brief and critical review on hydrofluorosis in diverse species of domestic animals in India. *Environmental geochemistry and health*, *40*(1), 99-114.
9. Li, H., Fan, J., Zhao, Y., Yang, J., Xu, H., Manthari, R. K., ... & Wang, J. (2021). Calcium alleviates fluoride-induced kidney damage via FAS/FASL, TNFR/TNF, DR5/TRAIL pathways in rats. *Ecotoxicology and Environmental Safety*, *226*, 112851.
10. Sandoval, D., Cota, D., & Seeley, R. J. (2008). The integrative role of CNS fuel-sensing mechanisms in energy balance and glucose regulation. *Annu. Rev. Physiol.*, *70*(1), 513-535.
11. Munoth, P., Tiwari, K., & Goyal, R. (2015, December). Fluoride and nitrate groundwater contamination in Rajasthan, India: A review. In *20th International Conference on Hydraulics*.
12. Ahmad, S., Singh, R., Arfin, T., & Neeti, K. (2022). Fluoride contamination, consequences and removal techniques in water: a review. *Environmental Science: Advances*, *1*(5), 620-661.
13. Valdez-Jiménez, L., Fregozo, C. S., Beltrán, M. M., Coronado, O. G., & Vega, M. P. (2011). Effects of the fluoride on the central nervous system. *Neurología (English Edition)*, *26*(5), 297-300.
14. Choi, A. L., Sun, G., Zhang, Y., & Grandjean, P. (2012). Developmental fluoride neurotoxicity: a systematic review and meta-analysis. *Environmental health perspectives*, *120*(10), 1362-1368.
15. D.H. Tran, Z.V. Wang, Glucose metabolism in cardiac hypertrophy and heart failure, *J. Am. Heart Assoc.* *8* (12) (2019), e012673.

16. Lopaschuk, G. D., & Stanley, W. C. (1997). Glucose metabolism in the ischemic heart. *Circulation*, 95(2), 313-315.
17. Han HS, Kang G, Kim JS, Choi BH, Koo SH. Regulation of glucose metabolism from a liver-centric perspective. *Exp Mol Med*. 2016 Mar 11;48(3):e218.
18. Poggiogalle E, Jamshed H, Peterson CM. Circadian regulation of glucose, lipid, and energy metabolism in humans. *Metabolism*. 2018 Jul;84:11-27.
19. Schnell O, Crocker JB, Weng J. Impact of HbA1c Testing at Point of Care on Diabetes Management. *J Diabetes Sci Technol*. 2017 May;11(3):611-617.
20. Eun YM, Kang SG, Song SW. Fasting plasma glucose levels and coronary artery calcification in subjects with impaired fasting glucose. *Ann Saudi Med*. 2016 Sep-Oct;36(5):334-340.
21. Barasch A, Gilbert GH, Spurlock N, Funkhouser E, Persson LL, Safford MM., DPBRN Collaborative Group. Random plasma glucose values measured in community dental practices: findings from the dental practice-based research network. *Tex Dent J*. 2013 Apr;130(4):291-7.
22. Garrison A. Screening, diagnosis, and management of gestational diabetes mellitus. *Am Fam Physician*. 2015 Apr 01;91(7):460-7.
23. Leighton E, Sainsbury CA, Jones GC. A Practical Review of C-Peptide Testing in Diabetes. *Diabetes Ther*. 2017 Jun;8(3):475-487.
24. Regnell SE, Lernmark Å. Early prediction of autoimmune (type 1) diabetes. *Diabetologia*. 2017 Aug;60(8):1370-1381.
25. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int*. 2011;80(12):1258–70.
26. Redmon JH, Elledge MF, Womack DS, Wickremasinghe R, Wanigasuriya KP. Additional perspectives on chronic kidney disease of unknown aetiology (CKDu) in Sri Lanka– lessons learned from the WHO CKDu population prevalence study. *BMC Nephrol*. 2014;15:125–35.
27. Ranasinghe H. Organic agriculture as a sustainable solution to chronic kidney disease unidentified (CKDu). *International Journal of Multidisciplinary Studies*. 2016;3(2):71–7.
28. anasinghe H, Ranasinghe M. Status gaps and way forward in addressing the chronic kidney disease unidentified (CKDu) in Sri Lanka. *Journal of Environmental Professionals Sri Lanka*. 2015;4(2):58–68.
29. sayanthooran S, Magana-Arachchi DN, Gunerathne L, Abeysekera TD, Sooriyapathirana SS. Upregulation of oxidative stress related genes in a chronic kidney disease attributed to specific geographical locations of Sri Lanka. *Biomed Res Int*. 2016;7546265.
30. Anjum KM, Mughal MS, Sayyed U, Yaqub A, Khalique A, Rashid MA, Yousaf MZ, Mumtaz N. Influence of increasing fluoride dose rates on selected liver and kidney enzymes profile in domestic chicken (*Gallus domesticus*). *J Anim Plant Sci*. 2014;24(1):77–80.