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UNVEILING THE COMPARATIVE TOXICITY OF ACUTE VS. CHRONIC ZINC OXIDE NANOPARTICLE EXPOSURE IN ALBINO MICE KIDNEYS: EVIDENCE OF METABOLIC AND MOLECULAR DISRUPTION

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Abstract

Zinc oxide nanoparticles (ZnONPs) are widely used in various industrial and biomedical applications; however, their potential health risks remain a growing concern. This study investigated the nephrotoxic effects of both acute and chronic ZnONPs exposure in male adult albino mice. Mice were intraperitoneally administered ZnONPs at a dose of 5 mg/kg body weight weekly for acute exposure (1 week) and twice weekly for chronic exposure (10 weeks). A glucose tolerance test (GTT) was performed to assess metabolic disruption. The results revealed that chronic ZnONPs administration impaired glucose tolerance, suggesting a diabetogenic effect. Moreover, ZnONPs significantly increased the expression of pro-inflammatory (NF-κB, TNF-α) and apoptotic (caspase-3) markers in renal tissues, with more pronounced effects observed under chronic exposure. Notably, a marked downregulation of the antioxidant protein Sirtuin-1 (SIRT1) was observed, particularly in chronically treated mice, indicating impaired redox homeostasis. Collectively, these findings demonstrate that ZnONPs induce renal toxicity through mechanisms involving inflammation, oxidative stress, and apoptosis, with severity increasing over time.

Keywords: ZnONPs, oxidative stress, inflammation, apoptosis, renal.

INTRODUCTION

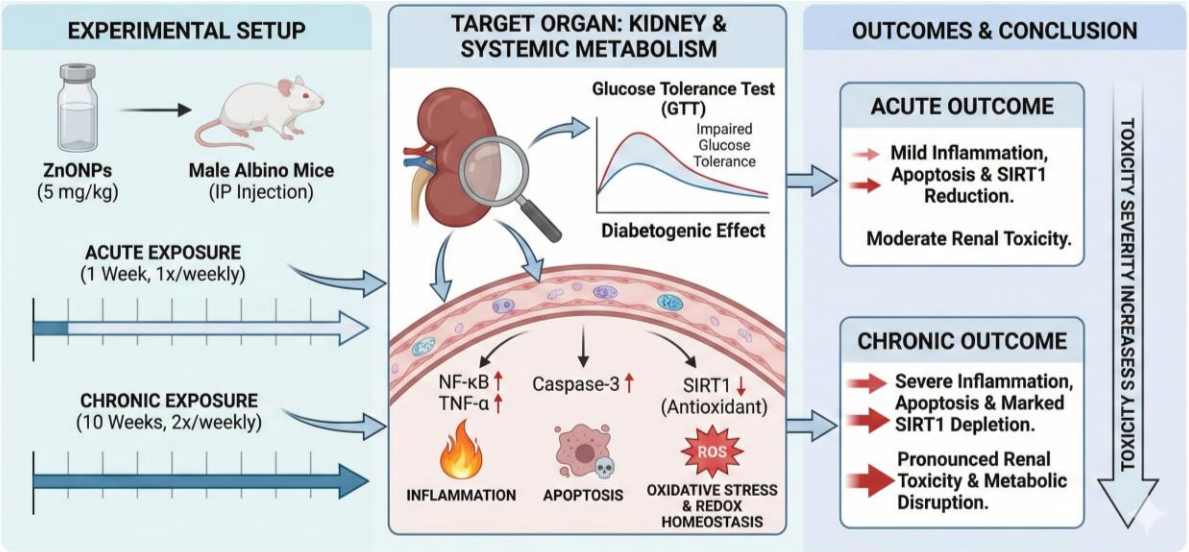


Fig. Graphical Abstract

1. Introduction

Nanoparticles are generally abundant in nature, as they are emitted into the environment from many natural processes such as photochemical reactions, volcanic eruptions, forest fires, and different industrial activities (Jeevanandam et al., 2018). Nanoparticles have a greater surface area because of their small size, so they may easily interact with organic surfaces and create numerous harmful effects. They may also cross all the natural barriers and produce harmful effects in vital organs such as the placenta and the brain. Similar features offered by various sorts of nanoparticles may also force an undesirable exposure to human health and the earth (Alhazza et al., 2023)(Saifi et al., 2018). Zinc oxide nanoparticles (ZnONPs) are broadly utilized in numerous fields, for example, dyes, food flavors, medication, and electronic industries. These are also used in cosmetics industries, especially in facial products and sunscreen. (Hou et al., 2018).

In recent years, with the remarkable increase in uses of ZnONPs, the health risks associated with its use are of concern. These NPs can enter the body from various routes such as skin, mouth, and digestive tract. It can interact with the cell and its organelles more closely which results in many toxicological effects. Airway exposure to ZnONPs is also a major risk factor (Hasanabadi et al., 2023)(Singh et al., 2019). Exposure to these nanoparticles results in reactive oxygen species (ROS) and activates specific transduction pathways in target cells. Uncontrollable ROS generation and antioxidant defense systems bring in some unique results leading to cell death. The oxidative stress mechanism of ZnONPs could be attributed to the combination of many phenomena, such as the production of ROS on the particle surface, generation of free radicles, and the interaction of ZnONPs with the cell leads to cell membrane damage (Dosoky et al., 2022), (Wei et al., 2021) and DNA damage (Shahzad et al., 2019). These nanoparticles have also shown some toxic effects on different cell lines such as human epidermal cells as well as blood

macrophages of mice. As both high and low doses of ZnONPs are having adverse effects.

The low dose oral exposure of ZnONPs in mice has enhanced the phagocytic activity in the mice. Moreover, exposure to high doses of ZnONPs caused edema, hepatocyte degeneration, swelling of the pancreas, and affected the digestive system (Liu et al. 2017). In in vivo research, ZnONPs were found to show a harmful effect on kidneys, livers, lungs, spleen, and pancreas (Adeniyi et al., 2023)(Senapati et al., 2015). ZnONPs reduced the catalase activity and superoxide dismutase in the kidney cortex. Further, it was found that the toxic doses of ZnONPs cause injurious inflammatory effects and oxidative stress in liver tissues (Kausar et al., 2023). ZnONPs may interfere with various metabolic pathways that trigger mitochondria and tissue damage in the kidney, which might be expected to ZnONPs nephrotoxicity. The mechanisms of molecular nephrotoxicity underlying ZnONPs stay uncertain (Yan et al., 2012)(Rana et al. 2022). It is also studied that oral exposure to zinc oxide nanoparticles (ZnONPs) induced many harmful effects in brain tissue including inflammatory cytokines, fragmentation of DNA, and apoptotic activation (Attia et al., 2018). Sirtuin 1 is the most commonly expressed in the mammalian brain (Stamatovic et al., 2019) and tubular cells of the kidneys. Sirtuins contribute to brain development and maintaining kidney homeostasis. Their down-regulation leads to chronic and acute neuro and renal diseases (Morigi et al. 2018). Very few studies evaluate the toxicity of ZnONPs in the brain and kidney (Alferah et al. 2018). The present study was conducted to determine the short- and long-term exposure of ZnONPs that causes toxicity in the brain and kidneys.

2. Materials and Methods

2.1. Chemicals

Zinc oxide nanoparticles (ZnONPs), particle size <50 nm, purity >97 percent, were purchased from Sigma Aldrich, Germany and used as received. Tris HCl, Acrylamide, Bisacrylamide, Sodium dodecyl sulfate (SDS), N, N, N', N'-tetramethyl ethylene diamine (TEMED), Ammonium persulfate (APS), Glycine, Ethanol, Skim milk powder, and Tween 20 were purchased from Sigma Aldrich, Germany company.

2.2. Preparation of Stock Solution of ZnONPs

ZnONPs suspension was prepared in 0.9% saline solution. The solution was ultra-sonicated (sonicator: 4000) for 30 minutes and the vortex was performed for 60 sec.

2.3. Animal Housing

Albino mice were purchased from the Veterinary Research Institute (Peshawar) and were kept in a breeding room in different cages (n=5) for one week to climatize with the conditions. The animals were randomly divided into three groups;

1. Control group
2. Chronic group (mice exposed to high dose i.e., ZnONPs 5 mg/kg twice a week for ten weeks)
3. Acute group (mice exposed to low dose i.e., ZnONPs 5 mg/kg once a week for one week).

The control group received only 0.9% saline solution. While the other two groups received ZnONPs in 0.9% saline solution.

2.4. Treatment of ZnONPs

ZnONPs were injected intraperitoneally (i.p), at 5 mg/kg to all the adult male albino mice, twice a week for ten weeks (high dose) and once a week for one week (low dose). All the experimental animals were sacrificed after the completion of the ZnONPs administration. Kidneys were collected in RNA later and Phosphate-buffered saline (PBS) solution (1:1). The tissues of the kidneys were homogenized with PBS solution in a homogenizer (Scilogex, Germany). The homogenate was then centrifuged for 25 min at 15000 rpm at 4◦C and supernatants were collected and stored at -70◦C for further experiment.

2.5. Glucose Tolerance Test

A glucose tolerance test was performed after 10 weeks of ZnONPs treatment. An injection of glucose was injected into the tail of the mouse and the glucose level was determined with a glucometer after several time intervals. Following the protocols (Nagy et al., 2018) (McDonough, et al., 2021), mice were put on fasting overnight for approximately 6-8 hours without food. Firstly, the blood glucose was checked with a glucometer at fasting. Then the mice were weighed, and the glucose solution was prepared as required (200 mg of glucose/kg body mass). With the sharp scissor, the tip of the tail was cut off 1-2 mm carefully. The first few drops of the blood were discarded to avoid hemolysis. A few drops of blood were placed on the test strip. Mice were injected intraperitoneally with a suitable amount of glucose solution. Then the glucose levels in the blood were measured at 15, 30, 60,120, and 180 minutes after glucose was injected, and readings were noted.

2.6. Western Blotting

According to Kurien et al.'s (2015) protocol, Western bot analysis was performed. Briefly, the sample was prepared in Eppendorf (E-tubes) and vertex was performed for 30 sec. The sample was heated at 96°C for 10-15 minutes for denaturation of the sample. Then the sample was kept on ice for 10 minutes. The extracted protein from the kidney tissues was quantitatively analyzed using a BioRad protein assay solution. The desired protein was loaded onto the 10-15% SDS-PAGE. All the samples were run in a single blot for comparison. The 10–245 kDa range molecular marker is used to determine the molecular weight of the protein and separate it according to its size (Espanani et al., 2015). Electro blotting procedure was used for the transfer of protein from gel to membrane. For this purpose, a Polyvinylidene difluoride (PVDF) membrane was used. Then the targeted protein was detected by using specific antibodies for blocking the non-specific sites. The gel membrane was placed in a dilute solution of 5% skim milk for 45 minutes on an orbital shaker (Insta Bioanalytik Pte. Ltd., Singapore). The membrane was incubated with primary antibodies overnight at 4oC. Then the membrane was incubated with secondary antibodies for at least 1-2 hrs. For detection, the enhanced chemiluminescence (ECL) (Amersham Pharmacia Biotech, Uppsala, Sweden) method was used for the relative quantitation of targeted protein. The western blotting luminal reagent was used as a chemiluminescent agent. Then the reaction product produced luminescence which can only be seen in a red-light dark room.

2.7. Statistical Analysis

The x-ray films were scanned and the exact density of the bands was analyzed through image J software. The data are expressed as the group mean ± SEM. Prism 6 (GraphPad Software, San Diego, CA) was used for one-way ANOVA with the Student t-test. Differences between groups were considered significant at $p< 0.05$. The data are presented as the mean ± SEM of 5 mice per group and are representative of three independent experiments. (Significance: *, # = $P \leq 0.05$, **, ## = $P \leq 0.01$, ***, ### = $P \leq 0.001$).

3. Results and Discussion

3.1. Chronic Exposure of ZnONPs Induced Diabetes in Albino Mice

The study was performed in which ZnONPs were administered chronically for 10 weeks to adult male albino mice. After the exposure of ZnONPs, a glucose tolerance test (GTT) was performed. Mice were kept on fasting for 6-8 hours. Then glucose 250 mg/kg was injected into the tail of the mouse. The glucose level was checked with a glucometer after several time intervals as shown in Fig. 1. At fasting, the glucose level of the mice

exposed to ZnONPs was 161 mg/dl. After 15 minutes the glucose level raised to 294 mg/dl. Then after half an hour, the glucose level reaches 250 mg/dl. The experiment continued and further readings were noted after 60 and 120 mints later and the results were 200 mg/dl and 166 mg/dl respectively. Our last reading was 157 mg/dl after 180 mints, which showed that the chronic exposure of ZnONPs on albino mice caused diabetes. This is the novel work to date as there is no such study exists. The GTT test revealed that in comparison to the control the chronic exposed animals had a high range of blood glucose.

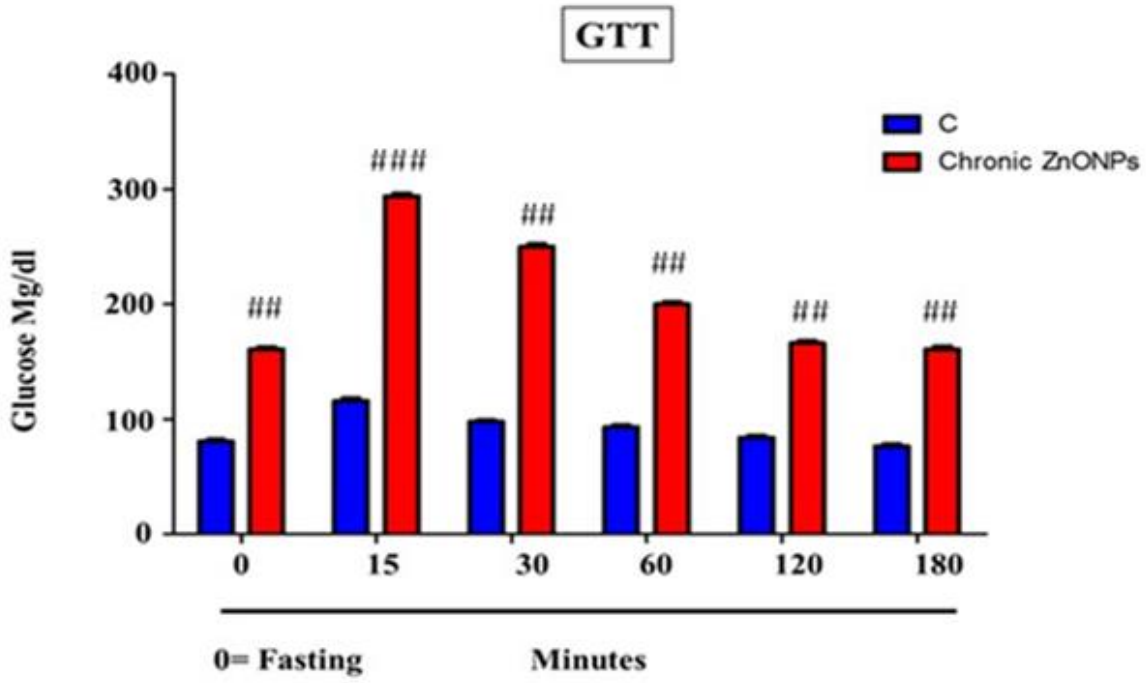


Fig. 1: Glucose Tolerance Test Performed After the Chronic Administration of ZnONPs (Statistical difference: #, * = 0.05, ##, ** = 0.01 and ###, *** = 0.001. Moreover, # = Control vs Chronic and * = Control vs Acute.)

3.2. Inflammation in Kidneys Caused by ZnONPs in Albino Mice

ZnONPs are causative agents of activation of NF-κB and TNF- α in the body. The NF-κB pathway is a significant indicator of inflammation (Roberti, et al., 2022). The ZnONPs were administered (5mg/kg) intraperitoneally (i.p.) to the male adult mice chronically for 70 days and acutely for 7 days. The mice were sacrificed and the homogenate of kidneys was subjected to western blotting and then different markers of inflammation were checked to know the extent of inflammation in the kidneys due to ZnONPs exposure. The results revealed that both chronic and acute exposure of ZnONPs caused renal inflammation in the mice but the protein expression of NF-κB and TNF-α are more chronic as compared to the acute exposure as given in the following Fig. 2a and 2b.

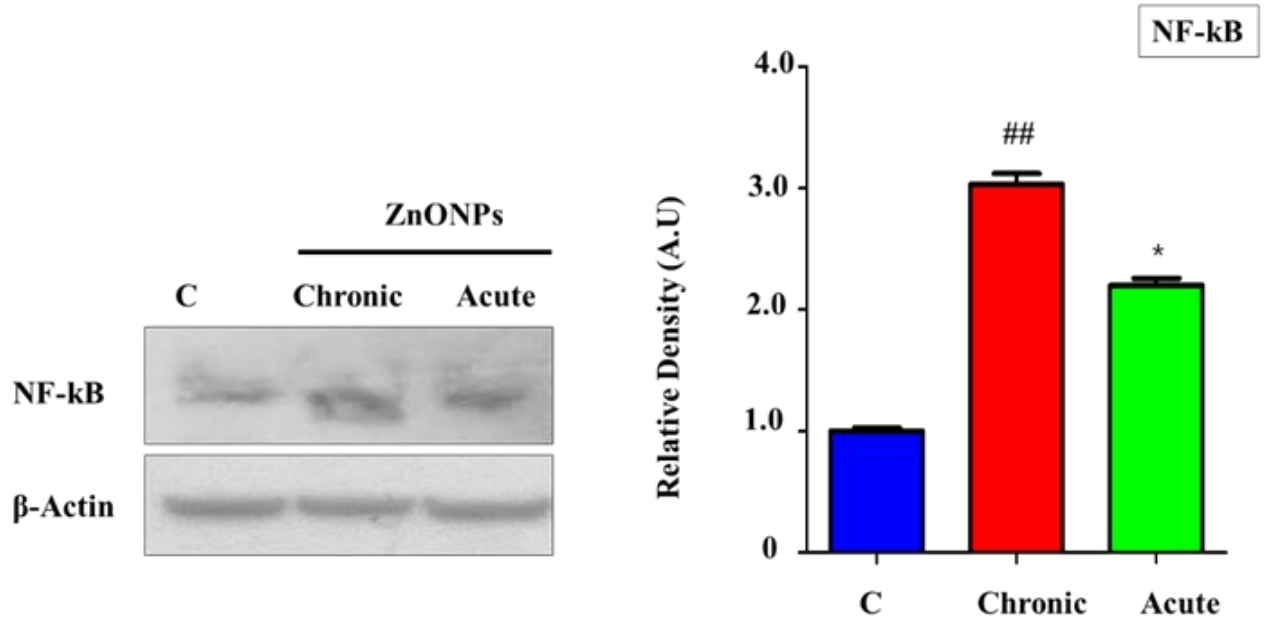


Fig. 2a: Increasing the expression of NF- κB in male adult albino mice exposed to ZnONPs in a Time-dependent manner

Comparing the present work with the earlier study by Faddah et al. (2012) in which two different doses of ZnONPs i.e., either 600 mg or 1 g/Kg body weight/day were tested to Wister albino rats for 5 days, which showed that ZnONPs caused renal toxicity by increasing inflammatory signs that include: interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP). Similarly, the present work concluded that administration of ZnONPs (5mg/kg) in a time-dependently manner caused renal toxicity by increasing different inflammatory marks.

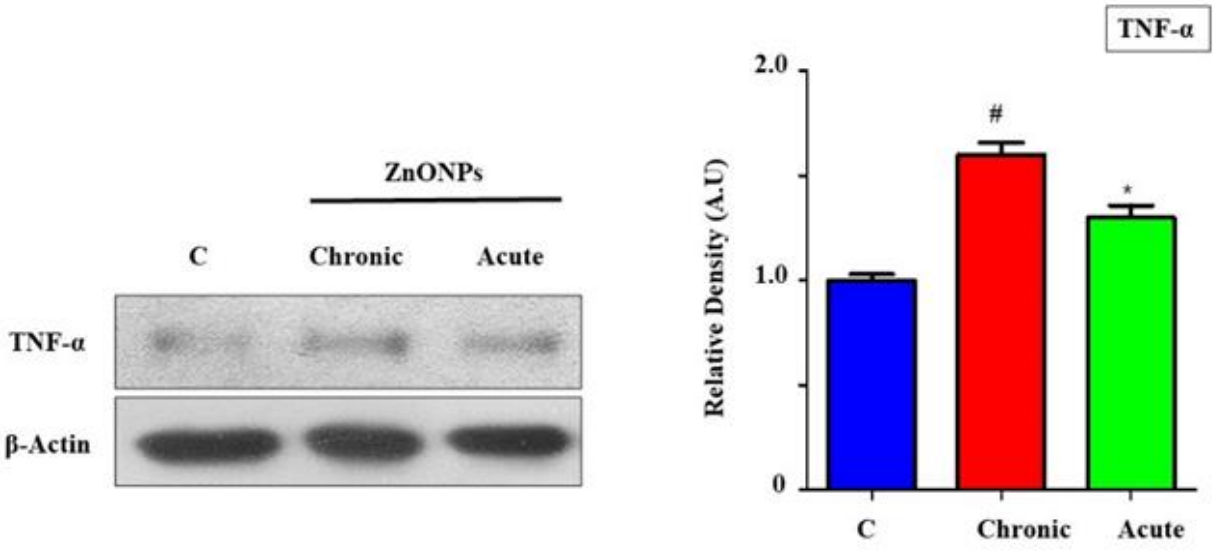
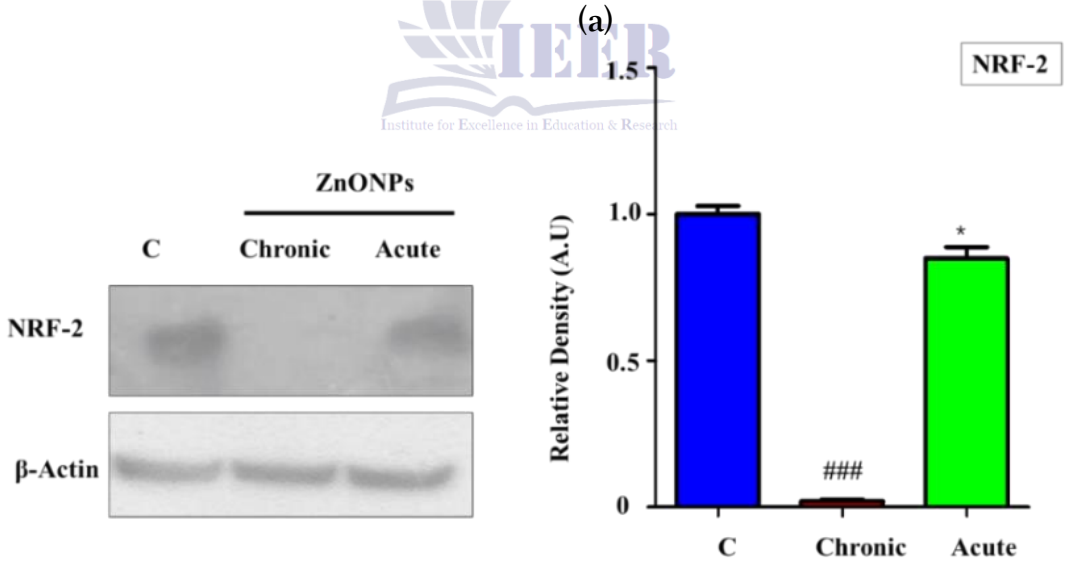


Fig. 2b : Elevating Expression of TNF-α in Albino Mice Exposed to ZnONPs time-dependently

3.3. Oxidative Stress in kidneys Caused by ZnONPs in Albino Mice

The Nrf-2 and HO-1 proteins form antioxidant protective systems in the body. The downregulation of Nrf-2 and HO-1 indicates that oxidative stress has occurred (Yang, et al 2022).The male adult albino mice were exposed to ZnONPs (5mg/kg) chronically for 10 weeks and acutely for 1 week. The chronic and acute administration of ZnONPs in male adult mice induced oxidative stress by inhibiting antioxidant proteins such as NRF-2 and HO-1 expressions time-dependently as shown in Fig. 3a and 3b. Western blot results of NRF-2 and β-actin with its histogram for all the three experimental groups (n=5/group) with or without ZnONPs administration along with their respective histogram were shown in the following Fig.6. (A) and (B). β-actin was used as a housekeeping gene. The density of proteins is expressed in arbitrary units (A.U.s) as the mean ± S.E.M. Chronic exposed mice were considerably different from normal and acute significantly different from control mice.

Rats were given their recommended treatment orally for 10 weeks, which showed that ZnONPs and Al_2O_3NPs alone or in combination caused nephrotoxicity, and hepatotoxicity, which further causes dysfunction in mitochondria which initiate the production of ROS and oxidative stress. The oxidative stress caused by inhibiting endogenous antioxidant system proteins, comprising of NRF-2 and HO-1 expression, further induced translocation of NF-κB into the nucleus to induce nephrotoxicity. The production of ROS can disturb mitochondrial function and also cause changes in the expression of genes that are involved in inflammation and apoptosis (Patergnani, et al. 2021). The graph shows that the expression of chronic exposure is greater as compared to the acute one.



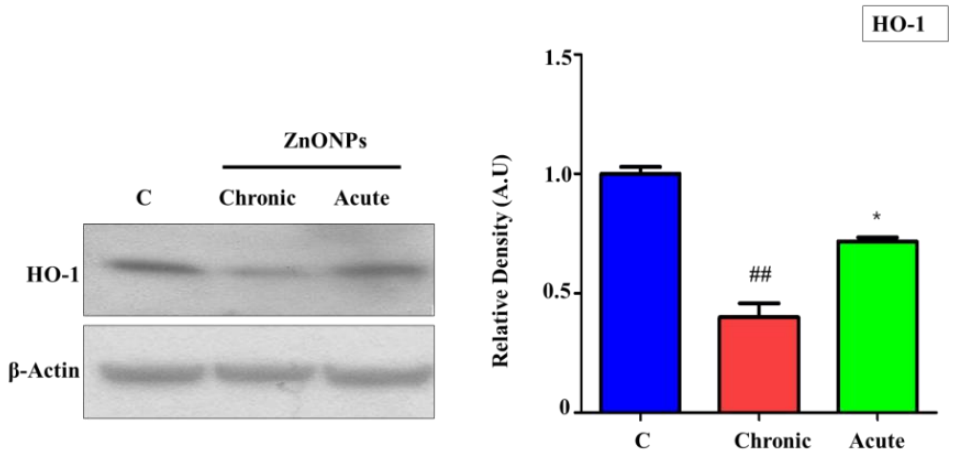
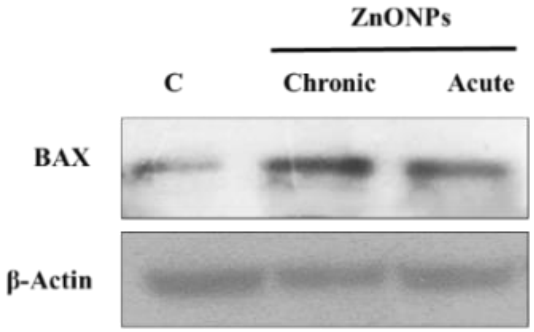


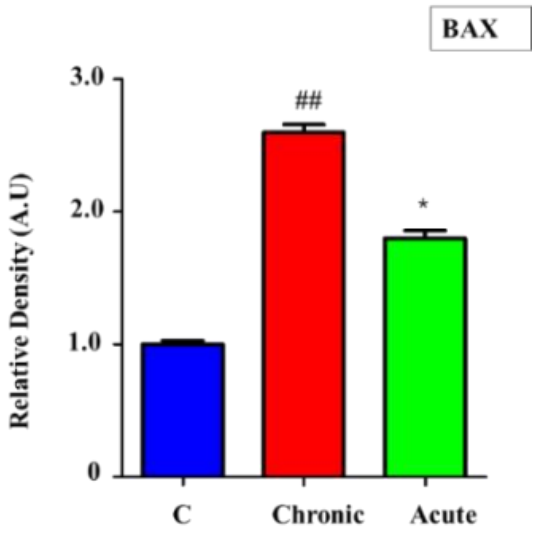
Fig. 3. (a) Oxidative stress in chronically and acutely exposed albino mice to ZnONPs: (b) Oxidative Stress Caused by inhibiting HO-1 antioxidant protein in time-dependently

3.4. ZnONPs Induced Apoptosis in the Kidneys of Male Adult Mice

Apoptosis plays a dual role in the progression of renal scarring, exerting both protective and detrimental effects depending on the context and extent of injury. In the present study, kidney homogenates from treated mice were subjected to immunoblotting analysis to assess the expression of key apoptotic markers. The results demonstrated that both acute and chronic ZnONPs exposures led to a marked increase in the expression of apoptotic proteins, including BAX, cleaved caspase-3, and fragmented PARP-1 (Fig. 4a–c). Notably, chronic exposure elicited a more pronounced upregulation of these markers compared to acute exposure, suggesting a more severe apoptotic response during prolonged treatment. These findings are consistent with previous reports indicating the involvement of caspase-3 in both inflammation and apoptosis (Yang et al., 2019; Opdenbosch et al., 2019). (Lan et al., 2021). In line with this, the current study highlights significant activation of caspase-3 and BAX in the kidneys of mice exposed to ZnONPs, particularly under chronic exposure conditions.(Khorsandi et al. (2018))

(a)


ZnONPs
C
Chronic
Acute
BAX
β-Actin


BAX
Relative Density (A.U)
3.0
2.0
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*
C
Chronic
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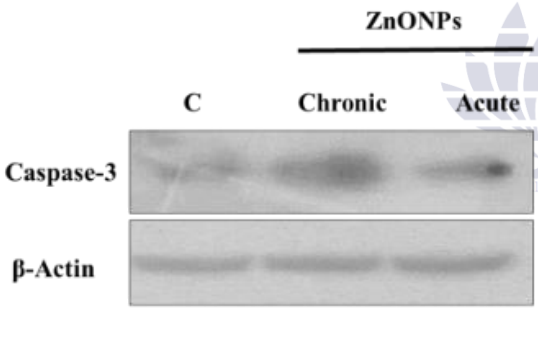
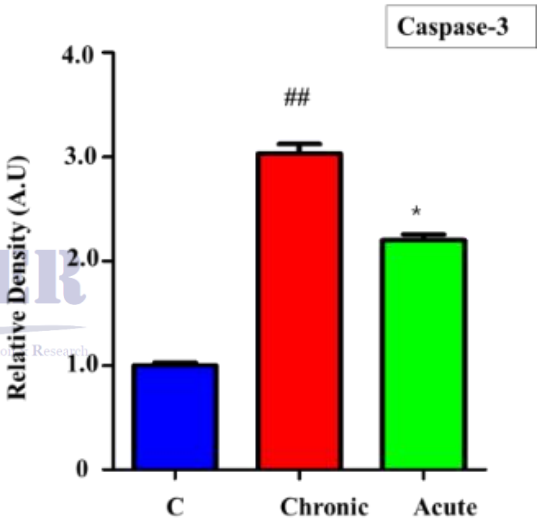
(b)


ZnONPs
C
Chronic
Acute
Caspase-3
β-Actin


Caspase-3
Relative Density (A.U)
4.0
3.0
2.0
1.0
0
##
*
C
Chronic
Acute

(c)

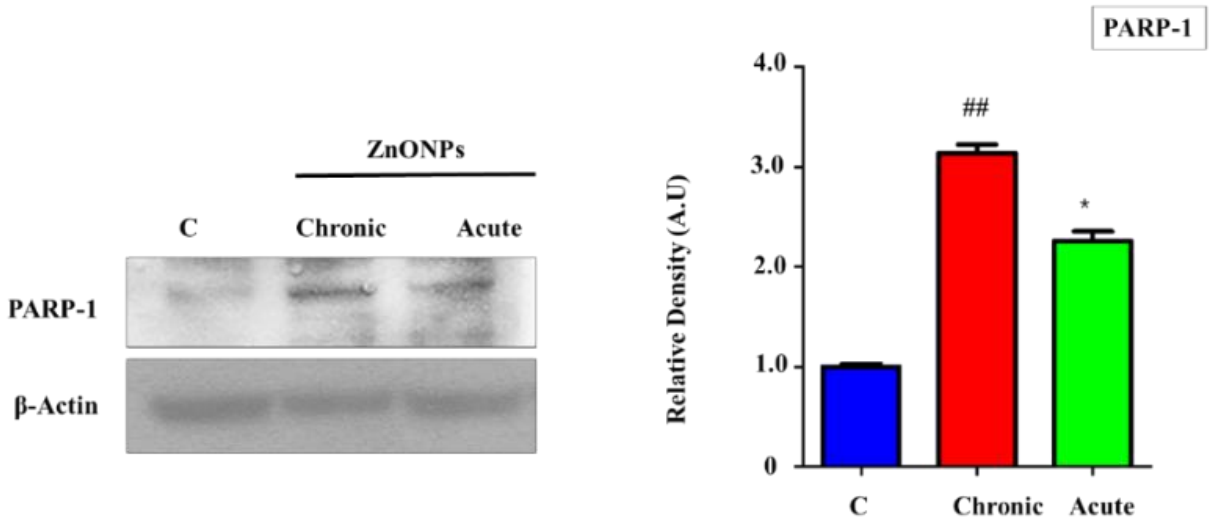


Fig. 4 (a) Chronic and Acute Exposure of ZnONPs Induced Apoptosis in the Kidneys of Male Albino Mice: (b) Increased in the Expression of caspase-3 caused Apoptosis : (c) Fragmentation of Apoptotic marker i.e., PARP-1 in the Kidneys of Albino mice

3.5. ZnONPs Induced SIRT1 Inhibition in the Kidneys of Male Adult Mice

SIRT1, an endogenous antioxidant protein, was evaluated to assess the impact of ZnONPs exposure on renal oxidative stress regulation. Immunoblotting results showed that both acute and chronic ZnONPs exposure led to a significant reduction in SIRT1 expression in the kidneys of treated mice compared to controls. Notably, chronic exposure caused a more severe suppression, with SIRT1 protein levels being almost undetectable, indicating a dose- and duration-dependent inhibitory effect (Fig. 5). These findings suggest that prolonged exposure to ZnONPs may severely impair the cellular antioxidant defense mechanism in renal tissue through downregulation of SIRT1.

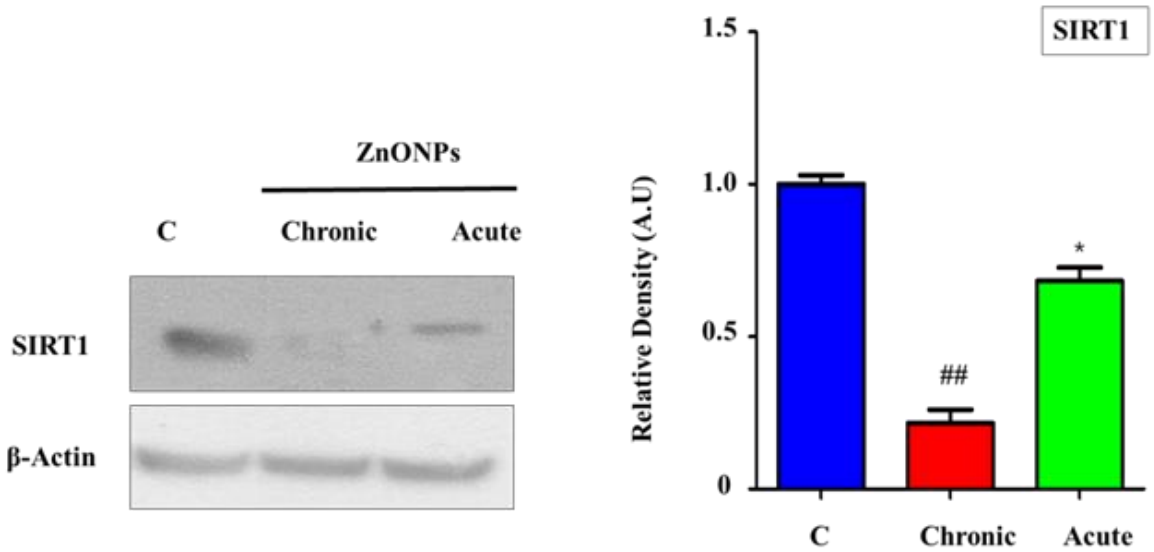


Fig. 5: Chronic and Acute Exposure of ZnONPs Induced SIRT-1 inhibition in the Kidneys of Male Albino mice

4. Conclusion

In the recent study, both chronic and acute exposure to ZnONPs is nephrotoxic as it induced inflammation, oxidative stress, and apoptosis in kidney tissues. So, it is concluded that both the doses are toxic and cause harmful effects on the kidneys. Moreover, it was concluded that chronic exposure deteriorates the renal system to extremely high levels. On the other hand, acute exposure caused a small level of toxicity as compared to chronic exposure. The short-term and long-term exposure of ZnONPs also suppresses SIRT-1 protein which helps in maintaining kidney function. Overall, the current findings suggest that ZnONPs are not human as well as environment friendly. So, a complete scheme to clear the areas where its concentration is high.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Ethics Decleration

Neuro Molecular Medicinal Research Center approves the ethical values according to the NIH standards.

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