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RESEARCH PAPER

A Novel Approach for Biological Applications in Mitigating Liver Damage from Carbon Tetrachloride with Nano Selenium

Motahare Homayouni [1], ***Hossein Najafzadehvarzi*** [2,3] *, ***Seyedeh Masoumeh Ghoreishi*** [2], ***Aliakbar Rajabzadeh*** [4]

[1] *Student Research Committee, Babol University of Medical Sciences, Babol, Iran*

[2] *Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran*

[3] *Department of Pharmacology, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran*

[4] *Department of Anatomy, Babol University of Medical Sciences, Babol, Iran*

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ABSTRACT

Nanotechnology has ushered in a new era of innovative solutions, particularly within the field of medicine. Selenium nanoparticles (SeNPs) represent a significant advancement in nanomedicine, offering unique properties and reduced toxicity compared to traditional selenium forms. This study explores the protective effects of SeNPs against liver toxicity induced by carbon tetrachloride (CCl4), a common model for liver damage research. SeNPs were synthesized using an efficient method with ascorbic acid and Tween 80 as stabilizers. Their size and morphology were characterized by UV-Vis spectroscopy and transmission electron microscopy (TEM). In vivo experiments on Wistar rats, divided into six groups, assessed SeNPs' efficacy in mitigating CCl4-induced liver damage. Biochemical and histopathological analyses evaluated liver function and tissue damage. The synthesized SeNPs exhibited uniform spherical morphology with sizes ranging from 60 to 80 nanometers. Biochemical assays showed that SeNPs significantly reduced elevated liver enzyme levels (AST, ALT, ALP), indicating strong protective effects. SeNPs also improved serum total protein and albumin levels, which were negatively impacted by CCl4. Histopathological findings revealed that SeNPs treatment markedly improved liver tissue structure, reducing fibrosis, necrosis, and inflammation. Additionally, SeNPs enhanced paraoxonase (PON) activity, suggesting reduced oxidative stress and improved liver protection. This study underscores the exceptional therapeutic potential of SeNPs in liver disease management, offering a safer and more effective alternative to traditional selenium. The observed improvements in biochemical markers and liver histology highlight the transformative impact of SeNPs in advancing medical treatments and addressing complex health issues.

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* *Corresponding Author Email: Najafzadehvarzi@gmail.com*

INTRODUCTION

Nanotechnology, which focuses on the creation and manipulation of nanoparticles, has made significant steps across various scientific fields, revealing new solutions to complex problems. Nanoparticles are defined as particles with at least one dimension ranging from 1 to 100 nanometers. In medicine, nanotechnology has led to the development of nanomedicine, a field dedicated to diagnosing, monitoring, and treating diseases. These nanoparticles, products of advanced nanotechnological methods, effectively tackle a wide array of pharmacological challenges across diverse medical conditions [1-3]. Selenium is a vital element in living organisms, known for its anti-oxidant and pro-oxidant properties, and its role in dietary supplements and biological systems. It acts as a supplement that improves hepatocellular function, protects cells from harmful reactive oxygen species, boosts cellular immunity, and lowers the risk of malignant diseases. However, despite its essential role in cellular function, selenium can become toxic at high concentrations [4-6]. Studies have shown that selenium nanoparticles (SeNPs) have garnered significant attention due to their lower toxicity, enhanced bioavailability, and distinctive properties, including an exceptionally high surface area compared to other forms of selenium [7, 8]. Additionally, selenium nanoparticles (SeNPs) are utilized in various medical fields due to their protective properties against cancer and bacterial infections. Their interaction with NH, C=O, COO^-, and C-N functional groups in proteins enhances their adsorption potential and biological activities. Furthermore, SeNPs not only upregulate glutathione peroxidase and induce glutathione S-transferase more effectively in the short term but also generate less oxidative stress [9].

Carbon tetrachloride (CCl_4) exposure is known to cause significant liver damage, primarily through the destruction of hepatocytes, which are the main functional cells of the liver. This damage leads to a cascade of pathological events including necrosis, inflammation, and fibrosis. Acute exposure to CCl_4 induces an inflammatory response resulting in acute hepatitis, characterized by widespread liver inflammation and cell death. With repeated or chronic exposure, the liver's ability to repair itself is overwhelmed, leading to progressive liver damage, fibrosis, and ultimately cirrhosis, a condition marked by severe scarring and impaired liver function. Due to its well-documented effects and reproducibility, CCl_4 is extensively utilized in experimental animal models to study liver fibrosis and evaluate potential therapeutic interventions. These models are crucial for understanding the mechanisms underlying liver injury and for developing strategies to prevent or reverse liver disease [10, 11].

The objective of the present study is to investigate the protective effects of nanoselenium against liver toxicity induced by CCl_4. Our findings show that the synthesized nano-selenium demonstrates considerably greater activity and successfully reduces the toxic effects of carbon tetrachloride. As a result, using nano-selenium eases concerns about the possible side effects of selenium.

MATERIALS AND METHODS

All chemical reagents were of analytical grade and used without further purification. Sodium selenite (Na_2SeO_3), Tween 80, and acid ascorbic were purchased from Sigma Aldrich. AST, ALT, and ALP were purchased from Pars Azmun, Tehran, Iran and Paraoxonase was obtained from ZellBio, Germany. Carbon tetrachloride was obtained from Merck. Current study was directed in line with the principles of declaration with the number: IR.MUBABOL.AEC.1401.016. Six group each containing five female Wistar rats 180-200 g (animal laboratory Babol University of Medical Sciences) were chosen and all experiments were done in triple set.

Synthesis of selenium nanoparticles

Selenium nanoparticle synthesized following the published article [12]. Initially, 0.2 mg of ascorbic acid was dissolved in water. Sodium selenite, at a quantity of 0.03 g, was added to a flask containing 90 mL of solution and stirred on a magnetic stirrer. 10 µL of Tween 80 were slowly and dropwise added to the selenium solution. After 30 minutes, the ascorbic acid solution was added dropwise. A color change from a clear solution to red indicated that the reaction had occurred. After 24 hours, the synthesized nanoparticles were separated using a centrifuge at 16,000 rpm. The synthesis of selenium nanoparticles was confirmed by UV spectroscopy at a wavelength of 300 nanometers. Transmission electron microscopy (TEM) imaging was performed to confirm the synthesis and size of the selenium nanoparticles.

Biochemical and pathological assessment

Six groups were chosen for our investigation including:

1- Group one received normal saline orally for a duration of 14 days.

2- Group two received a solution of CCl_4 diluted in olive oil (at a ratio of 1:3) at a dose of 2 mL/kg, twice a week for two weeks, administered intraperitoneally.

3- Group three received a solution of CCl_4 and olive oil (at a ratio of 1:3) at a dose of 2 mL/kg, twice a week for 14 consecutive days, and simultaneously received nanoselenium at a dose of 0.2 mg/kg orally.

4- Group four received a solution of CCl_4 and olive oil (at a ratio of 1:3) at a dose of 2 mL/kg, twice a week, and simultaneously received nanoselenium at a dose of 1 mg/kg orally for 14 consecutive days.

5- Group five received a solution of CCl_4 and olive oil (at a ratio of 1:3) at a dose of 2 mL/kg, twice a week, and simultaneously received nanoselenium at a dose of 2 mg/kg orally for 14 consecutive days.

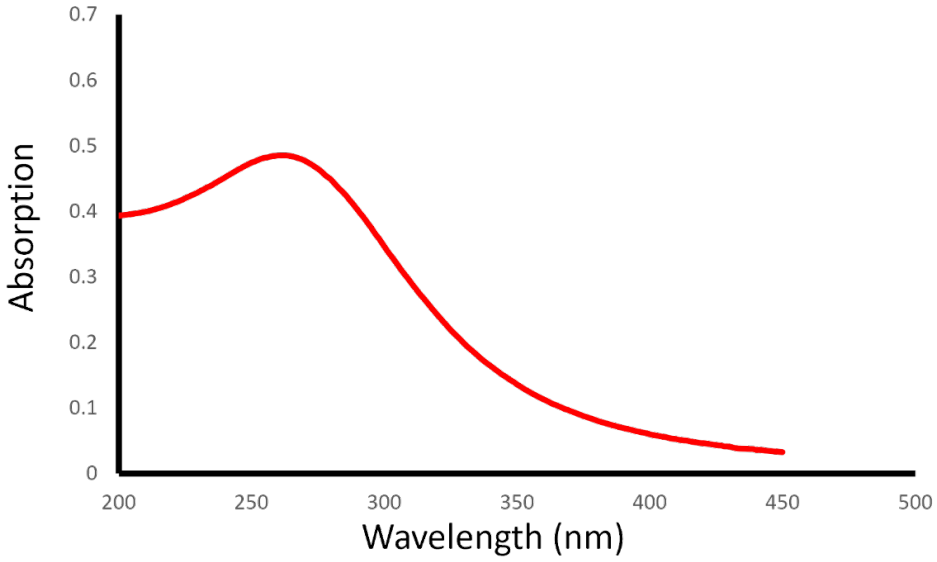

Fig. 1. UV-Vis of selenium nanoparticles.

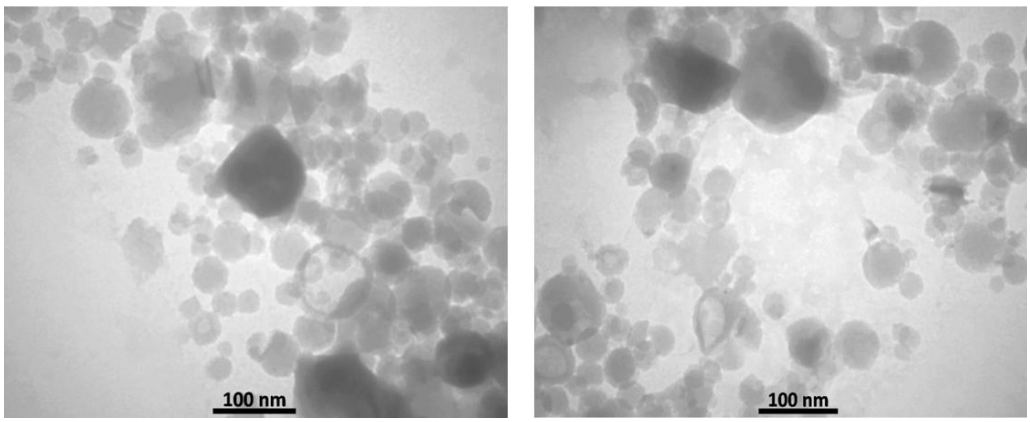

Fig. 2. TEM images of selenium nanoparticle synthesized with ascorbic acid.

6- Group six received a solution of CCl_4 and olive oil (at a ratio of 1:3) at a dose of 2 mL/kg, twice a week, and simultaneously received selenium at a dose of 2 mg/kg orally for 14 consecutive days.

After 14 days, and following ethical guidelines, blood samples were collected directly from the heart of different groups after anesthesia with ketamine-xylazine, with doses of 80 and 5 mg/kg respectively. The blood samples were centrifuged at 300 RPM for 20 minutes to separate the serum. The serum samples were used to measure and assess paraoxonase enzyme activity. Liver tissue was sectioned and stained for histopathological examination. Sections with a thickness of 5-6 micrometers were prepared and stained using the standard Hematoxylin-Eosin (H&E) staining method. The stained sections were then evaluated for liver tissue changes using a light microscope. At the end the activities of the paraoxonase enzyme, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total protein, and albumin were determined.

Statistical analysis

Statistical analysis was done using SPSS, Microsoft office (2013). For quantitative data analysis one-way analysis of variance followed by Tukey's test was applied. $P<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Characterization

To ascertain the surface plasmon resonance of selenium nanoparticles synthesized UV-Vis spectroscopic analysis was conducted. The spectrum revealed an absorption peak at 300 nm, which falls within the 200 to 350 nm range (Fig. 1). This absorption peak at 300 nm was attributed to the crystallinity of the selenium nanoparticles. Notably, these findings are consistent with those documented by Tohidi Moghadam *et al* [12]. The selenium nanoparticles synthesized using Tween 80 are observed in Fig. 2. Notably, a distinguishing feature of these synthesized nanoparticles is their remarkable uniformity. Additionally, these nanoparticles exhibit a spherical morphology with a size range of approximately 60-80 nanometers. The consistent uniformity of these nanoparticles highlights the effectiveness of Tween 80 as a capping agent in the synthesis process. Overall, these findings suggest that the use of Tween 80 in the synthesis of selenium nanoparticles results in the production of highly homogeneous and uniform nanoparticles.

Biochemical parameters examination

The AST level in serum is shown in Fig. 3. In the statistical analysis, the activity of the enzyme AST of group 2 was significantly higher compared to

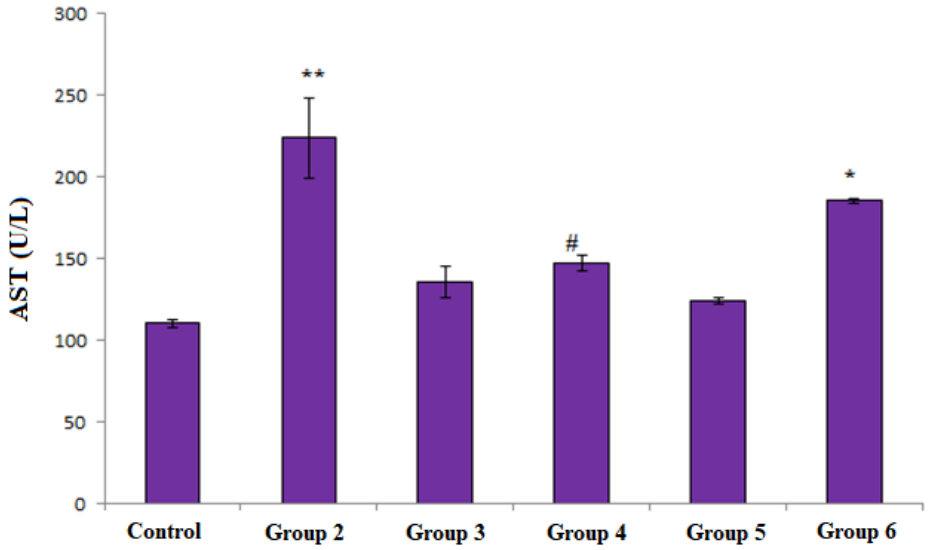

Fig. 3. AST serum level in different 6 groups.

other groups, with differences being statistically significant for all groups (P ≤ 0.03). The AST activity in Group 6, which received selenium, also showed a statistically significant difference compared to other groups (P ≤ 0.032). Additionally, the mean AST activity in Group 4 was significantly different from the control group (P ≤ 0.036). In liver diseases, AST levels often increase. AST is an enzyme found in the liver, heart, muscles, and other tissues. When the liver is damaged or inflamed, as in conditions like hepatitis, cirrhosis, or liver injury, AST can leak into the bloodstream, leading to elevated levels [13]. Our result showed that AST level increased in group 2 and decreased in all groups received nanoselenium. Reduction in AST levels means that synthesized nanoparticle might be mitigating liver

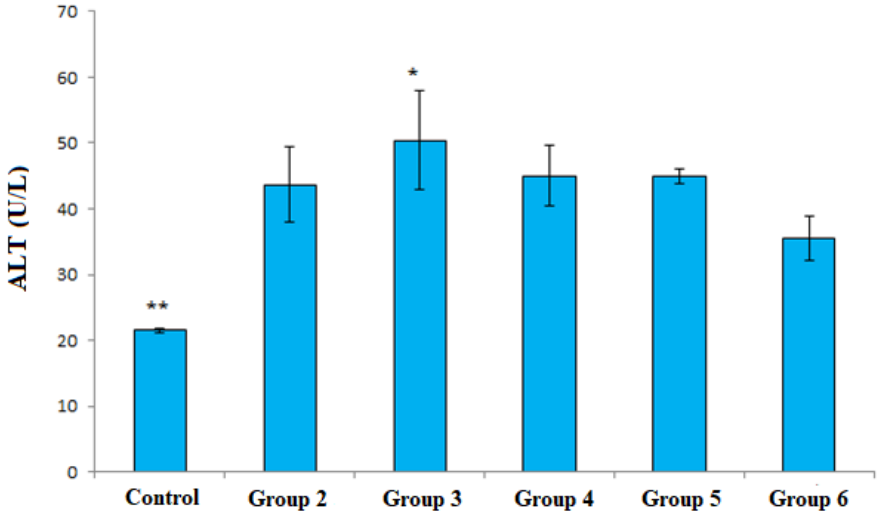

Fig. 4. ALT serum level in different 6 groups.

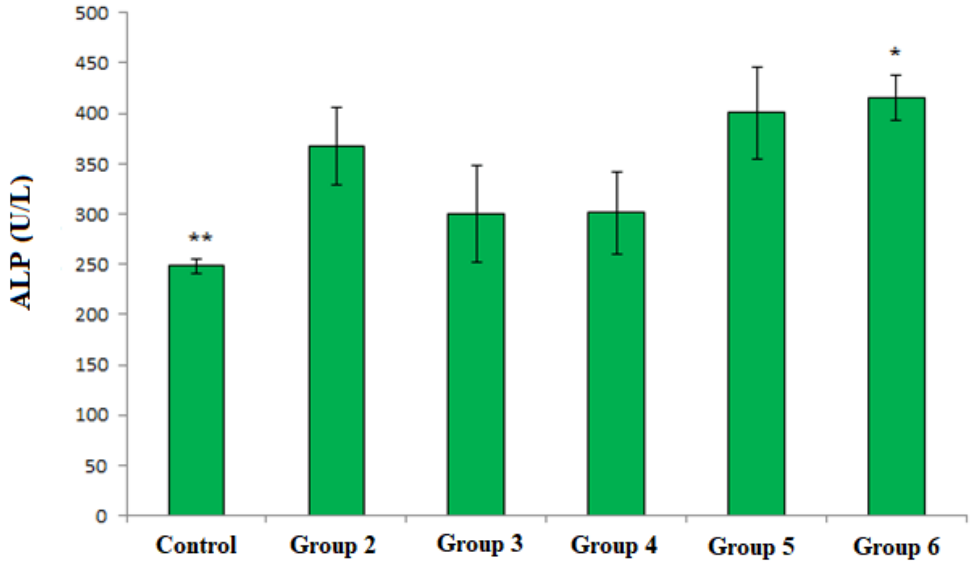

Fig. 5. ALP serum level in different 6 groups.

damage. Although selenium decreased AST level in serum too, is not as protective as nanoselenium.

Fig. 4 shows the ALT serum level. In the serum analysis, the activity of the enzyme ALT showed a statistically significant difference between the control group and other groups ($P \leq 0.02$). Additionally, the mean ALT activity in group 3 differed significantly from that in the selenium group ($P = 0.022$). The highest enzyme activity was observed in the group 3 with a value of 50.33 ± 7.51 U/L, while the lowest activity was recorded in the control group, with a value of 21.5 ± 0.28 U/L. In liver diseases, ALT levels often increase and is more specific to the liver compared to AST. While AST is found in several tissues, including the heart and muscles so its level can be influenced by factors other than liver damage, ALT is primarily found in the liver, making it a more sensitive

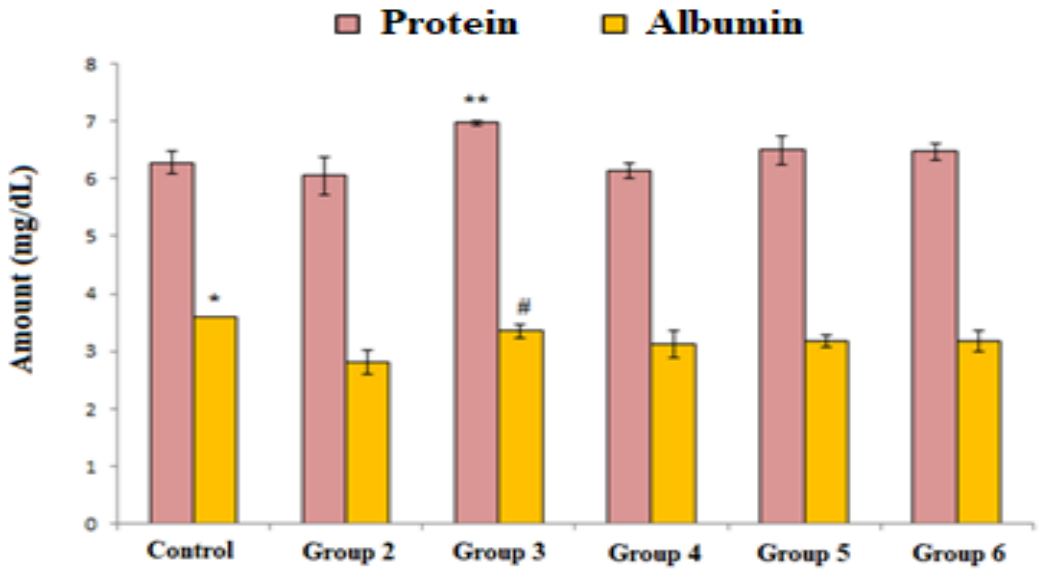

Fig. 6. Protein and albumin serum level in different 6 groups.

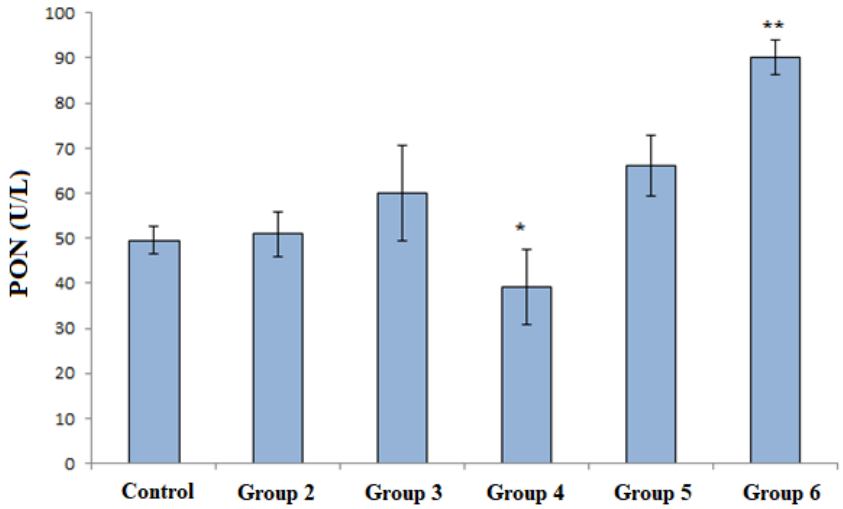

Fig. 7. PON serum level in different 6 groups.

indicator of liver damage [14, 15].

Our result showed that ALT increased in the group exposed to CCl_4 and other treatment groups means that while treatment with nanoselenium and selenium might be reducing overall liver damage (as evidenced by the decreased AST), it is not fully preventing or addressing the liver cell injury that still results in elevated ALT levels. Moreover, in the serum analysis of ALP enzyme activity (Fig. 5), it was observed that there was a statistically significant difference in the enzyme activity levels between the control group and groups 2, 5, and 6 ($P \leq 0.041$). Additionally, the mean ALP enzyme activity in group 3 ($P = 0.047$) and group 4 differed significantly from the group 6 ($P = 0.049$). The highest activity of this enzyme was observed in the group 6 with a measurement of 415.67 ± 22.85 U/L, while the lowest activity was recorded in the control group with the value of 248.55 ± 7.35. It is known that ALP levels are often associated with liver and biliary tract disorders [16].

Our result showed the reduction of ALP serum level in group 3 and 4 suggested that nanoselenium at doses of 0.2 and 1 mg/kg may serve as an effective protective agent. In more advanced liver diseases, where the liver's ability to produce proteins is severely impaired, total protein levels can decrease [16, 17]. This decrease is typically accompanied by a decrease in albumin levels. In the serum total protein analysis, a statistically significant difference in protein levels was observed between group 3 and groups 1, 2, and 4 ($P \leq 0.044$). The highest protein amount was in group 3, with a measurement of 6.96 ± 0.03 mg/dL, while the lowest amount was in group 2, at 6.05 ± 0.32 mg/dL. Also, albumin is a protein produced by the liver, and its levels in the blood can drop when the liver's ability to produce it is compromised [17, 18]. Decreased albumin levels can be a marker of liver dysfunction and may indicate severe liver disease or impaired liver function. The mean albumin levels showed the significantly reduction in group 2 in comparison to control group. The highest albumin level was in group 3, with a measurement of 3.35 ± 0.11 mg/dL, while the lowest was in group 2, at 2.8 ± 0.2 mg/dL that are showed difference statistically. As it is obvious in Fig. 6, exposure to CCl_4 reduced the protein and albumin levels while treatment with 0.2 mg/kg nanoselenium increased both protein and albumin levels.

Paraoxonase (PON) is an enzyme primarily associated with high-density lipoprotein (HDL) and has been studied for its role in oxidative stress and lipid metabolism [18, 19]. In the analysis of mean PON activity in the serum of rats from different groups, the highest enzyme activity was observed in the selenium-receiving group, with a measurement of 90.22 ± 3.83 U/L. The lowest enzyme activity was found in the group 4, with a measurement of 39.25 ± 8.26 U/L. The mean

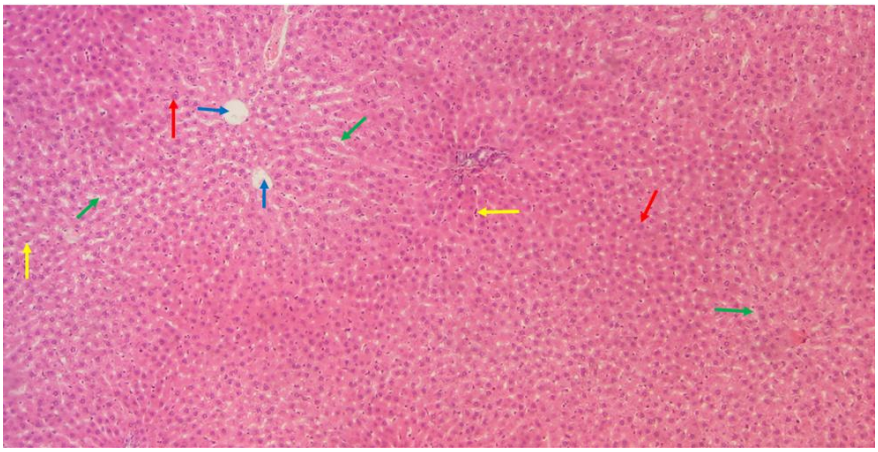

Fig. 8. Histopathological Study of the control group. Hepatic cords are arranged in rows and have a radial pattern. Central veins are clear and normal (blue arrow). Sinusoids have a normal size (green arrow). Hepatocytes have normal size and tissue structure, with rounded, euchromatic nuclei and normal cytoplasmic staining (red arrow). Kupffer cells are identifiable with elongated and dense (compact) nuclei (yellow arrow) and are present in normal numbers. There is no evidence of congestion or hyperemia in the vessels or sinusoids.

paraoxonase activity in group 6, which received selenium, differed significantly from all other groups ($P \leq 0.023$). Our result showed that PON increased in group 2 (rats which exposed to CCl_4) (Fig. 7). Growing in PON levels in response to CCl_4 could be indicative of an adaptive response to heightened oxidative stress. PON is involved in hydrolyzing oxidative byproducts and may increase in an attempt to mitigate oxidative damage and protect liver cells. In group 4 (rats which treated with 1 mg/kg nanoselenium) decrease the PON level. The decrease in PON levels following nanoparticle treatment suggests that the nanoparticles may be effective in reducing oxidative stress or damage caused by CCl_4. If the nanoparticles are reducing oxidative damage, the

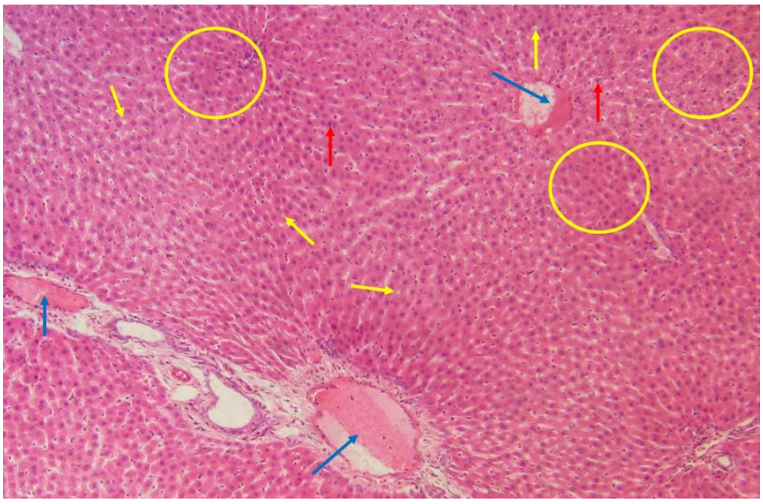

Fig. 9. Histopathological Study of the group receiving carbon tetrachloride. The radial arrangement of hepatocyte cords is largely disrupted, and the lumen of the sinusoids is often obliterated, indicating sinusoidal stenosis (yellow circle). Hepatocyte degeneration is evident, and some have undergone hypertrophy (red arrow). Vacuolization in the cytoplasm of hepatocytes is clearly visible (yellow arrow). Hyperemia in the portal vessels and the central vein is clearly observable (blue arrow)

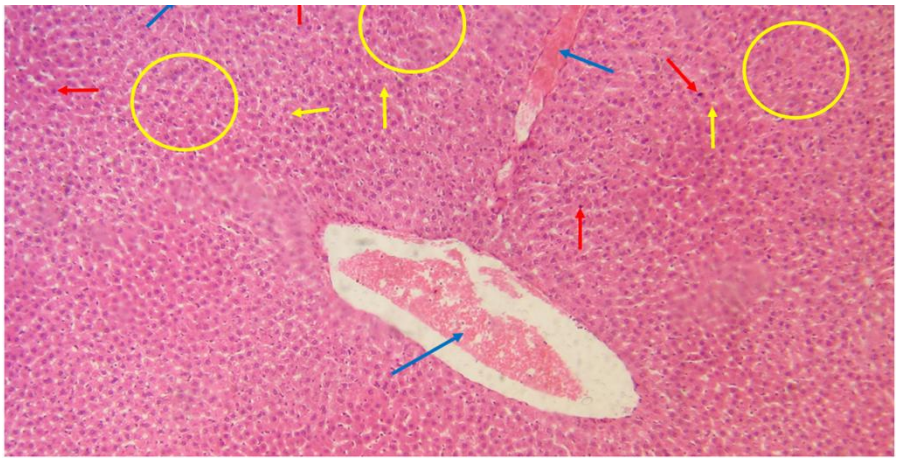

Fig.10. Shows the histopathological Study of the group 3. The radial arrangement of hepatocyte cords is somewhat disrupted, and sinusoidal stenosis is evident as the lumen of the sinusoids is obliterated (yellow circle). Hepatocyte degeneration is still present, and some of them have undergone hypertrophy (red arrow). Vacuolization in the cytoplasm of hepatocytes (yellow arrow) and hyperemia in the portal vessels and the central vein are also observable (blue arrow)

liver may require less PON to counteract oxidative stress, leading to a decrease in PON levels.

Histopathological study

Liver tissue was sectioned for each group and stained for histopathological examination. Our results showed that, in the control group, the liver cords are arranged in a row with a radial pattern. The central veins are clear and normal. The sinusoids are of normal size. The hepatocytes have normal size and tissue structure, with round, euchromatic nuclei and cells with normal cytoplasmic staining. Kupffer cells are identifiable with elongated and dense (compact) nuclei, and their number is normal. No signs of congestion or hyperemia are observed in the vessels or sinusoids (Fig. 8).

Also, in the liver tissue of the group 2, the radial arrangement of hepatocyte cords is largely disrupted, and the lumen of the sinusoids is often obliterated, indicating sinusoidal stenosis. Hepatocyte degeneration is evident, and some of them have undergone hypertrophy. Vacuolization in the hepatocyte cytoplasm is clearly visible. Hyperemia in the portal vessels and the central vein is also distinctly observable (Fig. 9). Furthermore, In the liver tissue of the group 3, the radial arrangement of hepatocyte cords is somewhat disrupted, and sinusoidal stenosis is evident as the lumen of the sinusoids is largely lost. Hepatocyte degeneration persists, and some of these cells have undergone hypertrophy.

Vacuolization in the hepatocyte cytoplasm and hyperemia in the portal vessels and central vein are also observable. In contrast to carbon tetrachloride group less signs have been observed in this group (Fig. 10). Moreover, In the liver tissue of the group 4, the radial arrangement of hepatocyte cords has somewhat normalized. Additionally, while the lumen of the sinusoids has normalized in some areas, mild sinusoidal stenosis still persists in most regions. Necrotic hepatocytes with cellular degeneration have decreased, and there are no signs of hypertrophic hepatocytes. Vacuolization in the hepatocyte cytoplasm remains present.

The intensity of hyperemia in the portal vessels and central vein has decreased (Fig. 11). Additionally, In the liver tissue of the group 5, the radial arrangement of hepatocyte cords has largely normalized, and the lumen of the sinusoids is normal in many areas, although mild sinusoidal stenosis is still observed in some regions.

Necrotic hepatocytes with cellular degeneration have significantly decreased, and there are no

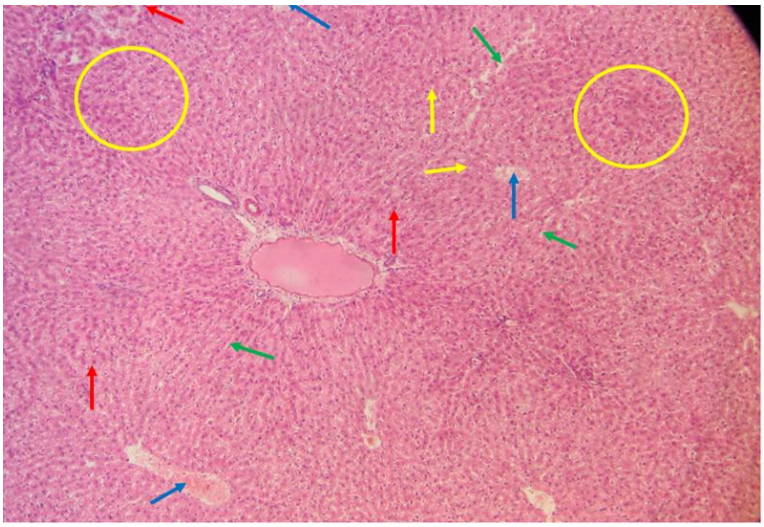

Fig. 11. Shows histopathological Study of the group 4. The radial arrangement of hepatocyte cords has somewhat normalized, and although the lumen of the sinusoids has normalized in some areas (green arrow), mild sinusoidal stenosis is still present in most areas (yellow circle). Necrotic hepatocytes with pyknotic nuclei (cellular degeneration) have decreased (red arrow), and there is no evidence of hypertrophic hepatocytes. Vacuolization in the cytoplasm of hepatocytes is still present (yellow arrow). The intensity of congestion (hyperemia) in the portal vessels and the central vein has decreased (blue arrow).

signs of hypertrophic hepatocytes. Vacuolization in the hepatocyte cytoplasm has improved considerably (Fig. 12). Further, In the liver tissue of the group 6, the radial arrangement of hepatocyte cords has largely normalized. However, the lumen of the sinusoids remains largely obliterated in most areas, indicating the presence of sinusoidal stenosis. Although necrotic hepatocytes with cellular degeneration have decreased, their number is higher compared to the previous groups

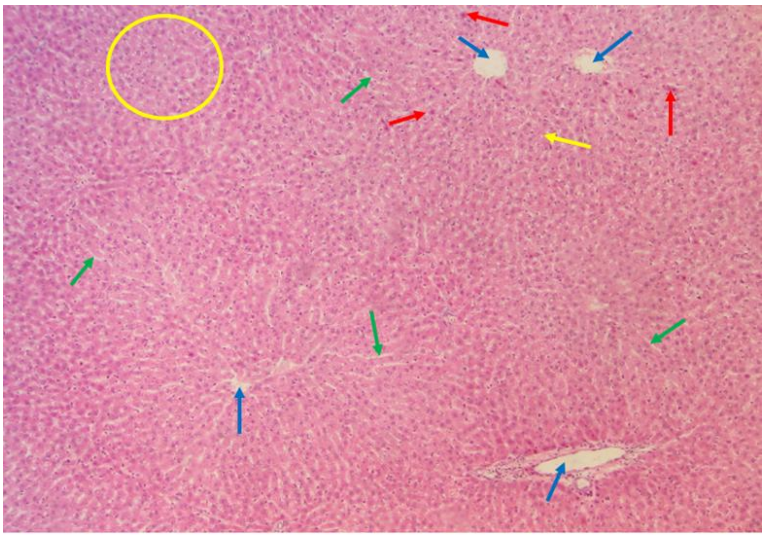

Fig. 12. Shows the histopathological study of the group 5. The radial arrangement of hepatocyte cords is largely normalized, and the lumen of the sinusoids is normal in many areas (green arrow), although mild sinusoidal stenosis is still observed in some areas (yellow circle). Cellular degeneration has been significantly reduced (red arrow), and there is no evidence of hypertrophic hepatocytes. Vacuolization in the cytoplasm of hepatocytes has improved significantly (yellow arrow). There is no congestion (hyperemia) in the portal vessels and the central vein (blue arrow).

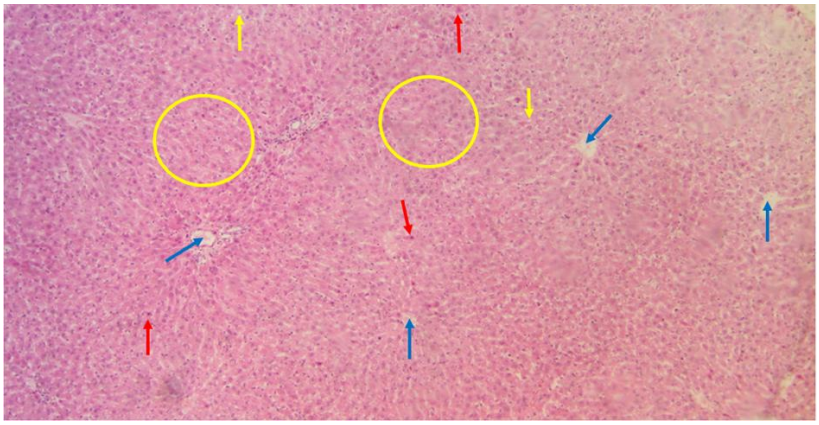

Fig. 13. Shows the histopathological Study of the group 6. The radial arrangement of hepatocyte cords is largely normalized. However, the lumen of the sinusoids is still obliterated in most areas, indicating the presence of sinusoidal stenosis (yellow circle). Although cellular degeneration has decreased, their quantity is higher compared to the previous group (red arrow). No hypertrophic hepatocytes are observed. Vacuolization in the cytoplasm of hepatocytes has somewhat diminished (yellow arrow). There is no congestion (hyperemia) in the portal vessels and central vein (blue arrow).

(Fig. 13).

All in all, our findings indicate that the synthesized nano-selenium exhibits significantly higher activity and effectively mitigates the toxic effects of carbon tetrachloride. Consequently, employing nano-selenium alleviates concerns about the potential side effects associated with selenium.

CONCLUSION

This study investigates the protective effects of synthesized selenium nanoparticles (SeNPs) against liver toxicity induced by carbon tetrachloride (CCl_4). Our results demonstrate that SeNPs exhibit significantly greater activity in mitigating liver damage compared to bulk selenium, highlighting their potential as a therapeutic agent. The synthesized SeNPs, characterized by their uniform spherical morphology and size range of 60-80 nanometers, show enhanced biological activity and reduced toxicity. Biochemical assessments revealed that SeNPs effectively reduced levels of liver enzymes such as AST, ALT, and ALP, which are markers of liver damage and dysfunction. SeNPs were notably more effective than conventional selenium in normalizing these enzyme levels, indicating their superior efficacy in alleviating oxidative stress and liver injury. Importantly, the analysis of paraoxonase (PON) activity revealed that SeNPs influenced PON levels in a manner consistent with their protective effects. While CCl_4 exposure increased PON levels as an adaptive response to oxidative stress, treatment with SeNPs resulted in decreased PON levels. Additionally, SeNPs positively impacted serum total protein and albumin levels, which were diminished by CCl_4 exposure, further supporting their protective role. Histopathological examination also confirmed that SeNPs treatment led to improved liver tissue morphology, with reduced fibrosis and necrosis compared to untreated controls.

In summary, the synthesized selenium nanoparticles offer a promising approach for mitigating liver toxicity, with superior protective effects compared to traditional selenium forms. The beneficial impact on liver enzyme levels, serum proteins, and PON activity underscores the potential of SeNPs in addressing liver diseases and alleviating concerns about selenium-related side effects. Future research should further explore the mechanisms of SeNPs' action and their efficacy in broader liver disease models.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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