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Hepato-Renal Dysfunction Induced by Nickel Oxide Nanoparticles and Prophylactic Role of Aloe vera: A Clinical Pathology Study

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Abstract— Background*: Nickel oxide nanoparticles (NiONPs) have unique advantages that enable their wide application in various industries. However, concerns are growing about the toxicity and safety of these particles for various body organs. Therefore, this study was prepared to estimate toxicity of NiONPs on liver and kidney function, and investigate the prophylactic role of Aloe vera (AV) against this toxicity.* ***Methods****: Thirty-two laboratory rats were recruited and separated into four groups (n=8) as follows: Control group included rats that were not dosed any treatment; NiONPs rats were treated with nickel oxide nanoparticles; NiONPs+AV rats were co-dosed of Aloe vera with nickel oxide nanoparticles; and finally, AV rats were provided only with Aloe vera. Then all rats were sacrificed, and samples were prepared for measuring clinical pathology parameters.* ***Results****: A notable augmentation in biochemical markers levels and MDA content, accompanied by a considerable reduction in antioxidants activities in NiONPs intoxicated rats compared to control group. Conversely, co-administration of NiONPs+AV demonstrated remarkable efficacy in improving toxic changes.* ***Conclusion****: Aloe vera has the potential to alleviate hepato-renal dysfunction caused by nickel oxide nanoparticles by improving clinical pathology parameters, and is recommended for the prevention of liver and kidney deterioration caused by toxic exposure to nanoparticles.*

Keywords— *Hepato-renal dysfunction; clinical pathology; oxidative stress; nanoparticles.*

I. INTRODUCTION

Nanotechnology represents an emerging field based on creation of engineered nanoparticles (1-100 nm) with unique advantages [1,2], thus contributing to nearly all areas of industry [3]. In contrast, the massive increase in production and environmental accumulation of engineered nanoparticles has been accompanied by an increase in unexpected adverse effects of their toxicity, especially on human health [4,5]. The superior ability of these particles to penetrate living cells makes them capable of disrupting the functions of many vital organs [6], including liver [7] and kidneys [8]. Engineered metal oxide nanoparticles, including nickel oxide nanoparticles (NiONPs), are among the most widely used [9]. Indeed, NiONPs are commercially available and vastly consumed in several industrial applications as sensors, photovoltaic, ceramics [10], and cosmetics, attracting researchers' interest in understanding their safety implications [11].

Furthermore, their toxicity has been documented in experimental studies of particular importance in toxicology [12,13]. Previous study has shown that NiONPs cause lung lesions in laboratory animals and induce an inflammatory response [14]. Another study demonstrated that NiONPs induce liver inflammation response by increasing serum hepatic biomarkers in rats [15]. In addition, these nanoparticles have been reported to induce cytotoxicity via reactive oxygen species (ROS) and promote apoptosis in human hepatocytes [16]. For centuries, plant extracts have been used as medicines for humans and animals [17]. Traditional herbal medicine is used to treat countless ailments, due to their unique therapeutic properties and active compounds [18,19]. Aloe vera (AV) belongs to the family Liliaceae, and it is a shrub, succulent, green-colored perennial pea [20]. It mainly grows in the dry areas of Africa and Asia [21]. AV is a rich source of many active phytochemicals including vitamins, enzymes, minerals, anthraquinones, amino acids, and others. Thus, AV exerts several biological efficiencies, most notably antioxidant and anti-inflammatory effects [22], besides it has shown potency in improving drug-induced hepatorenal toxicity [23,24]. In this study, a rat model was established to appreciate the possible role of Aloe vera in reducing the detrimental effects of NiONPs on liver and kidney function indicators.

II. MATRIALS AND METHODS

A. Nanoparticles and Aloe vera extract

Nickel oxide nanoparticles 20wt% water dispersion (NiONPs) with average particle size= 18nm (Figure 1) was obtained from US Research Nanomaterials, Inc. (Houston, USA). The product identified uses for research, and has the following characteristics: morphology= nearly spherical, crystal structure= cubic, color= dark gray, super fine purity=99.98%, true density= 6.67 g/cm3.

As for Aloe vera extract; it was purchased from the manufacturer, La Grande Pvt Ltd, located in New Delhi, in the form of aloe vera capsules specialized in promoting healthy digestion and improving immunity.

B. Rats grouping and doses

In this experiment, thirty-two adult male rats (albino), weighing (170 –185) gm. and aged (4 -6) months, were purchased from the experimental animal house of the research center in Iraq. The protocols were based on the ethical guidelines of the National Institutes of Health (1978), approved for the use of laboratory animals in research.

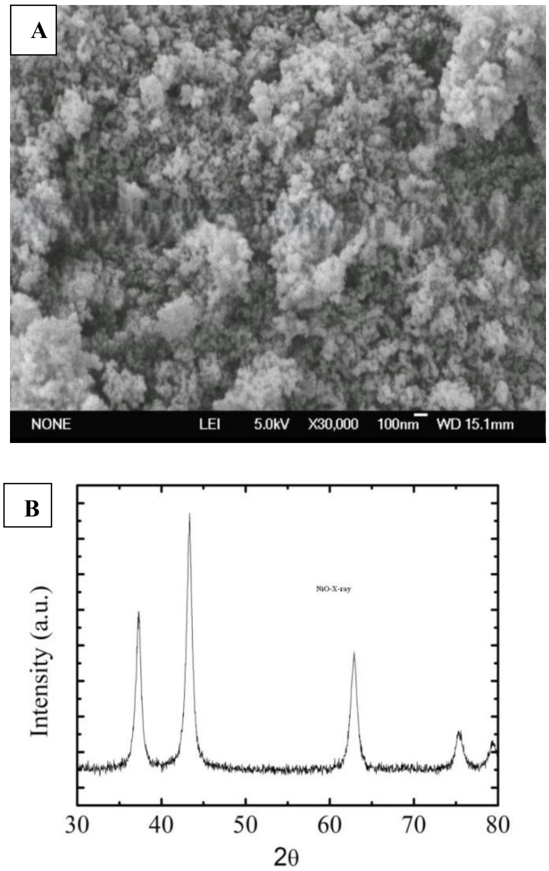

Fig. 1. A) Scanning electron microscopy (SEM) image of NiONPs, B) X-Ray image of NiONPs.

They were placed in designated cages under standard conditions of temperature and lighting, with ad libitum access to diet and water. Besides, they were adapted to these conditions for (14) days prior to initiating this study. Then all rats were set into four groups, (eight in each) as explained in table (1).

TABLE I. Experimental design and groups.

Groups	Administrations with dosing
Control	Untreated rats were employed as control.
NiONPs	Rats were dosed with 250 mg/kg nickel oxide nanoparticles according to Dumala et al. [25] , using a gavage tube for two consecutive weeks.
NiONPs +AV	Rats were administered nickel oxide nanoparticles plus AV extract at a dose of 300 mg/kg according to Arora et al. [26] suspended in DW over the course of the experiment (two consecutive weeks).
AV	Rats were received AV extract only at a dose of 300 mg/kg, by gavage tube for two consecutive weeks.

C. Blood sampling and tissue preparing

At the end of 14th day of the study, all laboratory experimental rats were anesthetized and then euthanized.

By puncturing the heart, blood samples were drawn and placed in designated test tubes. The samples were centrifuged at an appropriate speed for 20 minutes to separate the serum and stored at low temperatures until the necessary biochemical evaluations were performed. Besides, the two desired organs (liver and kidney) were cut off from each rat, cleaned with chilled saline, and adhesions were carefully removed. They were homogenized separately using a homogenizer equipped for this purpose, then centrifuged at an appropriate speed for 20 min, and the supernatants were collected and stored at low temperature to complete oxidative stress assessment.

D. Clinical pathology assessment

1- Hepato-renal functions markers

Serum levels of creatinine (CR), uric acid (UR), urea nitrogen (BUN), total protein (TP), alanine and aspartate amino-transferases (ALT and AST), alkaline phosphatase (ALP), gamma-glutamyl transaminase (GGT), and lactate dehydro-genase (LDH), were measured by private kits and performed according to the manufacturer's protocol and an automated device.

2- Oxidative stress markers

In prepared tissues homogenates of all studied rats, malondi-aldehyde (MDA) content was assessed spectrophotometrically with a specific standard curve described previously by Draper and Hadley [27]. Besides, the concentrations of following antioxidants: superoxide dismutase (SOD); glutathione pero-xidase (GPX); and catalase (CAT) were measured by comm-ercial colorimetric assay kits according to manufacturer's instructions with standard specific for each one.

E. Statistical analysis

Using Graph Pad Prism (version 9) software program, all data were statistically analyzed. The values were presented as mean ± standard error. One-way analysis of variance (ANOVA) and Tukey's multiple tests were applied to determine variances between groups. P-values less than 0.05 were set as significant.

III. Results

A. Effect of AV on hepato-renal functions markers

The results demonstrated that rats exposed to NiONPs showed a statistically considerable increase ($p < 0.0001$) in levels of serum biomarkers ALT, AST, ALP, GGT, LDH, TP, CR, BUN, and UR when compared to unexposed control group. Meanwhile, animals treated with NiONPs and Aloe vera showed significant decreases in these liver and kidney function markers: ALT, AST, and ALP ($p < 0.0001$); GGT ($p = 0.0001$); LDH ($p = 0.0012$); TP ($p = 0.0185$); CR ($p = 0.0387$), BUN ($p = 0.0013$) , and UR ($p = 0.0334$) compared to animals intoxicated with NiONPs .On the other hand, no significant variance was noticed between control group and rats treated with Aloe vera only as shown in figures (2,3).

B. Effect of AV on Oxidative stress markers

Regarding the levels of oxidative stress-related parameters, a remarkable excess ($p < 0.0001$) in MDA contents was observed in hepatic and renal tissues of rats exposed to NiONPs compared to unexposed control rats. Conversely, animals treated with NiONPs and Aloe vera extract showed a significant improvement in MDA levels (p= 0.0217 in liver tissue; p= 0.0022 in kidney tissue) compared to rats intoxicated with NiONPs.

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In both liver and kidney tissues, all analyzed antioxidant parameters (SOD, CAT, and GPx) in rats intoxicated with NiONPs demonstrated significantly ($p < 0.0001$) lower levels compared to control rats. While animals co-treated with NiONPs and Aloe vera showed significant amelioration in SOD ($p = 0.0171$ in liver tissue; $p = 0.0274$ in kidney tissue), CAT ($p < 0.0001$ in liver tissue; $p = 0.0005$ in kidney tissue), and GPx ($p = 0.005$ in liver tissue; $p = 0.0067$ in kidney tissue) levels compared to rats exposed to NiONPs (figures 4, 5).

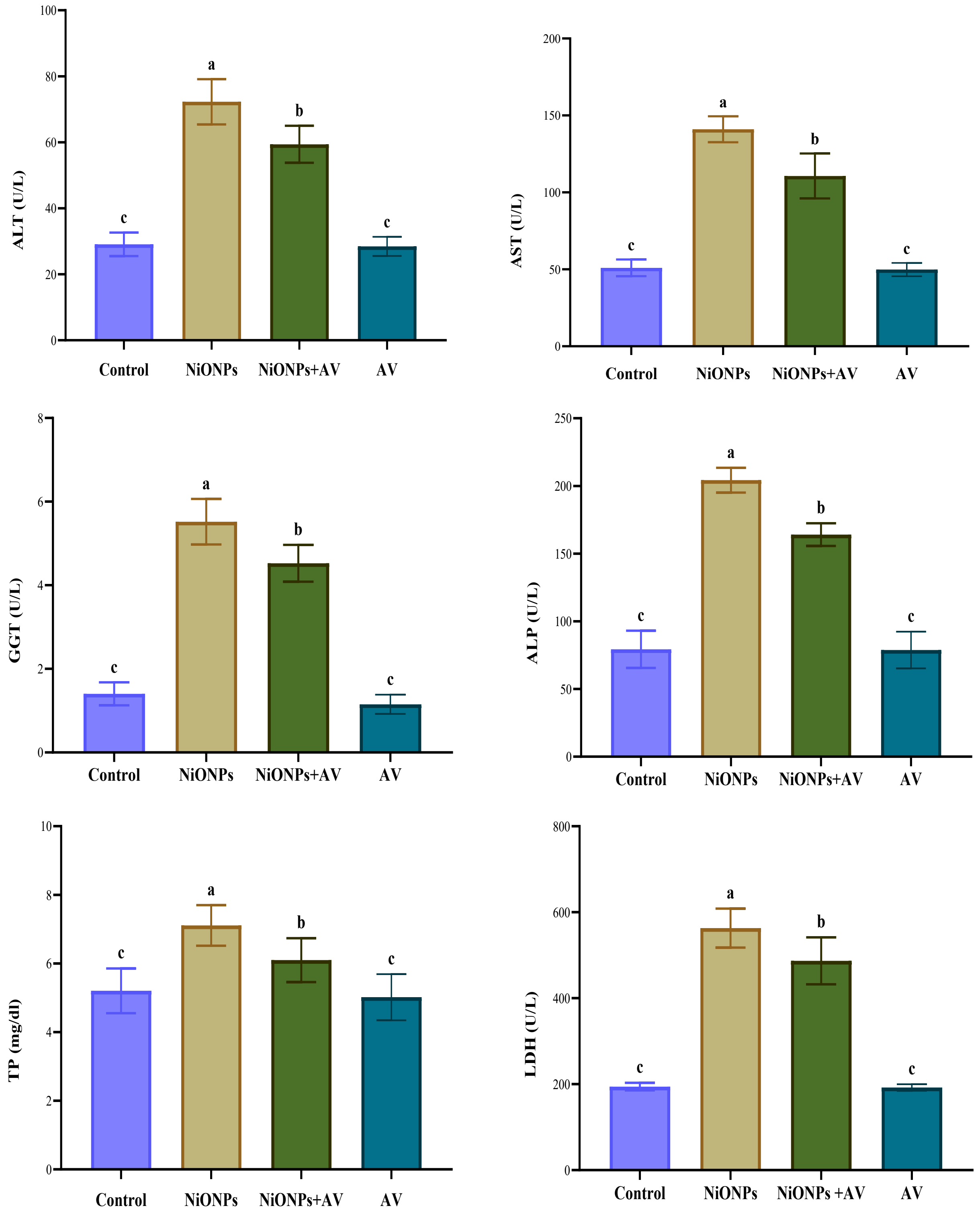


Fig. 2. Effect of AV on serum biomarkers levels (ALT, AST, GGT, ALP, TP, and LDH) in NiONPs-exposed rats. Note that different lowercase letters (a, b, c) refer to significant variance between experimental groups.

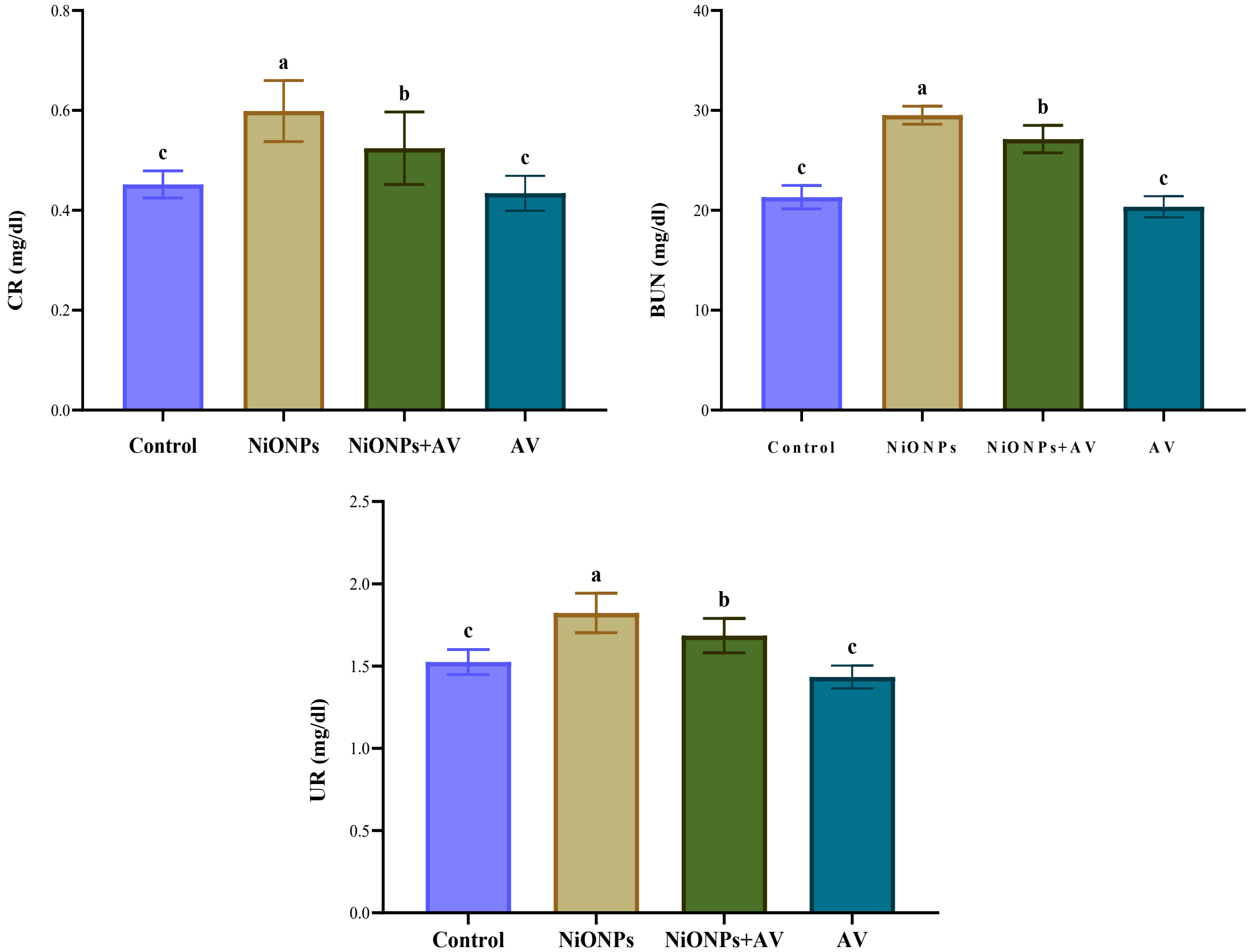
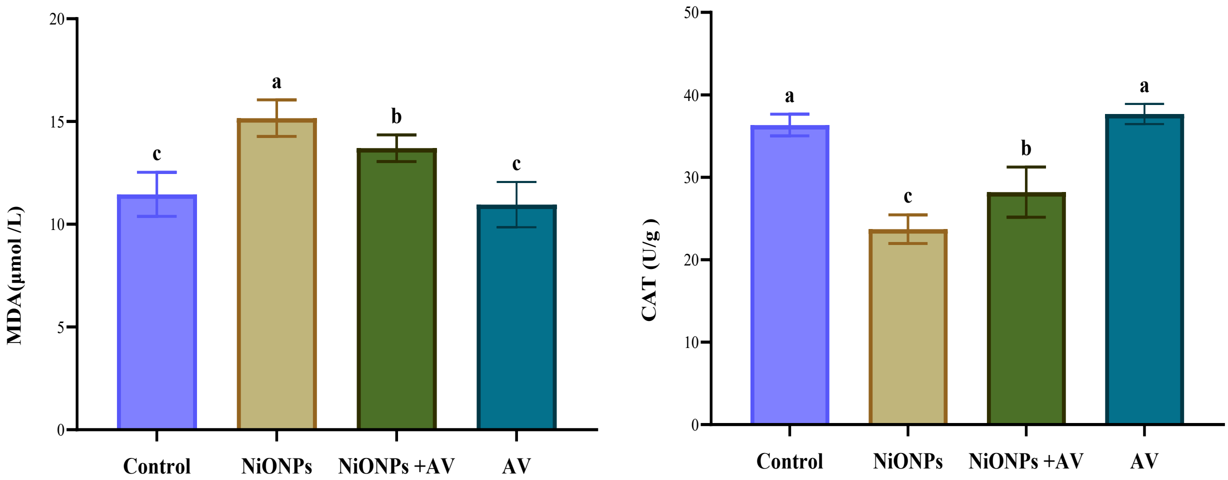


Fig. 3. Effect of AV on serum biomarkers levels (CR, BUN, and UR) in NiONPs-exposed rats. Note that different lowercase letters (a, b, c) refer to significant variance between experimental groups.



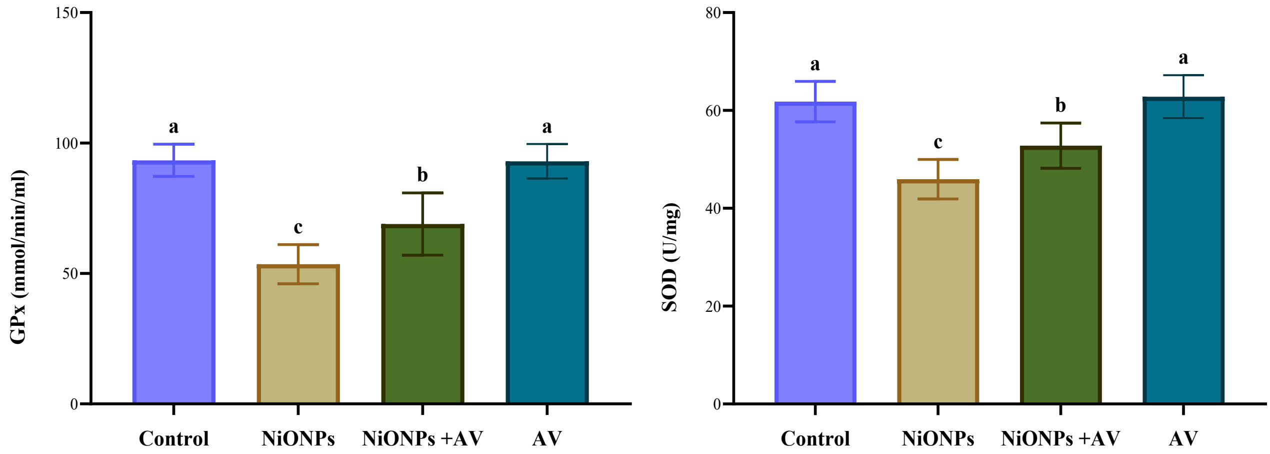


Fig. 4. Effect of AV on oxidative markers (MDA, CAT, GPX, and SOD) in liver tissue of NiONPs-induced hepato-renal dysfunction rats. Note that different lowercase letters (a, b, c) refer to significant variance between experimental groups.

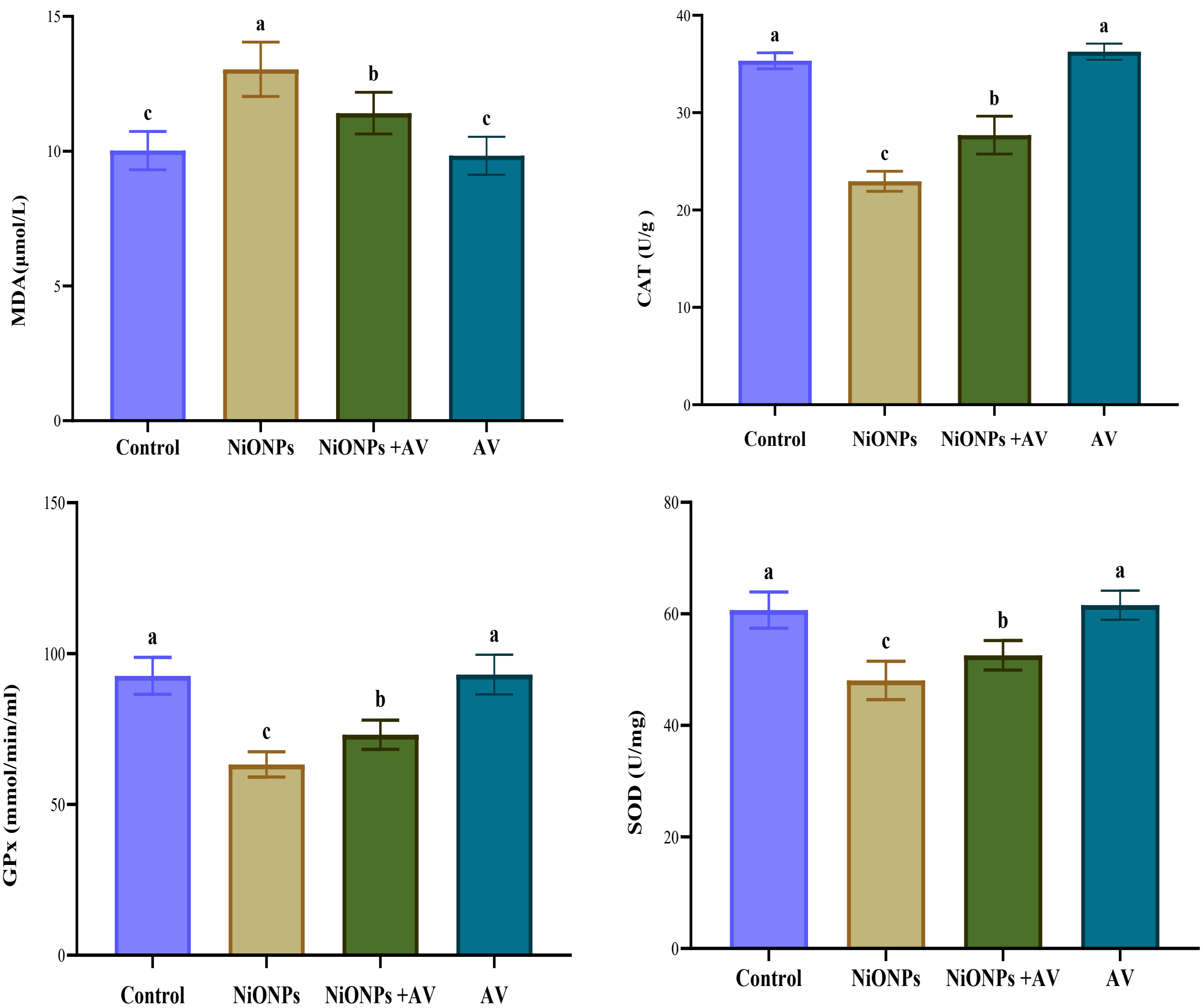


Fig. 5. Effect of AV on oxidative markers (MDA, CAT, GPX, and SOD) in renal tissue of NiONPs-induced hepato-renal dysfunction rats. Note that different lowercase letters (a, b, c) refer to significant variance between experimental groups.

IV. Discussion

This experiment confirmed the impaired hepatic and renal function caused by NiONPs in a rat model, through alterations in hepatic and renal biochemical indices of exposed rats, along with the induction of excessive lipid peroxidation and decreased antioxidant contents in liver and kidney homogenates. Serum liver enzymes concentrations critically reflect the integrity of the liver cell membrane [28]. The unique physicochemical properties of nanoparticles, and their extremely small size, enable them to aggregate in vital organs, including the liver and kidneys [29,30]. They can enter body through oral, inhaled, or dermal exposure [31]. In general, the toxicity of nanoparticles depends on their size, as smaller particles can enter and exit cells more easily [32]. The smaller size is inversely related to nanoparticle toxicity, in addition to larger surface area, higher surface-to-volume ratio, and greater catalytic activity [33]. It is worth noting that previous studies have proven how the small size of these particles allows facilities enter cells and penetrate biological barriers [34-36]. The intrinsic properties of nano-materials, such as molecular shape, surface area, surface layer, solubility, surface charge, and oxidation state, influence cell toxicity [37].

Our results demonstrated an obvious raise in serum hepatic enzyme activity levels in poisoned animals with NiONPs, which can be referred to enzyme leakage from fragile membranes of liver cells and the high permeability resulting from hepatocyte damage [38,39]. This consistent with findings of other previous studies reported that NiONPs caused liver dysfunction in laboratory animals [40,41]. Also, our study demonstrated significant increases in serum renal markers in rats intoxicated with NiONPs, suggesting impaired renal function [42].In a recent study, Karaboduk et al. (2024) revealed that NiONPs have toxic effects causing renal damage through increased serological concentrations of urea, uric acid and creatinine in a rat model [43]. A possible explanation is the biotransformation of these particles in the liver, their sequestration in the reticulo-endothelial structure, and subsequent excretion by the kidneys [44]. In addition, they can localize within renal tissue, leading to stimulation of tubular activity and changes in glomerular filtration permeability during filtration proceeding [45]. There is no doubt that mechanisms of nanoparticles toxicity are of critical pathological importance, as they are characterized by their cytotoxic effects [46], including increased production of ROS and accompanying inhibition of antioxidant activities [47]. Nanoparticles deposited in organs can produce ROS, which can cause oxidative stress and render cells unable to perform their redox-regulated physiological functions [48]. This is consistent with the current study, which showed increased oxidative stress in hepatic and renal tissues of rats intoxicated with NiONPs, besides reduction of antioxidant enzyme contents. Several studies have confirmed that NiONPs can induce a toxic response by rising generation of reactive oxygen species, inflammation, oxidative stress, and disruption of cellular organelles [49,50].

It's well-known that over production of ROS causes oxidative modification of proteins, DNA damage, and activation of inflammatory signaling, leading to apoptosis, necrosis, and genotoxic effects. During ATP synthesis in cell mitochondria, a certain amount of oxygen is not completely reduced, resulting in the formation of oxygen-containing radicals [51]. Metallic nanoparticles, which can be oxidized, reduced, or dissolved, can lead to cytotoxicity and genotoxicity. Their chemical instability can lead to the direct release of metals, which can produce free radicals that can stimulate oxidative stress [52].

On the other hand, the combined treatment of nickel oxide nanoparticles with Aloe vera resulted in decreased serum levels of liver and kidney biochemical markers as well as oxidative stress in in liver and kidney homogenates with increased antioxidant enzymes, indicating improved hepato-renal function, which may be attributed to the presence of phytochemicals in the extract and antioxidant factors [53]. In a previous study by Gupta and colleagues (2019), they were concluded that the supplementing with aquatic extract of Aloe vera was able to significantly protect the livers of mice from the toxicity caused by pesticides, as the data indicated that the pesticides obviously induced oxidative stress that was considerable reduced by application of plant extracts [54]. Allan and Wycliffe (2024) found that high doses of Aloe vera have renal protective benefits upon drug-induced nephrotoxicity in a rat model, via restoring biochemical parameters [55]. Hassan et al. (2025) confirmed the potential ameliorative effect of AV gel against liver damage caused by rats' exposure to cadmium by significantly reducing oxidative stress and modulating the expression levels of inflammatory mediators [56]. It is worth noting that, aloin and emodin are potent naturally anthraquinones ingredient that enhance the peroxyl radical scavenging activity of aloe vera extract and give it a protective effect against toxicity in various tissues and cells in the body[57].

V. Conclusion

Our result confirmed that Aloe vera can attenuate nickel oxide nanoparticles -induced hepato-renal dysfunction through the improvement of disturbed clinical pathology indices including biochemical markers, oxidative stress, and anti-oxidants. So Aloe vera can be considered as a protector against hepato-renal dysfunction and can be recommended to prohibit liver and kidney deterioration caused by exposition to toxic chemicals, particularly nanoparticles.

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