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THE ANTIOXIDANT ROLE OF SELENIUM IN PREVENTING NICKEL-RELATED KIDNEY DAMAGE IN RATS

Hichem SAKER[1], Salim GASMI[1*], Abdelkarim BENKHEDIR[2*], Samira BOUSSEKINE[1]

[1]University of Tebessa, Faculty of Sciences and Natural and Life Sciences, Tebessa, 12000, Algeria
[2]University of Tissemsilt, Tissemsilt, 38000, Algeria

Abstract: The aim of this study is to examine the protective and antioxidant effects of selenium on nickel-induced oxidative stress in male albino Wistar rats. For this purpose, 28 male albino Wistar rats of similar age and body weight were divided into four groups. The first group served as the control, the second group received only selenium with 2 mg/kg/day orally, the third group received only nickel with a dose of 10 mg/kg/day orally gavage, and the fourth exposure both selenium and nickel. The rats were monitored for four weeks to observe any changes in their kidney function and antioxidant activity. The results of the study showed that selenium had a protective effect against nickel-induced nephrotoxicity in male albino Wistar rats. Selenium was found to reduce the levels of oxidative stress markers, such as malondialdehyde and glutathione, as well as increasing the activity of antioxidant enzymes, such as superoxide dismutase and catalase. The results also showed that selenium had a protective effect against nickel-induced nephrotoxicity in male albino Wistar rats, as evidenced by an increase in the levels of creatinine, urea, and uric acid. Overall, this study suggests that selenium supplementation can protect against nickel-induced nephrotoxicity in male albino Wistar rats. Selenium has been found to reduce the levels of oxidative stress markers and increase the activity of antioxidant enzymes, thus protecting against oxidative damage. Therefore, selenium may be a useful supplement in preventing nephrotoxicity caused by nickel.

Keywords: oxidative stress, antioxidant, renal function, nickel, selenium, rat.

INTRODUCTION

Nickel is an environmental pollutant that can cause cancer (Genchi et al., 2020). It is used in nickel-cadmium battery manufacturing and nickel-based refineries. (MESHRAM et al., 2018). In consequence, it has adverse impacts on plants, daily consumption products, and in particular on animal and human health. (Buxton et al., 2019). Exposure to nickel can cause toxicity to many tissues, such as the kidneys, the liver, and lungs, on hematopoiesis, male and female reproduction and development. (Wrzecińska et al.,2021)

Furthermore, due to the permeability of the placenta barrier, Ionized blood nickel undergoes a transplacental passage explaining the risk of fetal toxicity when exposed to the mother, having teratogenic effects, increasing the frequency of embryonic resorption and stillbirth, decreasing the weight of viable neonates and increase the incidence of malformations. (Birkett et al., 2019)

The world of biological and medical sciences is inundated with a new concept, that of 'oxidative stress', This means that the cell no longer controls the presence of toxic oxygenated radicals. Currently, it is widely accepted that even though oxidative stress is not a disease, it is potentially implicated in many diseases as a trigger or linked to complications during their evolution. (Mutua and Laurel 2021)

Antioxidants (selenium, vitamin C, vit, A, GSH, carotenoids...) are important components in several respects. Selenium is a component of glutathione peroxidases, antioxidant enzymes that are one of the most important defenses against body aggressions produced by oxygen-free radicals, this is a component of the environment. It is widespread in the earth's crust and most plant and animal tissues. (Saxena et al., 2021)

Thus, we are interested in investigating their effect on hematological parameters and certain parameters of oxidative stress in rats.

MATERIALS AND METHODS

Chemicals

Nickel chloride (NiCl2; CAS Number 7718-54-9), nitro blue tetrazolium, N-(1-naphthyl) ethylene diamine and Tris-HCl, Thiobarbituric acid and trichloroacetic acid were purchased from Sigma (St. Louis, MO). Sodium selenite (Na2SeO3) supplied from Sigma-Aldrich (Germany). All other chemicals and reagents used in this study were of analytical grade. Double distilled water was used as a solvent.

Animals and treatment

We used twenty-eight (28) Wistar Albinos rats (140 ± 25g), which were provided by the Institute Pasteur (Algiers, Algeria). Rats have but in favorable conditions of temperature (T° 25± 2°C) and humidity (45%), at a cycle of 12 h day/night.

28 rats were used in this study, the rats were divided into 4 groups of 7 rats each, as follows:

• Control group (T)

• Nickel chloride group (Ni) : (10 mg/kg) (Iqbal et al.,2020)

• Sodium Selenite group (Se) : (2 mg/kg) (Zhang et al., 2019)

• Mixture group (Ni+Se) : Ni (10 mg/kg) + Se (2 mg/kg)

Biochemical markers in plasma

Plasma biochemical markers: creatinine, urea, and uric acid was measured using commercial kits from Spireact Spain.

Reduced Glutathione and malondialdehyde Analysis

***Correspondence**: Dr. Salim Gasmi, University of Tebessa, Faculty of Sciences and Natural and Life Sciences, Tebessa, Algeria, Tel: (+213)673203709, email: Salim.gasmi@univ-tebessa.dz.*

kidneys glutathione (GSH) levels were estimated using a colorimetric method as mentioned by Ellman (1959) and modified by Jollow et al (1974), based on the development of a yellow color when DTNB (5,5-dithio-bis-2-nitrobenzoic acid) is added to compounds containing sulfhydryl groups. Briefly, 500 µL of homogenate was mixed with 0.5 mL of 4% sulfosalicylic acid and centrifuged at 3500 rpm for 10 min; 200 µL of supernatant was mixed with 1 mL of phosphate buffer (0.1 M, pH 7.4), and 400 µL of 10 mM DTNB. Finally, the absorbance at 412 nm was recorded. The total GSH contents were expressed as µg GSH/mg protein. An assay of MDA is performed using the method of Esterbuer et al. (1992).

Antioxidant enzymes activity

Glutathione-s-transferase (GST) is determined by the method of Habig et al. (1974). Determination of peroxidized glutathione (GPx) is measured by the method of Flohe and Gunzler, (1984) using hydrogen peroxide (H2O2) as substrate. Catalase assay (CAT) is performed using the Cakmak and Horst 1991 method. SOD assay is evaluated using the Beauchamp and Fridovich (1971) methods. The principle of the method is based on the ability of the enzyme to inhibit the reaction between nitro blue-tetrazolium (NBT) and superoxide anion produced by the photo reaction of oxygen and riboflavin in the presence of an electron donor such as methionine.

Histological study

Kidney samples fixed for 48 h in 10% of the formalin were also successfully dehydrated in successive bans of alcohol cleaned with xylene and incorporated paraffin. Sections of the kidney (5mm) were prepared and stained with hematoxylin and eosin. Shown in microscopic observation.

Statistical analysis

The data are expressed as an average standard deviation (S.D). The variations between various groups were measured by one-way analysis (ANOVA) followed by the Dunnett multiple comparison test and the comparisons between treated groups were performed by non-matches. The results were considered statistically significant $p<0.05$.

RESULTS

Reduced Glutathione and Malondialdehyde

Treatment of rats with Ni (10 mg/kg body weight) results in a decrease highly significant ($p\leq0,001$) of the cellular glutathione content, a significant decrease ($p\leq0,01$) in rats treated with the combination NiSe compared with the control group. However, Se-treated group, no significant variation in kidney GSH compared to the control very significantly reduced ($p\leq0,01$), in the Ni group compared to the Se alone. A significant decrease ($P>0.005$) in combination-treated rats NiSe compared to the Se-treated group, and a significant increase ($P>0.005$) in combination-treated rats NiSe compared to the Ni-treated group.

A very significant increase ($P\leq0.001$) in kidney MDA levels in Ni-treated rats compared with controls. Whereas rats treated with Se have no significance and at the combination Ni+Se amount to highly significant variations ($P>0.001$) in MDA concentrations in the kidneys, in comparison to the control group, and a very highly significant increase (P 0.001) in rats treated with Ni compared to rats treated with Se, a highly significant increase ($P>0.001$) in combination-treated rats Ni+Se compared to the Se-treated group and a significant decrease ($P>0.005$) in combination-treated rats Ni+Se compared with the Ni-treated group (Figure 1).

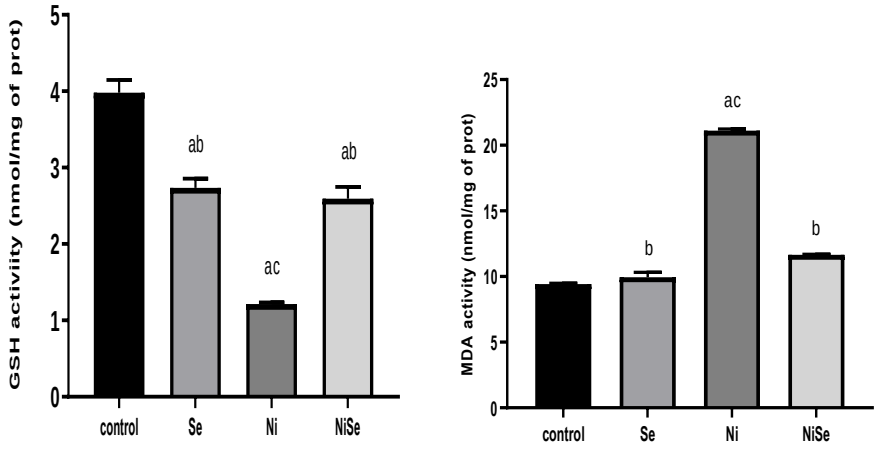

Fig. 1. Influence of Ni on Reduced Glutathione and Malondialdehyde Analysis. Data are means ± SD (n = 7). Different letters indicate a significant difference among different metal treatments at ($P<0.05$). (a) compared to the control group, (b) Ni group, and (c) (Se+Ni) group.

Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 33, issue 1, 2023, pp. 17 - 23

Antioxidant enzymes activity

Treatment of rats with Ni results in a very highly significant decrease (P≤ 0.001) in the enzymatic activity of glutathione peroxidase (GPx) in the kidneys compared to the control group. In contrast, there was a highly significant decrease (P≤0.001) in glutathione peroxidase (GPx) in rats treated with NiSe compared to controls, no differences show in rats treated with Se alone compared to controls, and a very highly significant decrease (P≤0.001) in rats treated with Ni compared to the group treated with Se, a highly significant decrease (P≤0.001) in rats treated with NiSe compared to the Se-treated group, a highly significant increase (P≤0.001) in rats treated with NiSe compared to the Ni-treated group.

Rats induced a very highly significant (P≤0.001) increase in the enzymatic activity of glutathione S-transferase (GST) in Ni-treated rats compared to controls, While, there was a highly significant increase (P≤0.001) in NiSe-treated rats compared to controls, a very highly significant increase (P ≤0.001) in Ni-treated rats compared to Se-treated rats, a highly significant increase (P≤0.001) in rats treated with NiSe compared to Se group and a significant decrease (P<0.05) in NiSe treated rats compared to Ni-treated group.

Highly significant decrease in CAT (P≤0.001) in Ni-treated rats compared to controls, a significant decrease (P<0.05) in rats treated with NiSe compared to controls, a highly significant decrease (P≤0.001) in Ni-treated rats compared to the Se-treated group, a significant decrease (P<0.05) in rats treated with NiSe compared to the Se-treated group, and a significant increase (P<0.05) in NiSe treated rats compared to Ni group.

Renal SOD activity was significantly lower in the Ni group than in the control group (p≤0.001). SOD activity was increased in the NiSe group compared to the Ni group, but this was not statistically significant (p<0.05) (Figure 2).

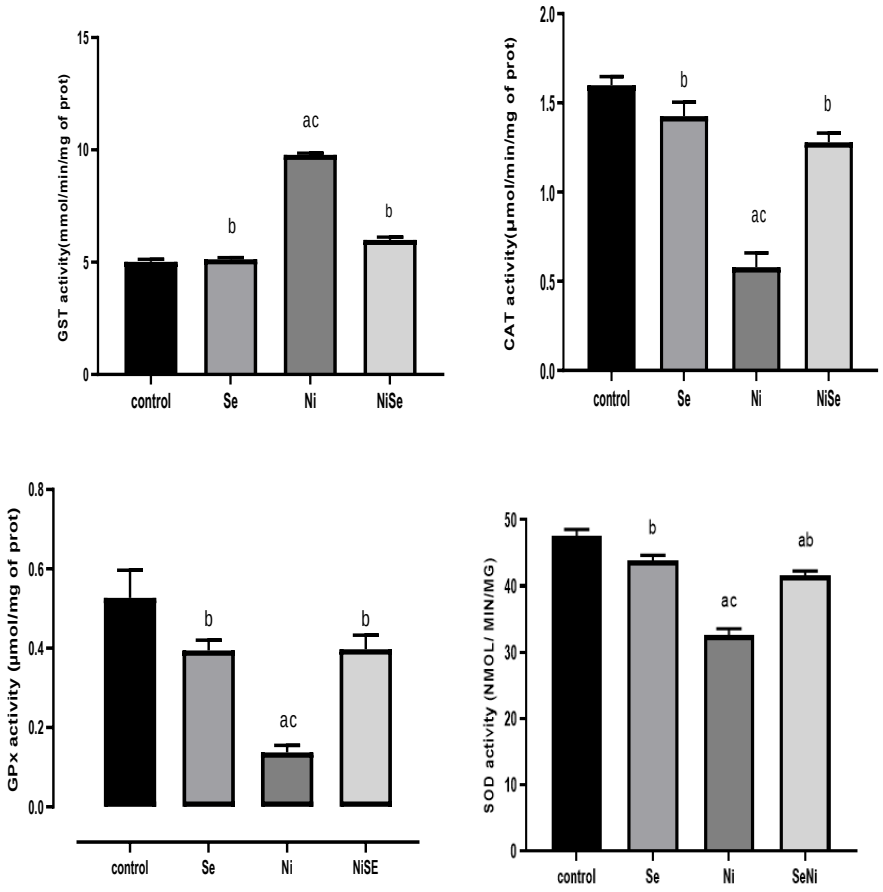

Fig. 2. Influence of Ni on Antioxidants enzymes activities: Superoxide dismutase (SOD), Glutathione Peroxidase (GPx), Glutathione-S-Transferase (GST) and Catalase (CAT). Data are means ± SD (n = 7). Different letters indicate a significant difference among different metal treatments at (P<0.05). (a) compared to the control group, (b) Ni group, (c) (Se+Ni) group.

Blood biochemical assay

The results show a significant increase in serum urea, creatinine, and A. uric levels in Ni-treated rats compared to controls, Se significantly reduces the content of urea and creatinine. Pretreatment of Ni+Se rats significantly reversible uric acid content compared to Ni-treated rats alone. Treatment with Se does not cause any significant change in renal function indices (Table 1).

Table 1.

Influence of Ni on biochemical assay: Urea, A. Uric and Creatine

Parameters	Urea	A. Uric	Creatine
C	7,10±0,21	50,12±4,96	50,06±3,18
Se	7,37±0,29^{b}	50,52±1,30^{b}	51,39±3,34^{b}
Ni	9,08±0,22^{ac}	66,55±2,33^{ac}	89,50±4,75^{ac}
Ni+Se	7,05±0,17^{b}	53,63±3,16^{b}	66,37±3,88^{ab}

Data are means ± SD (n = 7). Different letters indicate a significant difference among different metal treatments at (P<0.05). (a) compared to the control group, (b) Ni group, and (c) (Se-Ni) group.

Histopathology study

Renal tissue shows severe acute tubular necrosis and enlarged glomeruli cells showing a reduction in Bowman space. The convoluted distal and proximal tubules are dilated with a flattened epithelial lining (Figure 1). The kidneys of rats treated with Se and Ni show a similar appearance to the control (Figure 2). The results clearly indicate that kidney tissues that were damaged by the toxicity of Ni, and Se treatment had significant protection against Ni poisoning (Figure 3).

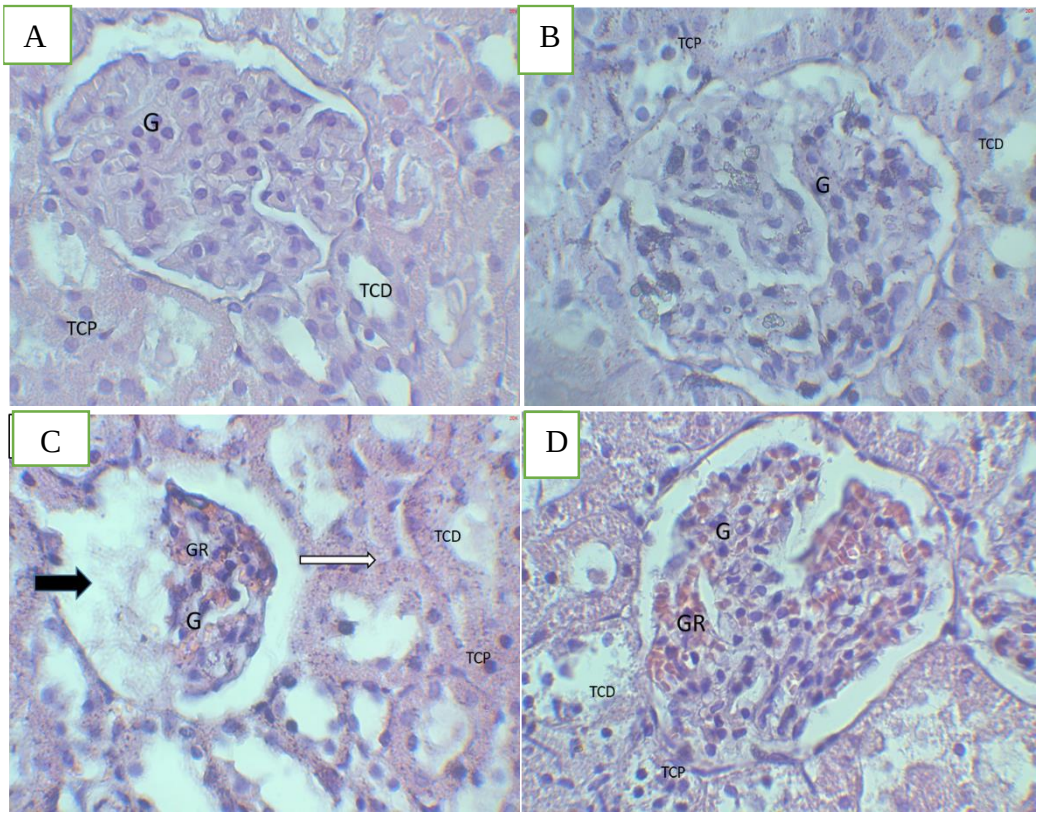

Fig. 3. Sections of the kidney of rats exposed to RO and Ni (H&E, x400). (A) Control group with normal histoarchitecture of glomeruli. (B) Se-administered group showing normal renal histological picture similar to the controls; (C) Ni alone treated group showing severe tubular and glomerular necrosis; (D) rats treated with a mixture of Se and NiCl2 (Se+Ni) showing restoration in the histological appearance with a marked reduction in Ni alone induced renal damage. G: glomerulus, TCP: Proximal tubule, TCD: Distal convoluted tubule
arrows indicate: necrosis of epithelial cells of proximal tubules, glomerular necrosis

DISCUSSION

A new concept has taken over the world of biology and medicine, "Oxidant stress" is one of the main mechanisms of toxicity associated with various xenobiotics in the environment (Wages et al.,2016; Henkler et al.,2010). It has been shown that several drugs, chemicals, and heavy metals modify kidney structure and function. (Lash, 2019; Flora, 2009; Sabolic, 2006) In this study, we examined selenium's protective role against nephrotoxicity induced by exposure to Ni in rats. The administration of Ni revealed a significant increase in serum creatine, urea, and uric acid. Moreover, there was a significant increase in urinary albumin levels as well as a decrease in urinary levels of creatinine. Urinary tests for creatinine and albumin have frequently been used as tools for the diagnosis of chronic renal failure (Shlipak et al., 2021). A significant increase in kidney function

Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 33, issue 1, 2023, pp. 17 - 23

improvements during exposure to Ni can result from cellular damage caused by excess free radicals. (Begum et al., 2022)

The first set of analyses examined indices of renal toxicity. Glutathione plays an important role in the cell's detoxification mechanisms and is the first line of antioxidant defense (Amari et al., 2020). Reduced glutathione therefore has a protective role of cells against toxic actions (Zwolak, 2020). Changes in GSH concentrations can be regarded as an especially sensitive indicator of oxidative stress. (Bjørklund et al., 2022) GSH levels were depleted in the Ni renal group relative to controls. (Salah et al 2022) The decrease of the GSH may be explained by several assumptions. Firstly, GSH plays an important role in the detoxification of free radicals and heavy metals (Qamar et al 2021). it interacts directly with high affinity for thiol groups (-SH) of GSH. (Daniel et al., 2020) Secondly, glutathione can also interact with the free radicals generated by this metalloid. (Teschke, 2022) Thirdly, Ni inhibits glutathione synthase and glutathione reductase (Šulinskienė et al., 2019). If little GSH is generated. All these factors lead to a sharp decrease in reduced glutathione (GSH) and an increase in oxidized glutathione (GSSG), and thus a decrease in GSH-dependent enzyme activity (Gan et al., 2019).

The whole body has nickel enzymes to counteract oxygen stress. (Das et al., 2020) However, these enzymes can be affected by nickel, which works through the loss of growth of antioxidant enzymes like CAT, and GPx. (Salah & Adjroud, 2022) As a result, it seems necessary to measure the activities of these enzymes to assess the impact of nickel as an oxidizing stress agent. GPx is an important antioxidant enzyme that regulates ROS levels. (GPx has the ability not only to reduce hydrogen peroxide to water but also hydroperoxides obtained through the oxidation of unsaturated fatty acids) thus protecting the cells from damage from nickel. (Owumi et al., 2020) Our results show a decrease in the activity of GPx in kidney tissue in rats treated with Ni. This decrease is mainly attributable to excess production of hydrogen peroxide and depletion of Se and GSH during Ni detoxification. (Das et al., 2022). This results in a decrease in the enzyme activity of GPx (GPx requires glutathione and Se to function effectively) (Zwolak, 2020).

Regarding glutathione S-transferase (GST), it plays an important role in the detoxification of xenobiotics and/or in protecting against harmful metabolites produced after macromolecule degradation after exposure to oxidative stress. (Demirci-Çekiç et al., 2022) Our results indicate a very substantial increase in the GST on kidneys. The GST therefore contributes to the detoxification and elimination of Ni and those metabolites. (Renu et al., 2021) The effect of Ni on GSH and the activities of antioxidant enzymes is accompanied by an increase in the number of free radicals as the hydroxyl radical, which in turn may induce lipid peroxidation (Šulinskienė et al., 2019), and as our results indicate, a very significant increase in Malondialdehyde (MDA), which is a biomarker for lipid peroxidation was observed in renal tissue.

Our results confirm those of (Das et al., 2020) a change in the anti-oxidant status of Ni-treated. This impairment is associated with an increase in lipid peroxidation and a decrease in cellular GSH. Furthermore, the treatment of rats with a combination of NiSe results in a significant improvement where the glutathione level, the enzymatic activities of GPx, GST, and the MDA level in the renal tissue are almost back to normal, this is due to the antioxidant effect of Se, which is a cofactor of many antioxidant enzymes such as glutathione peroxidase GPx, thioredoxin reductase, when the activity of these enzymes depends heavily on the supply of Se. (Kieliszek et al., 2019; Hariharan & Dharmaraj, 2020; Kieliszek et al., 2022). Catalase (CAT) is the second phase of the enzymatic defense system. It takes over the hydrogen peroxide previously produced by the SOD and metabolizes it into water. (Sardari, et al., 2022)

In kidney tissue, Ni decreases catalase activity (CAT), which suggests that Ni indirectly induces an increase in H2O2, bringing about oxidative stress. However, NiSe treatment showed an improvement with addition of nickel treatment only because the OH radical is a possible candidate. Indeed, a reduction in GPx and CAT activities leads to an increase in H2O2. This H2O2 in the presence of Cu can penetrate the Haber-Weiss cycle and produce the OH radical. (Moussa et al., 2019)

Our results confirm those of (Boutellaa et al., 2021) Conducted on rats exposed to oxidative stress by CCl4, Selenium supplementation has been shown to reduce the imbalance between pro-oxidants and antioxidants by raising the reduced level of glutathione and GPx.

Furthermore, Ni and Se are metalloid compounds with similar chemical properties, but with different biological effects. (Kumar and Prasad, 2021; Ramos-Inza et al., 2022; Campbell, 2022) Se has the ability to interact directly with Ni, which provides some protection from Ni toxicity.

Histopathology of renal sections revealed adverse cell lesions caused by nickel exposure. Changes in glomerular, nephritis, and necrosis hypertrophy caused by Ni, however, the absence of these lesions in Se-treated rats, as demonstrated by the results.

CONCLUSION

The results of this study show initially that administration of nickel chloride at 10 mg/kg body weight by oral administration in rats, caused nephrotic and histologic and haematotoxic effects. Second, our results demonstrate selenium supplementation as sodium selenite 2 mg/kg with Nickel improved most of the parameters examined.

AUTHORS CONTRIBUTIONS

Conceptualization, HS and SG; methodology, HS, SB, and SG; formal analysis and investigation, HS, AB, and SG; writing original draft preparation, HS and SB; conceptualization, BBA, SG and HS; writing review and editing, BBA, HS and SG. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors do not have any competing financial, professional, or personal interests from other parties.

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